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the OBSERVANT Research Group

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A novel, comprehensive tool for predicting 30-day mortality after surgical aortic valve replacement

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Key question

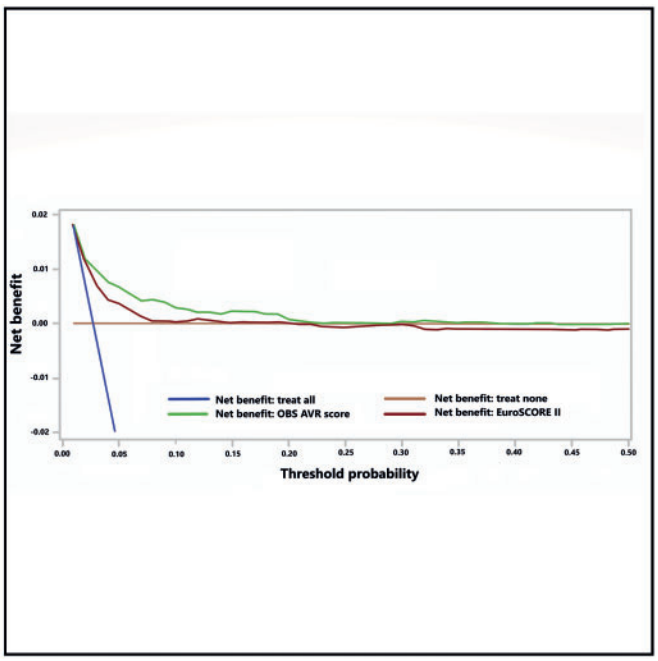
Could a specific mortality risk score for patients having SAVR be useful to predict their prognosis more accurately?

Key finding(s)

The OBS aortic valve replacement score showed good discrimination and calibration abilities in predicting 30-day mortality after SAVR.

Take-home message

The addition of a simple frailty scale to the model contributed to improved performance over the EuroSCORE II.



Abstract

OBJECTIVES: We sought to develop and validate a novel risk assessment tool for the prediction of 30-day mortality after surgical aortic valve replacement incorporating a patient's frailty.

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METHODS: Overall, 4718 patients from the multicentre study OBSERVANT was divided into derivation ($n = 3539$) and validation ($n = 1179$) cohorts. A stepwise logistic regression procedure and a criterion based on Akaike information criteria index were used to select variables associated with 30-day mortality. The performance of the regression model was compared with that of European System for Cardiac Operative Risk Evaluation (EuroSCORE) II.

RESULTS: At 30 days, 90 (2.54%) and 35 (2.97%) patients died in the development and validation data sets, respectively. Age, chronic obstructive pulmonary disease, concomitant coronary revascularization, frailty stratified according to the Geriatric Status Scale, urgent procedure and estimated glomerular filtration rate were independent predictors of 30-day mortality. The estimated OBS AVR score showed higher discrimination (area under curve 0.76 vs 0.70, $P < 0.001$) and calibration (Hosmer–Lemeshow $P = 0.847$ vs $P = 0.130$) than the EuroSCORE II. The higher performances of the OBS AVR score were confirmed by the decision curve, net reclassification index (0.46, $P = 0.011$) and integrated discrimination improvement (0.02, $P < 0.001$) analyses. Five-year mortality increased significantly along increasing deciles of the OBS AVR score ($P < 0.001$).

CONCLUSIONS: The OBS AVR risk score showed high discrimination and calibration abilities in predicting 30-day mortality after surgical aortic valve replacement. The addition of a simplified frailty assessment into the model seems to contribute to an improved predictive ability over the EuroSCORE II. The OBS AVR risk score showed a significant association with long-term mortality.

