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Angaben zur Veröffentlichung / Publication details:

Rehn, Patrick, Ioannis Tsoukakis, Peter Full, Maik von der Forst, Benjamin Niehaus, Dania Fischer, Felix C. F. Schmitt, et al. 2026. "Preoperative endothelial activation and stress index as a predictor of in-hospital mortality and postoperative complications in cardiac surgery with cardiopulmonary bypass: a retrospective cohort study." *European Journal of Anaesthesiology* 43 (6): 517–27. https://doi.org/10.1097/eja.0000000000002313.

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EJA

Eur J Anaesthesiol 2026; **43:**517–527

OPEN

ORIGINAL ARTICLE

Preoperative Endothelial Activation and Stress Index as a predictor of in-hospital mortality and postoperative complications in cardiac surgery with cardiopulmonary bypass

A retrospective cohort study

Patrick Rehn, Ioannis Tsoukakis, Peter Full, Maik von der Forst, Benjamin Niehaus, Dania Fischer, Felix C.F. Schmitt, Matthias Karck, Markus Alexander Weigand, Christoph Lichtenstern, Thomas Luft*, Rawa Arif* and Maximilian Dietrich*

BACKGROUND Patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) are at risk for peri-operative complications, often linked to endothelial dysfunction. The Endothelial Activation and Stress Index (EASIX) has shown potential in predicting outcomes in various patient cohorts.

OBJECTIVES We aimed to assess the prognostic value of EASIX for in-hospital mortality and postoperative outcomes in cardiac surgery patients with CPB.

DESIGN A retrospective cohort study.

SETTING A review of patients undergoing cardiac surgery with CPB at University Hospital Heidelberg from 2015 to 2023.

PATIENTS A total of 9642 patients were considered. After applying the exclusion criteria, 7233 patients with available preoperative levels of creatinine, lactate dehydrogenase, and platelet counts for EASIX calculation were included. The cohort was divided into a training group ($n = 4446$, until December 2019) and validation group ($n = 2787$, from January 2020).

MAIN OUTCOME MEASURES The primary endpoint was in-hospital mortality, with secondary outcomes including ventilator days, ICU stay, and postoperative bleeding. Multivariate logistic regression was performed and ROC curve analyses were used to assess model performance and the added predictive value of EASIX.

RESULTS EASIX predicted in-hospital mortality in the training cohort [odds ratio (OR) per $\log_2$ increase 2.08, $P < 0.001$]. In the validation cohort, adding EASIX to the model significantly increased the AUC from 0.74 to 0.78 ($P = 0.012$). EASIX >2.32 is associated with an OR for mortality of 9.37 in the training, and for 4.47 in the validation cohort. Patients with EASIX >2.32 had significantly more ICU and ventilator days ($P < 0.001$) and higher risk of postoperative bleeding.

CONCLUSION Preoperative EASIX is a validated, cost-effective tool for predicting in-hospital mortality and postoperative bleeding in patients undergoing cardiac surgery with CPB. It may enhance risk stratification and guide peri-operative management in high-risk patients.

Published online 10 November 2025

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Received 18 December 2024 **Accepted** 26 September 2025
0265-0215 Copyright © 2025 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the European Society of Anaesthesiology and Intensive Care.
DOI:10.1097/EJA.0000000000002313
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KEY POINTS

- Question: Can Endothelial Activation and Stress Index (EASIX) prognosticate in-hospital mortality in patients undergoing cardiac surgery with cardiopulmonary bypass?
- Findings: In this retrospective cohort study, higher EASIX scores were statistically significant predictors of in-hospital mortality.
- Meaning: Incorporating EASIX into preoperative evaluations could improve patient risk stratification.

Background

Cardiovascular disease is among the most common causes of death in Europe. According to a 2016 review by the European Society of Cardiology, cardiovascular disease accounts for 45% of all deaths in Europe each year. This corresponds to approximately 4 million deaths annually.[1] A subset of these patients require complex cardiac surgery using cardiopulmonary bypass (CPB), which enables surgery during cardiac arrest.[2]

It is hypothesised that the endothelium is involved in the pathogenesis of peri-operative complications during cardiac surgery.[3–5] The endothelium, a thin layer of cells lining the blood vessels, plays a crucial role in the peri-operative period by influencing vascular function, haemostasis, and inflammation, key factors in postsurgical wound healing.[6,7] The endothelium is central to the pathogenesis of coronary vascular disease.[6,8,9] In this respect, endothelial dysfunction has a significant influence on development of postoperative complications in cardiac surgery such as severe haemorrhage, thrombotic events, vasoplegia and microcirculatory alterations.[3,4,10,11] Recent studies indicate that CPB leads to pathophysiological processes associated with endothelial activation and dysfunction, such as coagulation and inflammation.[10,12] Interestingly, elevated endothelial biomarkers suggesting the degradation of the glycocalyx, an integral component of the endothelium, have been found in the serum of patients undergoing cardiac surgery using CPB.[13] If endothelial dysfunction is already present preoperatively, the additional stress of CPB may promote decompensation, creating a diagnostic challenge during preoperative evaluation, as no routine marker for endothelial dysfunction currently exists.[11,14] Markers for endothelial dysfunction such as Syndecan-1 are primarily used in the context of research and are not part of any routine laboratory screen.

The "Endothelial Activation and Stress Index" (EASIX) has the potential to fill the diagnostic gap in preoperative risk stratification. It is calculated as the ratio of the product of creatinine and lactate dehydrogenase (LDH) to the platelet count: creatinine (mg dl^{-1}) × LDH (U l^{-1})/platelet count (10^9 l^{-1}).[15] Importantly, this score can be measured routinely without additional cost, as these measurements are typically included in the standard preoperative laboratory screen. EASIX score was originally developed to assess endothelial damage before stem cell transplantation and to predict mortality after endothelial complications.[15] More recent studies have examined EASIX as both a marker of endothelial dysfunction and a prognostic tool. It has been shown to reliably predict mortality in patients following allogeneic stem cell transplantation and graft-versus-host disease, COVID-19, sepsis and in patients with severe liver disease.[15–19] Furthermore, EASIX has demonstrated the ability to predict the risk of sepsis even before the initiation of conditioning chemotherapy in the context of stem cell transplantation.[20,21] In previous studies EASIX was shown to correlate with serum levels of NT-proBNP,[22] sCD141 (soluble thrombomodulin),[23] angiopoietin-2,[17,24] interleukin-18,[16,17,23,24] and low IGF1,[16] all of which are markers for endothelial damage. This highlights the ability of EASIX to provide information about the status of the endothelium. Common risk stratification tools for patients undergoing cardiac surgery include the (logistic) EuroSCORE. Endothelial dysfunction is not explicitly captured by this scoring system. It incorporates personal, clinical, and procedural measures to estimate in-hospital mortality. It is widely used and has been updated several times.[25–28] Compared to EASIX, the EuroSCORE requires more patient data and is more complex to calculate.[27,28]

The increased vulnerability of the endothelium due to high prevalence of vascular diseases, combined with the stress of extracorporeal circulation, may render cardiac surgery patients more susceptible to endothelial damage. We therefore hypothesise that EASIX may serve as a predictive marker for patient outcomes following cardiac surgery using CPB, and could aid in identifying individuals at risk for endothelial complications.