Keywords: Aortic valve replacement • Frailty • Score • Performance • Aortic stenosis

ABBREVIATIONS

AIC	Akaike information criterion
AUC	Area under curve
EuroSCORE	European System for Cardiac Operative Risk Evaluation
GSS	Geriatric Status Scale
H–L	Hosmer–Lemeshow
IDI	Integrated discrimination improvement
NRI	Net reclassification index
OBSERVANT	OBservational Study of Effectiveness of AVR-TAVI procedures for severe Aortic steNosis Treatment
SAVR	Surgical aortic valve replacement
TAVR	Transcatheter aortic valve replacement

INTRODUCTION

Current risk score systems for predicting mortality after cardiac surgery were not specifically developed to estimate the risk of patients undergoing surgical aortic valve replacement (SAVR). As a consequence, they may provide an imprecise estimate of the operative risk, particularly in high-risk patient categories [1]. Furthermore, they did not consider patients' functional decline related to cardiac diseases and other comorbidities. In view of this limitation, it is recommended that the Heart Teams perform an individual evaluation of comorbidities not included in the current risk scores [2]. In particular, frailty is one of the most important risk factors contributing to an unfavourable risk/benefit ratio for SAVR [3]. The aim of the present subanalysis of the OBservational Study of Effectiveness of AVR-TAVI procedures for severe Aortic steNosis Treatment (OBSERVANT) study was to develop a novel, comprehensive and user-friendly scoring system including frailty for mortality risk assessment in patients undergoing SAVR.

MATERIALS AND METHODS

OBSERVANT (OBS) is a prospective, multicentre study that enrolled consecutive patients undergoing SAVR or transcatheter aortic valve replacement (TAVR) for aortic stenosis at 93 Italian centres (34 cardiology centres and 59 cardiac surgery centres) between December 2010 and June 2012. The study was performed by the Italian National Health Institution in cooperation with the Italian Ministry of Health, the National Agency for Regional Health Services, Italian Regions and Italian scientific societies and federations representing Italian professionals involved in the treatment. The study protocol was approved by the local ethics committee of the coordinating institution (Policlinico San Donato). All patients gave an informed consent to participate to this study. Data on frailty were not gathered at 4 centres, and these were excluded from this analysis. Details of the study included and excluding criteria, as well as covariates definition criteria, have been previously published [4, 5].

For the purpose of this study, patient's frailty was graded according to the Geriatric Status Scale (GSS) [6]: (0) patients who walk without help, perform basic activities of daily living (eating, dressing, bathing, bed transfers), have bowel and bladder continence and are not cognitively impaired; (1) patients with bladder incontinence only; (2) one (two if incontinent) or more of "needing assistance with mobility or activities of daily living", "has cognivive impairment with no dementia", or "has bowel or bladder incontinence"; and (3) two (three if incontinent) or more of "totally dependent for transfers or one or more activities of daily life", "bowel and bladder, incontintinence" and diagnosis of dementia. Frailty was considered significant if GSS was 1–3.

Outcomes

The primary outcome of this analysis was 30-day death from any cause. The secondary outcome was late all-cause mortality. Data on late mortality were gathered by a record linkage with the National Hospital Discharged Records database and the Tax Registry Information System, provided by the Italian Ministry of Health through a collaboration with the Italian National Program for Outcome Evaluation (AGENAS). This approach warranted a complete follow-up for all patients residing in Italy.

Statistical analysis

The study cohort was randomly divided into 2 data sets, i.e. the derivation data set ($n = 3539$, 75.0%) and the validation data set

($n = 1179$, 25.0%). A cross-validation procedure was applied to identify the best predicted model avoiding overfitting. Univariate analyses were performed on all candidate covariates of the derivation data set to identify predictors of the primary outcome. Multiple logistic regression analysis was performed using the derivation data set. A stepwise procedure with a bootstrap approach was used, and 100 samples were extracted with a size of 70% of the derivation data set. A stepwise procedure was applied to each sample (probability to stay = 0.05; probability to entry = 0.1). Variables selected in at least 50% of the stepwise procedures were included in the model.

Additional covariates were selected using a forward selection comparing the Akaike information criterion (AIC) for the models with and without each covariate. The model with the lowest AIC was selected for each forward step, until the inclusion of a new covariate determined an increase in the AIC value. Almost all risk factors were included as categorical covariates. Age was used as a continuous variable starting from 60 years.

The model was then tested in the validation data set for calibration, using the Hosmer–Lemeshow (H–L) statistic, and for discrimination, using the receiver-operating characteristic curve analysis. A comparison of the OBS AVR score and European System for Cardiac Operative Risk Evaluation (EuroSCORE) II for the prediction of 30-day mortality in the overall data set was performed. The improvement of discrimination of the OBS AVR score as compared to EuroSCORE II was estimated by calculating the net reclassification index (NRI) and integrated discrimination improvement (IDI) [7]. Decision curve analysis was performed to evaluate the net benefit of the OBS AVR score over the EuroSCORE II [8]. Finally, to evaluate the adaptability of the new score for the long-term prediction of mortality, Kaplan–Meier curves stratified by deciles of the OBS AVR score were plotted.

Statistical analysis was performed using SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC, USA).

RESULTS

A total of 4718 patients who underwent SAVR from the OBSERVANT study were included in the present analysis (Fig. 1). There were no significant differences in baseline characteristics between the derivation and validation data sets (Table 1). Thirty-day mortality was 2.5% in the derivation data set and 3.0% in the validation data set.

The predictive model built on the derivation data set is reported in Table 2. The multivariate logistic regression showed that age, chronic obstructive pulmonary disease, concomitant coronary revascularization, frailty stratified according to the GSS, urgent procedure and estimated glomerular filtration rate were significant independent predictors of 30-day mortality. The equation to calculate this score is reported in the Supplementary Material.

The discrimination ability of the OBS AVR score assessed by the area under curve (AUC) of receiver-operating characteristic curve was 0.77 in the derivation data set and 0.76 in the validation data set, whereas the calibration ability assessed by H–L test was 3.67 ($P = 0.893$) and 3.75 ($P = 0.881$), respectively. The performance of the OBS AVR score was compared with that of the EuroSCORE II in the overall series. The OBS AVR score showed higher discrimination [AUC 0.76 vs 0.70, difference 0.06 (0.02–0.10), $P < 0.001$] and calibration (H–L test 4.09 vs 12.48, $P = 0.847$ vs $P = 0.130$) ability. The better performance in discrimination of the OBS AVR score was confirmed by NRI (0.46, $P = 0.011$) and IDI (0.023, $P < 0.001$) analyses. Finally, the net benefit in predicting 30-day mortality with the use of OBS AVR score instead of EuroSCORE II was demonstrated by the decision curve analysis (Fig. 2).

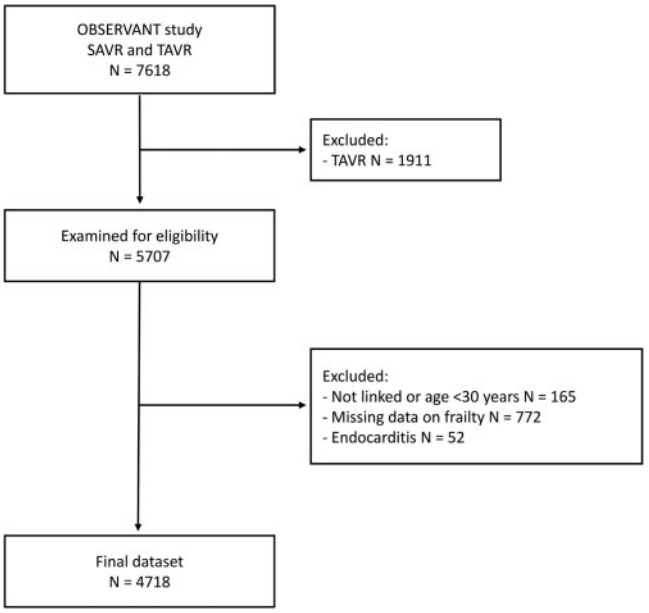

Figure 1: Study flowchart. SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement.

Kaplan–Meier estimates showed a significant association between increasing OBS AVR score and 5-year survival ($P < 0.001$) (Fig. 3). A landmark analysis excluding patients who died within 30 days after the procedure confirmed a significant association between the OBS AVR score and 5-year survival ($P < 0.001$) (Supplementary Material, Fig. S1).