Methods

Study design and ethics

This retrospective, monocentric cohort study was conducted at University Hospital Heidelberg, Germany. Methodology and results are reported according to STROBE-guidelines for cohort studies.[31] Ethical approval for this study (reference number S-623/2023) was provided by the local Ethical Committee of the Medical Faculty of Heidelberg University, Alte Glockengießerei 11/1, 69115 Heidelberg, Germany on 15 November 2023. Requirement for informed consent was waived by the Ethical Committee of the Medical Faculty of Heidelberg University due to the retrospective design of the study. The Declaration of Helsinki guideline was followed.

Study cohort and data collection

Patients aged 18 years and older who underwent cardiac surgery using CPB at University Hospital Heidelberg,

Department of Cardiac Surgery from April 2015 to August 2023 were included regardless of the clinical indication, with the exception of heart transplants and salvage procedures. The necessary laboratory analyses for calculation of EASIX (platelet count, creatinine and LDH) were required within 7 days before surgery, but if results were not available within this time frame the most recent set before surgery was used in each case. Patients with EASIX available within 1 to 7 days before to surgery were compared to patients with no EASIX available within this timeframe to explore potential bias. Recorded baseline and outcome data included age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) class score, logistic EuroSCORE, indication and urgency of surgery, preoperative left ventricular ejection fraction (LVEF), CPB time, postoperative complications, ventilator days and in-hospital mortality.

The cohort was divided into a training cohort (surgery from April 2015 until December 2019) and a validation cohort (surgery from January 2020 to August 2023).

In accordance with previously published literature, high-risk thresholds were applied as follows: an EASIX value exceeding 2.32 was considered high-risk, and patients with a Logistic EuroSCORE >14 were classified as high-risk.[20,21,29,30] We used these cut-offs to make our analysis more clinically applicable. All patient data were gathered retrospectively by an automated query of electronic medical reports stored in the internal database of University Hospital Heidelberg. The request included epidemiological data, laboratory values, risk factors and survival data as well as type, details and date of surgery. The date of survival assessment was November 2023.

Laboratory analyses and cardiac assessment

EASIX was calculated as published: LDH (U l^{-1}) × creatinine (mg dl^{-1})/platelet count (10^9 l^{-1}).[15] LDH, creatinine and platelets were measured as part of our routine laboratory screen. Left ventricular function was assessed using LVEF. We defined good left ventricular function as LVEF ≥50%, moderately impaired LV-function as LVEF 31–49%, highly impaired LV-function as LVEF 21–30% and very highly impaired LV-function as LVEF ≤20%. We recorded the total time of CPB during surgery.

Endpoints

The primary endpoint was in-hospital mortality. For secondary endpoints, we evaluated ventilator days, length of ICU stay and postoperative bleeding. Bleeding was defined as being related to the surgical procedure and causing significant haemodynamic instability or necessitating a transfusion.

Statistical methods

Descriptive statistics were performed with all relevant data. Median [IQR], and minimum and maximum values were calculated. Comparison of metric values between groups was conducted using the Mann–Whitney *U* test, while categorical variables were analysed using the χ^2 test. For comparison of metric variables across more than two groups, the Kruskal–Wallis test was applied.

Multiple logistic regression analysis was performed for both primary and secondary outcomes in the training cohort. Two logistic regression models were calculated and compared, to evaluate the predictive power of EASIX for in-hospital mortality. Model 1 included personal characteristics (age, BMI, sex) with and without EASIX. Model 2 included Model 1 together with clinical assessments (left ventricular function) and procedure-related characteristics (type of surgery), again with and without EASIX. The models were developed using the training cohort and validated in the independent cohort.

Odds ratios (ORs) for age were scaled to represent a 5-year increase to improve clinical interpretability, rather than the effect per single year. Continuous variables such as the EASIX score were categorised using predefined clinical cut-offs (<0.92, 0.92–2.32, >2.32), as previously validated in other patient groups. Multivariate logistic regression analyses were performed with the categorical EASIX variable, using the lowest category (<0.92) as the reference group.

Receiver operating characteristic (ROC) curves and the area under the curve (AUC) were used to assess model performance. The models were validated by applying them to the validation cohort and calculating predicted probabilities for mortality. To compare the predictive power of the models and the statistical significance in AUC-differences, we conducted the DeLong test for paired ROC curves. Metric variables are reported as median [IQR], and categorical variables are presented as absolute and relative frequencies.

In order to assess the predictive performance of EASIX in comparison to the established logistic EuroSCORE, logistic regression analyses were conducted on the full study cohort without using a separate validation set. ROC curves, DeLong tests for AUC comparison and net reclassification improvement (NRI) were used to assess model performance. Three models were evaluated: EASIX, EASIX plus logistic EuroSCORE and logistic EuroSCORE.

A Cox regression analysis was conducted to explore the association between EASIX and mortality at 400 days. Given the significant proportion of censored data and loss to follow-up, the present analysis was regarded as strictly exploratory and descriptive in nature. Statistical analysis was conducted using SPSS version 29.0 and R Studio 4.4.2. Validation was performed in RStudio, using the pROC package for ROC curve analysis and DeLong testing.

Results:
Patient characteristics

The overall cohort consisted of 9642 patients. Of these 127 heart transplants and 62 salvage procedures were excluded, and for 2220 the necessary laboratory analyses for calculation of EASIX (platelet count, creatinine and LDH) were unavailable within 7 days prior to surgery. The remaining 7233 made up the training cohort ($n = 4446$) and the validation cohort ($n = 2787$) (Fig. 1). Baseline characteristics of the training and validation cohorts are presented in Table 1. Comparison of patients with and without EASIX within the timeframe of 1 to 7 days before surgery revealed a bias. The differences are presented in Table 1, Supplemental Digital Content, http://links.lww.com/EJA/B218. Patients without EASIX presurgery were at higher risk compared to patients with EASIX values as they had more emergency surgery (42.2% vs. 7.3%) and more salvage surgery interventions (4.8% vs. 0.8%). Of note, there was a very high in-hospital mortality rate in the patients with salvage surgery (42.5%) and a higher median EASIX (2.43, range 1.21 to 6.69) compared with patients with elective, urgent and emergency surgery (3.2% mortality, median EASIX 1.08, range 0.78 to 1.54, $P < 0.001$). This was why we decided to exclude patients with salvage surgery from our primary analysis.

The validation cohort was older, had higher ASA scores and more often underwent emergency surgery. EASIX values differed significantly between the cohorts (Training cohort: median [IQR] 1.09 [0.80 to 1.57], validation cohort 1.04 [0.75 to 1.50], $P < 0.001$).