The OBS AVR score showed higher discrimination than EuroSCORE II in the subsets of patients who underwent elective SAVR (AUC 0.74 vs 0.68, $P < 0.001$), urgent SAVR (AUC 0.69 vs 0.61, $P < 0.001$), SAVR without concomitant coronary revascularization (AUC 0.75 vs 0.69, $P < 0.001$) and SAVR with concomitant coronary revascularization (AUC 0.78 vs 0.70, $P < 0.001$).

DISCUSSION

The rapid development of transcatheter technology has led to unprecedented changes in the invasive treatment of heart valve disease and revealed the unmet need of a more comprehensive assessment of patients' operative risk. A multidisciplinary evaluation of a patient's individual operative risk is of utmost importance in the decision-making process [2, 9], and it would be desirable to use a simple, novel risk scoring system, which takes into account their age-associated functional decline apart from the conventional risk factors.

The present analysis of the multicentre OBSERVANT study sought to derive and internally validate a user-friendly risk score for predicting 30-day mortality specifically for SAVR including a simplified assessment of patients' frailty.

The main findings of this analysis are: (i) the OBS AVR score showed high discrimination and calibration in both the derivation and validation data sets; (ii) this new risk score

Table 1: Characteristics of patients in the derivation and validation data sets

Clinical variables	Derivation data set, *N* = 3539 (%)	Validation data set, *N* = 1179 (%)	*P*-value
Age (years), mean ± SD	73.1 ± 9.3	73.4 ± 8.9	0.264
Age (years), median (IQR)	74.8 (68.2–79.6)	75.3 (68.9–79.6)	
Female, *n* (%)	1665 (47.1)	541 (45.9)	0.474
Body mass index (kg/m^2), *n* (%)			0.876
<18.5	38 (1.2)	14 (1.1)	
18.5–25	1096 (32.8)	375 (32.2)	
≥25	2269 (65.9)	753 (66.7)	
eGFR (ml/min/1.73 m^2), *n* (%)			0.076
>90	654 (18.9)	237 (20.6)	
45–90	2376 (68.7)	747 (64.8)	
15–45	366 (10.6)	147 (12.8)	
≤15	62 (1.8)	22 (1.9)	
Chronic dialysis, *n* (%)	49 (1.4)	17 (1.4)	0.883
Chronic liver disease, *n* (%)	67 (1.9)	21 (1.8)	0.233
Previous PCI, *n* (%)	249 (7.04)	95 (8.1)	0.245
Diabetes, *n* (%)	216 (6.1)	52 (4.4)	0.029
COPD, *n* (%)	370 (10.5)	110 (9.4)	0.273
Oxygen dependency, *n* (%)	39 (1.1)	18 (1.5)	0.242
Smoking habit, *n* (%)	681 (19.8)	232 (20.2)	0.798
Active malignancy, *n* (%)	34 (1.0)	10 (0.9)	0.563
Unstable angina, *n* (%)	176 (5.0)	50 (4.3)	0.334
Coronary artery disease, *n* (%)	1162 (32.9)	397 (33.8)	0.232
Previous MI, *n* (%)	125 (3.5)	40 (3.4)	0.173
Previous cardiac surgery, *n* (%)	138 (3.9)	37 (3.1)	0.999
NYHA class IV, *n* (%)	238 (6.7)	66 (5.6)	0.345
Stroke or TIA, *n* (%)	84 (2.4)	28 (2.4)	0.999
Peripheral arteriopathy, *n* (%)	495 (14.1)	169 (14.4)	0.790
Previous vascular surgery, *n* (%)	75 (2.1)	21 (1.8)	0.473
Porcelain aorta, *n* (%)	44 (1.2)	17 (1.5)	0.594
GSS frailty score 1–3, *n* (%)	670 (19.4)	239 (20.7)	0.345
Pulmonary hypertension, *n* (%)	193 (5.8)	59 (5.3)	0.518
Left ventricular ejection fraction, *n* (%)			0.057
>50	2860 (82.3)	975 (84.8)	
30–50	564 (16.2)	154 (13.4)	
<30	52 (1.5)	62 (1.8)	
Moderate-to-severe mitral regurgitation, *n* (%)	420 (12.0)	142 (12.1)	0.886
Urgency procedure, *n* (%)	123 (3.5)	51 (4.3)	0.180
Critical preoperative state, *n* (%)	70 (2.0)	19 (1.6)	0.429
Concomitant coronary revascularization, *n* (%)	901 (25.7)	314 (27.1)	0.365
EuroSCORE II (%), mean ± SD	3.2 ± 3.8	3.3 ± 5.0	0.344
EuroSCORE II (%),median (IQR)	2.1 (1.3–3.7)	2.1 (1.3–3.6)	

COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; EuroSCORE: European System for Cardiac Operative Risk Evaluation; GSS: Geriatric Status Scale; IQR: 25th–75th interquartile range; MI: myocardial infarction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; TIA: transient ischaemic attack.

demonstrated to have a better predictive performance than the EuroSCORE II; (iii) patients' frailty assessed by the simple GSS classification was independently associated with the 30-day mortality after SAVR and demonstrated to be among the most significant contributing factors for mortality in this patient population; and (iv) the 30-day predicted mortality risk estimates showed a significant association with long-term mortality.

The OBS AVR score demonstrated good calibration and discriminative ability. These characteristics were maintained after validating the model in an independent cohort of patients. Nevertheless, the performance of the score might have been affected by the low number of mortality events encountered during the study period.

These findings are in line with those of the most currently used scoring systems for the prediction of mortality after cardiac surgery. Indeed, the EuroSCORE II, the Society of Thoracic Surgeons-Predicted Risk of Mortality and the Germany Aortic Valve Score II demonstrated AUC for the prediction of early mortality ranging from 0.74 to 0.81 with a goodness of fit ranging from 0.41 to 0.86 when validated in internal data sets, but poorer performances when validated in external cohorts [10–14].

Currently, the EuroSCORE II and the Society of Thoracic Surgeons-Predicted Risk of Mortality scoring systems are the recommended tools for stratifying patients according to their individual risk before the intervention [2]. They have been validated in large cohorts of patients and demonstrated to have similar performance in predicting early mortality after valve surgery [15]. The OBSERVANT study collected data that allows only EuroSCORE II to be calculated independently for each patient enrolled.

In our analysis, we demonstrated that OBS AVR score outperforms the accuracy of EuroSCORE II in predicting 30-day

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mortality after aortic valve surgery. In particular, our model showed a higher discrimination [AUC 0.76 vs 0.70, difference 0.06 (0.02–0.10), $P < 0.001$] and calibration (H–L test 4.09 vs 12.48, $P = 0.847$ vs $P = 0.130$).

Furthermore, the higher accuracy of our model is confirmed by the decision curve analysis (Fig. 2), NRI (0.46, $P = 0.011$) and IDI (0.02, $P < 0.001$) that demonstrate the benefit in correctly identifying patients at real risk when OBS AVR score is used instead of EuroSCORE II for predicting 30-day mortality.

Several prospective and retrospective studies demonstrated that patients' clinical vulnerability is an independent predictor of mortality after SAVR regardless the preoperative estimated risk stratification [16–18]. Several clinical and functional assessment tools have been proposed and showed to predict either morbidity or mortality after SAVR [3]. To date, none of the principal risk scoring systems currently used for mortality estimation after SAVR incorporates patients' frailty assessment. In the present analysis, we observed that the use of the simple GSS for frailty assessment independently predicts 30-day mortality (OR 2.33, $P < 0.001$) after SAVR and is among the variables that have most weight in our regression model.

Finally, although the most commonly used scoring system for estimating outcomes after SAVR is related to in-hospital and 30-day mortality, Barili *et al.* [19] previously demonstrated that the predicted risk stratification by the STS, EuroSCORE II and ACEF scores can be used as a surrogate of long-term mortality risk estimate. In our analysis, Kaplan–Meier estimates of long-term survival in patients classified within deciles of OBS AVR score demonstrated a significant relationship between increasing a score's value and death at 5 years. This finding corroborates the notion that early mortality prediction scoring models can reasonably serve as an index of long-term outcomes after cardiac surgery [20].