In-hospital-mortality was not significantly different between the training and validation cohorts (training cohort 3.2%, validation cohort 2.9%, $P = 0.525$). Median CPB-time was 107 [84 to 140] min in the training and 122 [95 to 166] min in the validation cohort ($P < 0.001$). Postoperative bleeding occurred more frequently in the validation cohort than in the training cohort (6.8% vs. 4.8%, $P < 0.001$).

Primary outcome: in-hospital mortality

The multivariate logistic regression analysis of the training cohort included age, sex, BMI, left ventricular function, surgery type and preoperative endocarditis (Model 2) and EASIX. EASIX independently predicted in-hospital mortality (OR per $\log_2$ step 2.08 (CI 1.78 to 2.43), $P < 0.001$). Odds ratios of the remaining variables of the logistic regression model are presented in Table 2.

The added predictive value of EASIX was validated in the independent cohort using ROC curve analysis. Adding EASIX to Model 2 increased the AUC-ROC from 0.74 to 0.78, representing a statistically significant improvement ($P = 0.002$). A simplified model (Model 1), which included only personal detail (age, sex, BMI) and EASIX, demonstrated strong discriminative ability with an AUC-ROC of 0.72, which was not statistically different from that of Model 2 without EASIX ($P = 0.47$). However, removing EASIX from Model 1 resulted in a significant decrease in discriminative ability, with an AUC-ROC of 0.60 ($P = 0.02$). ROC curves and AUC-ROC values for all models are presented in Fig. 2.

In the logistic regression model for in-hospital mortality, both EASIX $\log_2$ (OR 1.69 (95% CI, 1.49 to 1.90), $P < 0.001$) and the logistic EuroSCORE (OR 1.04 (95% CI 1.03 to 1.04), $P < 0.001$) were significantly associated with increased odds of death in the whole cohort (Table 3).

Fig. 1 Enrollment and allocation of cohorts.

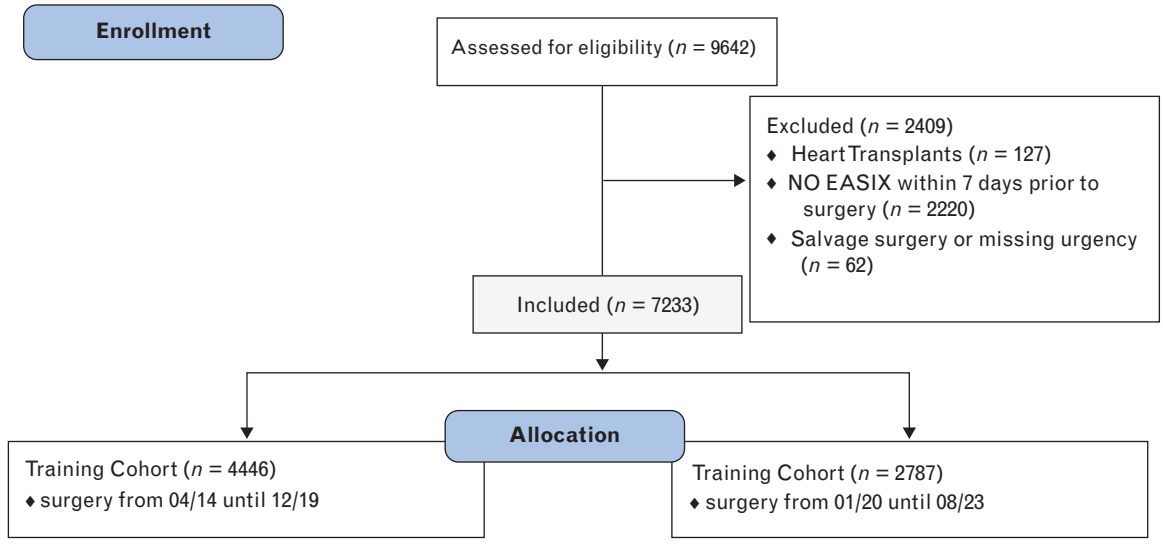


Table 1 Baseline characteristics

Characteristic	Overall $n = 7233$	Training cohort $n = 4446$ 01/2015 to 12/2019	Validation cohort $n = 2787$ 01/2020 to 08/2023	*P*-value
Age, years	69 [61 to 75]	70 [61 to 76]	67 [60 to 74]	<0.001
Sex, male	5319 (73.5)	3248 (73.1)	2078 (74.6)	0.251
BMI, kg m^{-2}	27 [24 to 30]	27 [24 to 30]	27 [24 to 30]	0.561
ASA 4 and 5	1443 (20.0)	754 (17.0)	689 (24.7)	<0.001
Urgency of surgery				<0.001
Elective	4772 (79.2)	3206 (83.0)	1563 (56.1)	
Urgent	1443 (20.0)	986 (22.2)	941 (33.8)	
Emergency	534 (7.4)	251 (5.6)	283 (10.2)	
Indication of surgery				<0.001
CABG	3454 (47.8)	2139 (48.1)	1315 (47.2)	
Valve	2134 (29.5)	1387 (31.2)	747 (26.8)	
Thoracic aorta	644 (8.9)	325 (7.3)	319 (11.4)	
Combination	1001 (13.8)	595 (13.4)	406 (14.6)	
CPB time, min	113 [88 to 149]	107 [84 to 140)	122 [95 to 166]	<0.001
LVEF ≤ 30%	585 (8.1)	374 (8.4)	211 (7.6)	0.208
EASIX	1.08 [0.78 to1.55]	1.09 [0.80 to1.57]	1.04 [0.75 to 1.50]	<0.001
ICU stay, days	1 [1 to 3]	1 [1 to 2]	1 [1 to 3]	<0.001
Ventilator time, h	16 [11 to 19]	16 [12 to 19]	15 [10 to 18]	<0.001
Postoperative bleeding	403 (5.6)	213 (4.8)	190 (6.8)	<0.001
In-hospital mortality	3.1%	3.2%	2.9%	0.525

Data are given as median [IQR] or *n* (%). Valve, included surgery on any valve (aortic, mitral, pulmonal, tricuspid). Combination: included any combination of above surgery categories (CABG, valve, thoracic aorta). BMI, body mass index; CABG, coronary artery bypass graft; IQR, interquartile range; LVEF, left ventricular ejection fraction.

The area under the ROC curve (AUC) improved when EASIX and logistic EuroSCORE were combined. The DeLong test confirmed a statistically significant improvement in discriminatory power for the combined model versus the EuroSCORE alone ($P = 0.03$). ROC curves and AUC-ROC values for all models are presented in Fig. 3. Net reclassification improvement (NRI) analysis showed a positive NRI of 0.102, suggesting improved risk stratification.

Predefined EASIX cutoffs

For the following analyses we used the predefined cutoffs. EASIX < 0.93 was the third IQR for the healthy cohort included in the prospective Endothelial Cell Dysfunction and Outcome study (EndoCDO-H, NCT05502887). EASIX > 2.32 is a validated predictor of risk of sepsis measured before starting conditioning therapy for allogeneic stem cell transplantation.[20,21] We conducted a multivariate logistic regression analysis including EASIX, age, sex, BMI, left ventricular function, surgery type and presurgery endocarditis. An EASIX > 2.32 was independently associated with in-hospital mortality in both the training cohort (OR 9.37 (95%, CI 5.31 to 16.54), $P < 0.001$) and the validation cohort (OR 4.48 (95%, CI, 2.22 to 9.02), $P < 0.001$). Odds ratios of the remaining variables of the logistic regression models are presented in Table 4.

Secondary outcomes

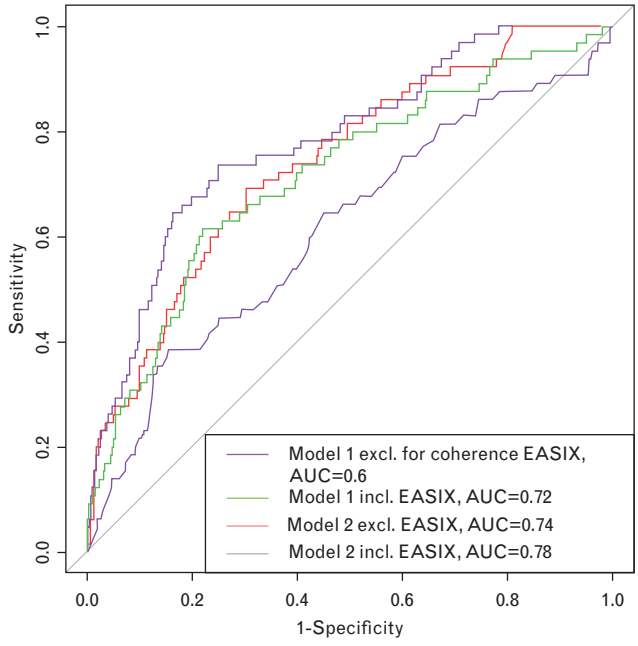
To better understand the relationship between EASIX and mortality, we studied the association of this marker with postoperative bleeding, duration of mechanical ventilation, and duration of stay on the ICU.

Table 2 Multivariate logistic regression analysis of in-hospital mortality (continuous EASIX) for the training cohort

Variable	OR	95% CI		*P*-value
		Lower	Upper	
$EASIXlog_2$	2.078	1.779	2.429	<0.001
Age (per 5 years)	1.143	1.041	1.258	0.006
Sex, male	2.356	1.613	3.447	<0.001
BMI >30 kg m^{-2}	0.763	0.528	1.200	0.276
LVEF ≥ 50% (ref)	1.0			<0.001
LVEF 31 to 50%	2.224	1.491	3.316	<0.001
LVEF 21 to 30%	3.727	2.211	6.282	<0.001
LVEF ≤ 20%	3.926	1.330	11.589	0.013
CABG (ref)	1.0			<0.001
Valves (1)	1.363	0.865	2.148	0.182
Combination (2)	1.942	1.165	3.235	0.011
Thoracic aorta (3)	4.245	2.317	7.776	<0.001
Preoperative endocarditis	1.930	0.913	4.082	0.085

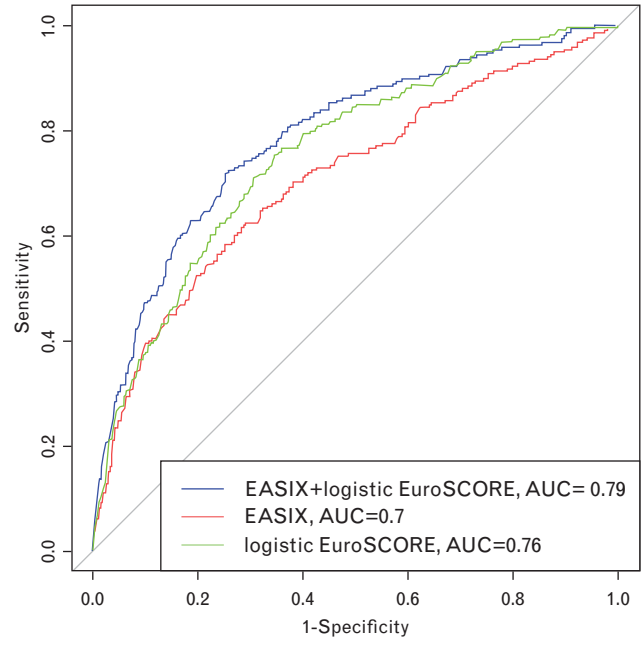
Valve, included surgery on any valve (aortic, mitral, pulmonal, tricuspid). Combination, included any combination of above surgery categories (CABG, valve, thoracic aorta). BMI, body mass index; CABG, coronary artery bypass graft; CI, confidence interval; LVEF, left ventricular ejection fraction; OR, odds ratio. $EASIXlog_2$ represents the Endothelial Activation and Stress Index after log base 2 transformation; the odds ratio per 1-unit increase reflects the change in odds associated with a doubling of the raw EASIX value. $n = 4426$ no. of events: 139.

Fig. 2 ROC curves for hospital mortality prediction models (validation cohort).



The purple curve represents Model 1 (age, BMI, sex), the green curve represents Model 1 incl. EASIX, the red curve represents Model 2 (age, BMI, sex, left ventricular function, and type of surgery) and the blue curve represents Model 2 incl. for coherence EASIX. The addition of EASIX significantly improves performance of Models 1 and 2 (*P*-value 0.001 and 0.02, respectively).

Fig. 3 Receiver operating characteristic (ROC) comparing the discriminative ability of three logistic regression models for in-hospital mortality: logistic EuroSCORE alone (green line), EASIX alone (red line) and the combined model of EASIX and logistic EuroSCORE (blue line).



The combined model showed improved discriminative performance compared to logistic EuroSCORE alone ($P = 0.03$, DeLong test). Analyses were performed in the full cohort and are descriptive in nature.

Multivariate logistic regression analysis with the endpoint postoperative bleeding revealed a significant association with EASIX > 2.32 in both, training and validation cohort (training: OR 1.75 (95% CI 1.12 to 2.75), $P = 0.014$; validation: OR 1.83 (95% CI 1.14 to 2.95), $P = 0.012$) (Table 2, Supplemental Digital Content, http://links.lww.com/EJA/B218).

The significant increases in days on ICU and hours of mechanical ventilation with high EASIX are shown in Fig. 4. To test if the association with high EASIX holds true in a multivariable setting, we defined the median ventilation time (>16 h) and time of ICU stay (>1 day) of the whole cohort as endpoints in our logistic regression. An EASIX score > 2.32 was significantly associated with ventilation time >16 h and >1 ICU days in both the training and validation cohort (Tables 3 and 4, Supplemental Digital Content, http://links.lww.com/EJA/B218).

Table 3 **Logistic regression analysis of in-hospital mortality for the whole cohort**

		95% CI		
Variable	**OR**	**Lower**	**Upper**	***P*-value**
$EASIXlog_2$	1.69	1.49	1.90	<0.001
Logistic EuroSCORE	1.04	1.03	1.04	<0.001

CI, confidence interval; OR, odds ratio. $EASIXlog_2$ represents the Endothelial Activation and Stress Index after log base 2 transformation; the odds ratio per 1-unit increase reflects the change in odds associated with a doubling of the raw EASIX value. $n = 7196$ no. of events: 218.