Interestingly, the higher predicted classes showed a significant gap in overall mortality at 5 years. This finding could be useful to identify a subset of patients that could benefit from a less invasive treatment for severe aortic stenosis than SAVR. Indeed, survival analysis stratified by the OBS AVR score showed that the 2 highest deciles had a rather low 5-year survival (67.4% and 55.1%) (Fig. 3). This finding suggests that, even in an era when TAVR is indicated mostly for high-risk patients, at least 20% of patients in this series might have benefited from transcatheter treatment.

Table 2: Independent predictors of 30-day mortality in the derivation data set

Covariates	Beta	Odds ratio	*P*-value
Age	0.05	1.05	0.045
Female gender	-0.02	0.98	0.921
BMI			
>25 (reference)	–	–	
18.5–25	0.23	1.25	0.354
≤18.5	0.96	2.61	0.174
eGFR (ml/min/1.73 m^2)			
>90 (reference)	–	–	
45–90	0.79	2.20	0.105
15–45	1.39	4.00	0.010
≤15	2.39	10.92	0.000
Diabetes	0.07	1.07	0.858
COPD	1.19	3.28	0.000
GSS frailty 1–3	0.84	2.33	0.000
LVEF < 30%	0.77	2.16	0.118
Urgent procedure	1.40	4.04	0.000
Concomitant coronary revascularization	0.49	1.63	0.040
Intercept	-5.72		

BMI: body mass index; CI: confidence interval; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; GSS: Geriatric Status Scale; LVEF, left ventricular ejection fraction.

Limitations

A few limitations might bias the present findings. First, the GSS is a simple stratifying method of frailty, which may not capture and grade several aspects of age-related functional decline. We may expect that newer and more detailed frailty scales may provide a better stratification of the decline in cognition and physical activity and the associated risk of early and late mortality. In fact, the GSS is an indirect measure of functional and cognitive well-

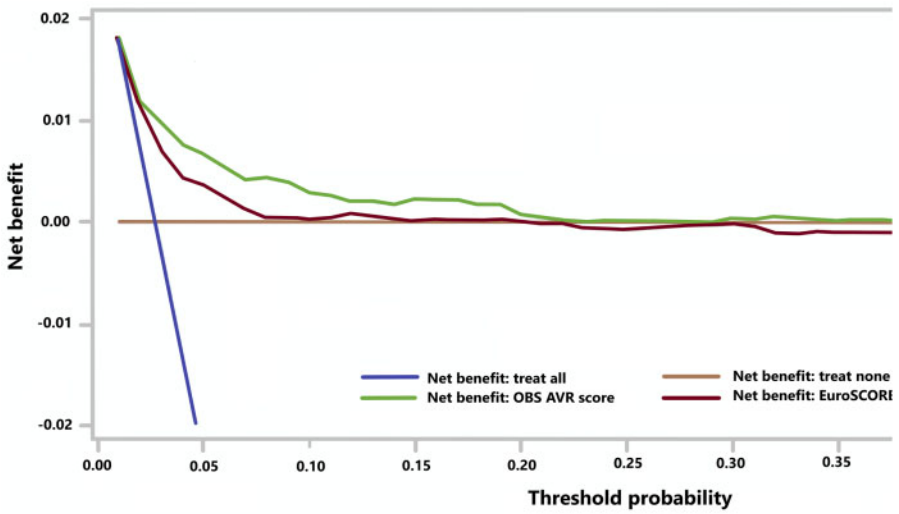
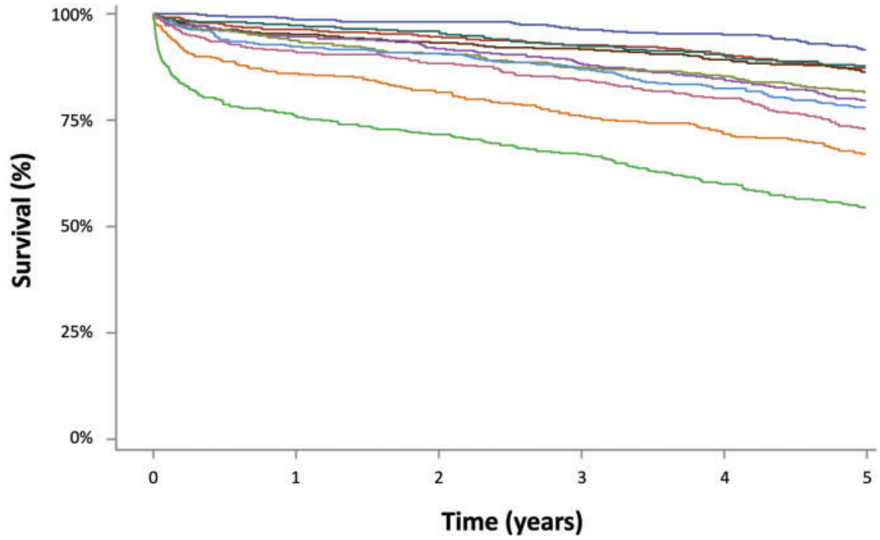