Supportive descriptive analyses with the entire cohort

The combined patient (training and validation) cohort ($n = 7233$) was used to perform logistic regression models with hospital mortality as endpoint. Both EASIX (log_2-transformed) and logistic EuroSCORE were found to be independent predictors of hospital mortality ($P < 0.001$ for both). The combined model, including EASIX and the logistic EuroSCORE, achieved a significantly higher AUC than the model with the logistic EuroSCORE alone ($P = 0.03$, DeLong test). NRI also favoured the inclusion of EASIX (NRI = 0.10), with most of the benefit from upward reclassification of true cases ($NRI^+ = 0.11$). Among men, the addition of EASIX again led to a statistically significant improvement in model performance (DeLong $P = 0.037$; NRI = 0.12). Among women, a similar trend was observed, although the improvement did not reach conventional statistical significance (DeLong $P = 0.06$; NRI = 0.12).

In a Cox regression model including both $EASIXlog_2$ and the logistic EuroSCORE, EASIX significantly improved

Table 4 Multivariate logistic regression analysis of in-hospital mortality (EASIX cutoffs) for the training and validation cohort

Variable	Training cohort			*P*-Value	Validation cohort			*P*-value
	OR	95% CI			OR	95% CI		
		Lower	Upper			Lower	Upper	
EASIX <0.92 (ref)	1.000			<0.001	1.000			
EASIX 0.92 to 2.32	2.106	1.234	3.595	0.006	1.675	0.914	3.067	0.095
EASIX >2.32	9.373	5.313	16.538	<0.001	4.478	2.223	9.021	<0.001
Age (per 5 years)	1.120	1.020	1.234	0.018	1.154	1.025	1.295	0.017
Sex, male	2.437	1.665	3.565	<0.001	2.053	1.255	3.359	0.004
BMI >30 kg m^{-2}	0.798	0.530	1.203	0.282	1.028	0.615	1.718	0.917
LVEF ≥ 50% (ref)	1.0			<0.001	1.0			<0.001
LVEF 31 to 50%	2.151	1.440	3.214	<0.001	1.389	0.808	2.390	0.235
LVEF 21 to 30%	3.635	2.151	6.143	<0.001	1.906	0.845	4.298	0.12
LVEF ≤ 20%	4.699	1.666	13.248	0.003	8.213	3.066	21.996	<0.001
CABG (ref)				<0.001	1.0			<0.001
Valves (1)	1.365	0.866	2.152	0.180	1.194	0.601	2.376	0.613
Combination (2)	2.076	1.249	3.451	0.005	3.055	1.612	5.788	<0.001
Thoracic aorta (3)	4.219	2.300	7.739	<0.001	4.082	1.999	8.334	<0.001
Preoperative Endocarditis	1.839	0.873	3.874	0.109	2.959	1.407	6.221	0.004

Valve, included surgery on any valve (aortic, mitral, pulmonal, tricuspid). Combination, included any combination of above surgery categories (CABG, valve, thoracic aorta). BMI, body mass index; CABG, coronary artery bypass graft; CI, confidence interval; LVEF, left ventricular ejection fraction; OR: odds ratio. EASIX was categorised into three predefined groups (<0.92, 0.92 to 2.32 and >2.32) based on previously validated clinical thresholds; the reference category is EASIX < 0.92. Training: $n = 4426$ no. of events: 139 EASIX <0.92: $n = 1576$, EASIX 0.92 to 2.32: $n = 2360$, EASIX >2.32: $n = 490$. Validation: $n = 2770$ no. of events: 78 EASIX <0.92: $n = 1119$, EASIX 0.92 to 2.32: $n = 1362$, EASIX >2.32: $n = 289$.

model fit compared to a model with the logistic EuroSCORE alone (likelihood ratio test, $\chi^2 = 109.7$, $P < 0.001$). Kaplan–Meier analysis using predefined clinical cutoffs for EASIX (low < 2.32; high ≥ 2.32) and logistic EuroSCORE (low < 14; high ≥ 14) showed a synergistic risk stratification effect. Patients with both high EASIX and high EuroSCORE had the worst survival, while those with low values on both scales had the best outcomes. However, due to the large number of censored observations and loss to follow-up, the 400-day survival analysis is considered strictly descriptive and exploratory.

Full results of 400-day survival analysis are reported in the Supplements (Table 6, Supplemental Digital Content, http://links.lww.com/EJA/B218 and Figure 2, Supplemental Digital Content, http://links.lww.com/EJA/B218).

The combined patient (training and validation) cohort was further used to perform multivariate logistic regression for each subgroup of surgical intervention with endpoint in-hospital mortality. An EASIX score >2.32 was statistically significant in predicting in-hospital mortality with odd ratios >5 for each type of surgery (Figure 1, Supplemental Digital Content, http://links.lww.com/EJA/B218).

Finally, the impact of the single EASIX variables (LDH, creatinine, platelets) on in-hospital mortality was tested in the combined cohort. All three variables were significantly associated with the endpoint with the expected OR (>1 for LDH and creatinine, <1 for platelets) (Table 5, Supplemental Digital Content, http://links.lww.com/EJA/B218).

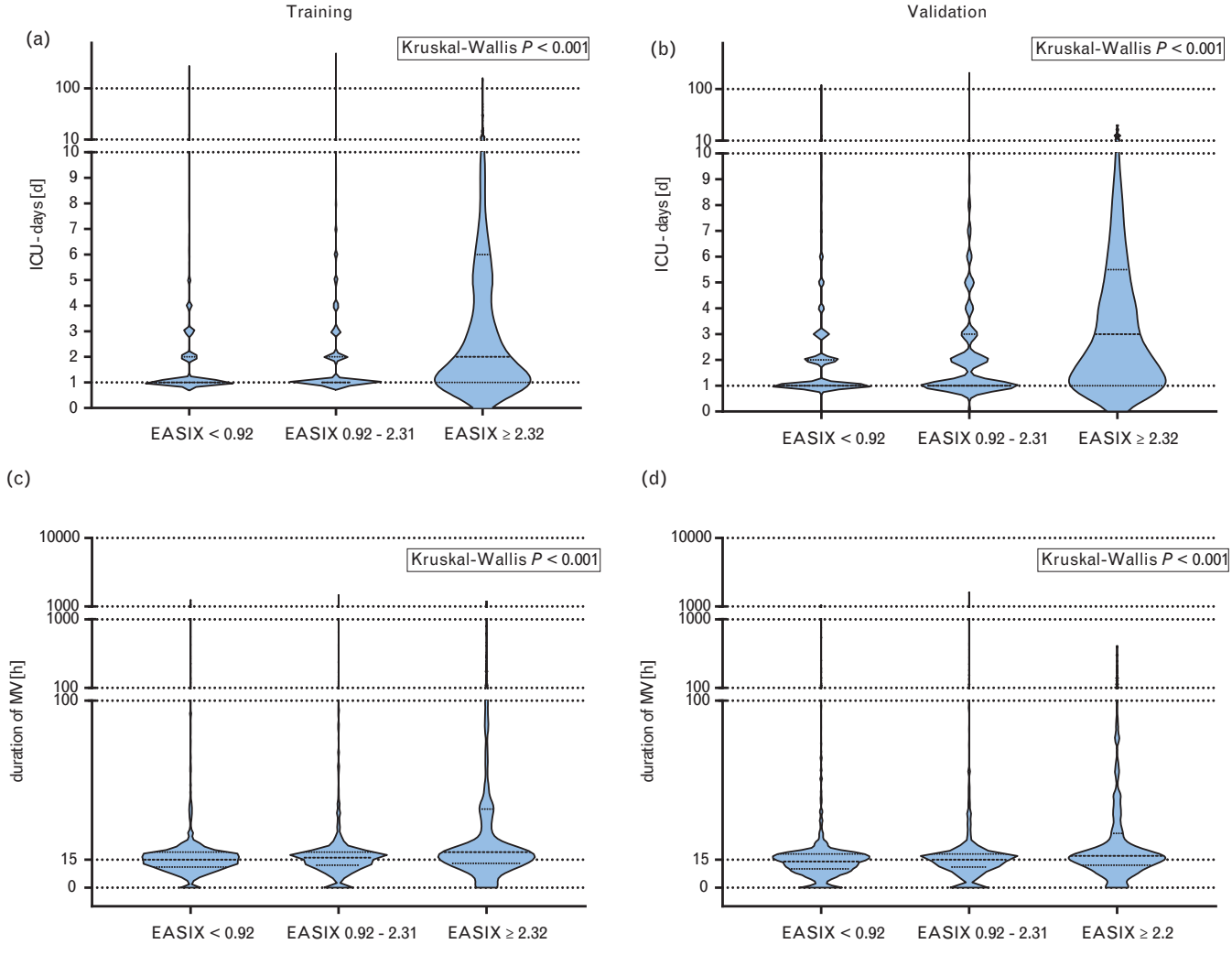
Discussion

In this large cohort study of patients undergoing cardiac surgery with CPB, we demonstrate that the EASIX score can potentially serve as an independent predictor of in-hospital mortality. The objective of this study was to assess the relative and cumulative predictive value of EASIX, a marker with a defined pathophysiological connotation, but not to outperform existing scores predicting hospital mortality

We used a temporal split-sample design, with patients undergoing surgery before January 2020 assigned to the training cohort and those from January 2020 onward to the validation cohort. This approach was chosen to emulate prospective external validation while avoiding potential information leakage between cohorts. The observed differences in baseline characteristics probably reflect temporal changes in referral patterns, surgical case mix, and peri-operative management. These differences underline the importance of validating prognostic tools across distinct patient groups and may strengthen the generalisability of our findings.

We report EASIX both as a continuous $\log_2$-transformed variable and as a categorical variable based on predefined cut-offs. The continuous EASIX $\log_2$ captures the full variability of the score and has superior statistical power for model discrimination and reclassification analyses (ROC, AUC, NRI). This approach avoids potential loss of information that may occur when applying thresholds. On the other hand, categorical EASIX presentation facilitates bedside clinical interpretation by identifying risk groups, using cut-offs validated in other clinical contexts such as allogeneic stem cell transplantation.[20,21] However,

Fig. 4 ICU days and duration of mechanical ventilation (MV) for the predefined EASIX cutoffs for the training cohort (a, c) and validation cohort (b, d).



these thresholds have not yet been validated in cardiac surgery and should be interpreted cautiously. Future prospective studies are needed to establish specific cut-offs in this setting. Therefore, presenting both formats enables a comprehensive statistical assessment while offering an initial framework for exploring potential risk stratification in future studies.

Endothelial dysfunction plays a key role in patients with cardiovascular diseases. Microvascular alterations in coronary arteries often lead to chronic ischaemia of the heart, which, in turn, leads to the formation of insufficient vascular collaterals.[32] The endothelium is essential for rapid angiogenesis.[33] In this context, endothelial cells use LDH for efficient angiogenesis.[34] Therefore, higher LDH levels may indicate increased endothelial activity and dysfunction. Additionally, kidney function is related to endothelial dysfunction, leading to elevated creatinine levels. The glomerular endothelium, in particular, is highly susceptible to glycocalyx damage.[8] Moreover, creatinine is a well established and independent predictor of cardiovascular mortality.[35–37] Healthy endothelial cells exhibit anticoagulant properties, while damaged endothelial cells with degraded glycocalyx release prothrombotic and platelet-aggregating agents, resulting in increased platelet consumption.[4,38] Co-ordinated changes in the three markers (rising LDH and creatinine, reduced platelets) are typical for severe endothelial complications such as transplant-associated thrombotic microangiopathy (TA-TMA) and the closely related atypical haemolytic uraemic syndromes (aHUS).[39,40]

These pathophysiological mechanisms are encapsulated by the EASIX score, offering a plausible explanation for

its potential strong prognostic capacity in patients undergoing cardiac surgery. Several studies have shown that endothelial integrity is compromised during cardiac surgery using CPB.[3,41,42] In fact, CPB appears to contribute to the shedding of the glycocalyx, as demonstrated by rising Syndecan-1 levels after CPB in the study by Dekker *et al.* In parallel, the authors observed microvascular alterations, which could lead to organ damage.[41] In patients already at risk of postoperative complications it seems reasonable to assess preexisting endothelial dysfunction. EASIX may help in preoperative risk evaluation, as our study has shown its strong prognostic value for in-hospital mortality, ICU stay duration, ventilator days, and postoperative bleeding. To our knowledge, no comparable surrogate exists for bedside evaluation of potential endothelial dysfunction. The endothelium can be considered a distinct organ, consisting of approximately 10^{13} cells and spanning an area of roughly 4000 to 7000 m^2, with functional heterogeneity as a hallmark of endothelial cells in different tissues, organs and clinical contexts.[43–46] EASIX reflects a systemic response of the organism to heterogeneous endothelial challenges, and thus adds valuable information to the risk stratification of patients undergoing cardiac surgery with CPB. EASIX may therefore become a pragmatic surrogate, particularly in the absence of validated, clinically available endothelial biomarkers. This potential utility supports the need for further prospective investigation of such indices in the peri-operative setting.

Since EASIX was first described, numerous subsequent studies have been conducted.[15–19,21,23,24,47–54] While each of the markers included in EASIX can be influenced by a range of nonendothelial pathophysiological processes their combined alteration has been associated with endothelial injury in multiple clinical settings. For example, EASIX has been successfully applied to predict mortality in sepsis patients, further underscoring its value in detecting endothelial dysfunction.[18] Similar to its association with CBP, Syndecan-1 levels have also been shown to predict sepsis mortality and kidney failure in children undergoing cardiac surgery with CPB.[55,56], Syndecan-1, a biomarker indicating glycocalyx shedding, is elevated after surgery using CPB [5,41,57,58] and correspondingly, some cardiac surgery patients develop severe vasoplegia.[3] Thus, EASIX has potential to become a cost-effective and user-friendly tool for preoperative assessment of endothelial dysfunction. However, the ability of preoperative EASIX to predict renal complications has yet to be investigated.