Figure 2: Decision curves of the predicted probabilities of 30-day mortality estimated by the OBS AVR score and the European System for Cardiac Operative Risk Evaluation II. EuroSCORE: European System for Cardiac Operative Risk Evaluation.



OBS AVR score deciles (%)

<0.49	427	420	418	410	405	390
0.49-0.75	461	445	437	428	418	403
0.76-0.93	367	356	351	338	330	321
0.94-1.16	454	431	422	415	404	391
1.17-1.39	427	403	391	376	361	339
1.40-1.77	429	401	388	374	365	347
1.78-2.38	428	394	387	371	352	333
2.39-3.28	428	389	377	360	342	311
3.29.5.34	428	367	348	324	306	286
>5.34	427	324	305	285	255	231

Figure 3: Kaplan–Meier estimates of 5-year survival stratified by deciles of the OBS AVR score.

being, while newer frailty index provides an objective assessment of physical performance and cognition. Still, the use of a simple tool to assess patients' frailty allows physician to obtain a rapid and comprehensive evaluation of patients' clinical status in the decision-making process and compliance of participating centres in clinical research. Second, the low number of mortality events encountered during the study period might have affected the statistical power of our analysis. Third, baseline characteristics of the study population assumed a rather low risk of early mortality and this might have affected the discriminatory power of our model. Finally, an external validation of the proposed model is required to confirm the prognostic value and generalization of the OBS AVR score in patients undergoing either SAVR or TAVR.

CONCLUSION

The OBS AVR score, derived and internally validated using a national multicentre database, showed good calibration and discriminative ability in predicting 30-day mortality after SAVR. The addition of a simple frailty scale into the model contributed to improved performance over the EuroSCORE II. The OBS AVR score should be externally validated in patients undergoing SAVR and TAVR.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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Conflict of interest: Corrado Tamburino is a consultant for Medtronic and speaker honoraria for Meril. Marco Barbanti is a consultant for Edwards Lifesciences and an advisory board member for Medtronic and Biotronik. Fausto Biancari, Stefano Rosato, Giuliano Costa, Paola D'Errigo, Francesco Cerza, Aldo Rosano and Fulvia Seccareccia report no conflict of interest.

Author contributions

Fausto Biancari: Conceptualization, Writing—review and editing. **Stefano Rosato:** Writing—original draft, Data curation, Formal analysis, Methodology, Software. **Giuliano Costa:** Writing—original draft, Conceptualization. **Marco Barbanti:** Writing—original draft, Conceptualization, Supervision, Validation. **Paola D'Errigo:** Writing—original draft, Data curation, Formal analysis, Methodology. **Corrado Tamburino:** Visualization, Validation. **Francesco Cerza:** Visualization, Validation. **Aldo Rosano:** Visualization, Validation. **Fulvia Seccareccia:** Conceptualization, Writing—review and editing, Supervision, Validation, Funding acquisition.

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