Beyond its prognostic utility, the EASIX score may enable clinically meaningful risk stratification for targeted therapeutic interventions aimed at preserving or restoring endothelial integrity. Since pathophysiological mechanisms of endothelial damage are encapsulated in the EASIX score, higher scores may indicate a preexisting vulnerability of the vascular barrier. This preexisting damage may potentially be modifiable through pharmacological intervention. For instance, statins have demonstrated protective effects on the endothelium by enhancing nitric oxide bio-availability and reducing oxidative stress and inflammation.[59,60] Also, SGLT-2 inhibitors have shown protective properties by reducing oxidative stress.[61,62] Similarly, Angiotensin-Converting Enzyme (ACE) inhibitors and Angiotensin-II-Receptor Blockers improve endothelial function by increasing bradykinin levels.[63–66] Sulodexide, a glycosaminoglycan with glycocalyx-stabilising properties, has demonstrated anti-inflammatory and endothelial-protective effects, suggesting potential benefit in patients with vascular dysfunction.[67–70]

To investigate whether patients with elevated EASIX scores benefit from endothelial-targeted therapies, future prospective trials must stratify patients based on their endothelial risk profile. High-risk individuals may significantly benefit from endothelial-stabilising pharmacotherapy, while patients with lower risk profiles are unlikely to benefit and could obscure the treatment effect in unstratified analyses. EASIX might become a simple yet potentially effective option for risk stratification. Pabst *et al.* found that statin prophylaxis improved survival after stem cell transplantation predominantly in patients with intermediate pretransplant EASIX values. [71] Accordingly, stratified trial designs are essential to detect therapeutic efficacy in biologically plausible subgroups and avoid false-negative results.

The primary strength of this approach is its simplicity. All necessary analyses are inexpensive to obtain and are part of standard laboratory screens. An online tool designed by Luft *et al.* already exists to calculate the risk of mortality at graft-versus-host-disease (GVHD) onset based on EASIX in patients undergoing allogeneic stem cell transplantation. After further validation, a similar tool could be developed for patients undergoing cardiac surgery with CPB, facilitating the broader implementation of EASIX in this setting. This may add to standard risk calculators for cardiac surgery. Our analysis demonstrated that adding EASIX to the logistic EuroSCORE significantly enhances its prognostic accuracy. Interestingly, this is the case even though the logistic EuroSCORE already incorporates creatinine and surrogates of endothelial damage such as extracardiac arteriopathy. This clearly shows the additional value of EASIX in the context of risk prediction in this patient cohort. One of the most used risk calculation scores for patients undergoing cardiac surgery is the EuroSCORE II – a refinement of the logistic EuroSCORE. This score together with the logistic EuroSCORE are far more complicated to calculate and show similar prognostic power.[27,28] However, despite odds ratios of >5 for the surgical interventions reported here, mortality rates of the high-risk cohort did not exceed 20% (EASIX > 2.32) or 30% (EASIX > 2.32 and logistic EuroSCORE > 14) within 6 months, so that

further improvement to characterise highest risk patients may require better combinations of risk scores.

Our study has several limitations. First, we did not measure endothelial serum markers to further substantiate the endothelial nature of EASIX as reported before.[16,17,22–24] Next, monocentric design affects its generalisability. Additionally, the retrospective design may account for potential confounders. Furthermore, the predictive power of individual models for complex biological systems is inherently limited. It is important to note that EASIX should not be the only source of information for stratifying patients into risk groups and modifying therapy accordingly. However, EASIX can add valuable information to better stratify patients at risk for adverse outcomes after surgery. Preselection based on the availability of LDH, creatinine, and platelet counts in the same laboratory screen could introduced a selection bias, although the highest risk patients excluded in our study also had highest EASIX scores. However, the large sample size in both cohorts should mitigate this limitation.

Conclusion

Our study demonstrates the potential of the EASIX score as a validated prognostic tool for patients undergoing cardiac surgery with CPB, specifically for predicting in-hospital mortality and postoperative bleeding. By integrating common laboratory analyses, the EASIX score offers a simple, cost-effective method to identify high-risk patients preoperatively, improve risk stratification and guide peri-operative management. However, further prospective, multicentre studies are necessary to validate these findings and identify targeted interventions to optimise peri-operative clinical management for high-risk patients, based on stratification of endothelial dysfunction.

Acknowledgements relating to this article

Assistance with the study: as authors using Generative AI and AI-assisted technologies we recognise the ethical responsibilities associated with these tools. In accordance with best practices and principles of scientific integrity, we declare that during the preparation of this work, the authors used the ChatGPT 4.2 (OpenAI, San Francisco, USA) program to revise grammar and enhance language coherence. Following the use of these tools, the authors meticulously reviewed and edited the content to ensure its compliance with the requirements. Consequently, the authors assume full responsibility for the integrity and accuracy of the publication.

Funding: this work was supported by institutional resources. There was no external funding.

Conflict of interests: none.

Presentation: none.

This manuscript was handled by Dan Longrois.

References

1 Townsend N, Wilson L, Bhatnagar P, *et al.* Cardiovascular disease in Europe: epidemiological update 2016. *Eur Heart J* 2016; **37**:3232–3245.
2 Kunst G, Milojevic M, Boer C, *et al.* 2019 EACTS/EACTA/EBCP guidelines on cardiopulmonary bypass in adult cardiac surgery. *Br J Anaesth* 2019; **123**:713–757.
3 Abou-Arab O, Kamel S, Beyls C, *et al.* Vasoplegia after cardiac surgery is associated with endothelial glycocalyx alterations. *J Cardiothorac Vasc Anesth* 2020; **34**:900–905.
4 Achneck HE, Sileshi B, Parikh A, *et al.* Pathophysiology of bleeding and clotting in the cardiac surgery patient: from vascular endothelium to circulatory assist device surface. *Circulation* 2010; **122**:2068–2077.
5 Pesonen E, Passov A, Andersson S, *et al.* Glycocalyx degradation and inflammation in cardiac surgery. *J Cardiothorac Vasc Anesth* 2019; **33**: 341–345.
6 Rajendran P, Rengarajan T, Thangavel J, *et al.* The vascular endothelium and human diseases. *Int J Biol Sci* 2013; **9**:1057–1069.
7 Barrientos S, Stojadinovic O, Golinko MS, *et al.* Growth factors and cytokines in wound healing. *Wound Repair Regen* 2008; **16**:585–601.
8 Jourde-Chiche N, Fakhouri F, Dou L, *et al.* Endothelium structure and function in kidney health and disease. *Nat Rev Nephrol* 2019; **15**:87–108.
9 Godo S, Takahashi J, Yasuda S, *et al.* Endothelium in coronary macrovascular and microvascular diseases. *J Cardiovasc Pharmacol* 2021; **78**:S19–S29.
10 Backer D de, Dubois M-J, Schmartz D, *et al.* Microcirculatory alterations in cardiac surgery: effects of cardiopulmonary bypass and anesthesia. *Ann Thorac Surg* 2009; **88**:1396–1403.
11 Brettner F, Chappell D, Schwartz L, *et al.* Vascular endothelial dysfunction during cardiac surgery: on-pump versus off-pump coronary surgery. *Eur Surg Res* 2017; **58**:354–368.
12 Murkin JM. Monitoring and optimization of the microcirculation during CPB. *J Thorac Dis* 2019; **11**:S1489–S1491.
13 Wu Q, Gao W, Zhou J, *et al.* Correlation between acute degradation of the endothelial glycocalyx and microcirculation dysfunction during cardiopulmonary bypass in cardiac surgery. *Microvasc Res* 2019; **124**: 37–42.
14 Giacinto O, Satriano U, Nenna A, *et al.* Inflammatory response and endothelial dysfunction following cardiopulmonary bypass: pathophysiology and pharmacological targets. *Recent Pat Inflamm Allergy Drug Discov* 2019; **13**:158–173.
15 Luft T, Benner A, Jodele S, *et al.* EASIX in patients with acute graft-versus-host disease: a retrospective cohort analysis. *Lancet Haematol* 2017; **4**: e414–e423.
16 Luft T, Benner A, Terzer T, *et al.* EASIX and mortality after allogeneic stem cell transplantation. *Bone Marrow Transplant* 2020; **55**:553–561.
17 Luft T, Wendtner C-M, Kosely F, *et al.* EASIX for prediction of outcome in hospitalized SARS-CoV-2 infected patients. *Front Immunol* 2021; **12**: 634416.
18 Xu H-B, Ye Y, Xue F, *et al.* Association between endothelial activation and stress index and 28-day mortality in septic ICU patients: a retrospective cohort study. *Int J Med Sci* 2023; **20**:1165–1173.
19 Schult D, Rasch S, Schmid RM, *et al.* EASIX is an accurate and easily available prognostic score in critically ill patients with advanced liver disease. *J Clin Med* 2023; **12**:2553.
20 Korell F, Schreck N, Müller-Tidow C, *et al.* Pretransplant EASIX and sepsis after allogeneic stem cell transplantation. *Intensive Care Med* 2022; **48**: 753–755.
21 Korell F, DeFilipp Z, Schreck N, *et al.* Validation of preconditioning EASIX for prediction of sepsis after allogeneic stem cell transplantation. *Intensive Care Med* 2023; **49**:1408–1410.
22 Finke D, Hund H, Frey N, *et al.* EASIX (endothelial activation and stress index) predicts mortality in patients with coronary artery disease. *Clin Res Cardiol* 2024; **114**:1008–1018.
23 Kordelas L, Terzer T, Gooley T, *et al.* EASIX-1year and late mortality after allogeneic stem cell transplantation. *Blood Adv* 2023; **7**:5374–5381.
24 Merz A, Germing U, Kobbe G, *et al.* EASIX for prediction of survival in lower-risk myelodysplastic syndromes. *Blood Cancer J* 2019; **9**:85.
25 Nashef SA, Roques F, Michel P, *et al.* European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg* 1999; **16**: 9–13.
26 Roques F, Nashef SA, Michel P, *et al.* Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. *Eur J Cardiothorac Surg* 1999; **15**:816–822. discussion 822–3.
27 Roques F, Michel P, Goldstone AR, *et al.* The logistic EuroSCORE. *Eur Heart J* 2003; **24**:881–882.
28 Nashef SAM, Roques F, Sharples LD, *et al.* EuroSCORE II. *Eur J Cardiothorac Surg* 2012; **41**:734–744. discussion 744-5.
29 Shanmugam G, West M, Berg G. Additive and logistic EuroSCORE performance in high risk patients. *Interact Cardiovasc Thorac Surg* 2005; **4**:299–303.

30 Kobayashi KJ, Williams JA, Nwakanma LU, *et al.* EuroSCORE predicts short- and mid-term mortality in combined aortic valve replacement and coronary artery bypass patients. *J Cardiac Surg* 2009; **24**:637–643.
31 Elm E von, Altman DG, Egger M, *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med* 2007; **4**:e296.
32 Chilian WM, Mass HJ, Williams SE, *et al.* Microvascular occlusions promote coronary collateral growth. *Am J Physiol* 1990; **258**:H1103–H1111.
33 Moraes F, Paye J, Mac Gabhann F, *et al.* Endothelial cell-dependent regulation of arteriogenesis. *Circ Res* 2013; **113**:1076–1086.
34 Parra-Bonilla G, Alvarez DF, Alexeyev M, *et al.* Lactate dehydrogenase a expression is necessary to sustain rapid angiogenesis of pulmonary microvascular endothelium. *PLoS One* 2013; **8**:e75984.
35 Jose P, Skali H, Anavekar N, *et al.* Increase in creatinine and cardiovascular risk in patients with systolic dysfunction after myocardial infarction. *J Am Soc Nephrol* 2006; **17**:2886–2891.
36 Schillaci G, Reboldi G, Verdecchia P. High-normal serum creatinine concentration is a predictor of cardiovascular risk in essential hypertension. *Arch Intern Med* 2001; **161**:886–891.
37 Wannamethee SG, Shaper AG, Perry IJ. Serum creatinine concentration and risk of cardiovascular disease: a possible marker for increased risk of stroke. *Stroke* 1997; **28**:557–563.
38 Michelson AD, Barnard MR, Krueger LA, *et al.* Circulating monocyte-platelet aggregates are a more sensitive marker of in vivo platelet activation than platelet surface P-selectin: studies in baboons, human coronary intervention, and human acute myocardial infarction. *Circulation* 2001; **104**:1533–1537.
39 Moiseev IS, Tsvetkova T, Aljurf M, *et al.* Clinical and morphological practices in the diagnosis of transplant-associated microangiopathy: a study on behalf of Transplant Complications Working Party of the EBMT. *Bone Marrow Transplant* 2019; **54**:1022–1028.
40 Matošević M, Kos I, Davidović M, *et al.* Hemolytic uremic syndrome in the setting of COVID-19 successfully treated with complement inhibition therapy: an instructive case report of a previously healthy toddler and review of literature. *Front Pediatr* 2023; **11**:1092860.
41 Dekker NAM, Veerhoek D, Koning NJ, *et al.* Postoperative microcirculatory perfusion and endothelial glycocalyx shedding following cardiac surgery with cardiopulmonary bypass. *Anaesthesia* 2019; **74**:609–618.
42 Nussbaum C, Haberer A, Tiefenthaller A, *et al.* Perturbation of the microvascular glycocalyx and perfusion in infants after cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 2015; **150**:1474–1481. e1.
43 Augustin HG, Kozian DH, Johnson RC. Differentiation of endothelial cells: analysis of the constitutive and activated endothelial cell phenotypes. *Bioessays* 1994; **16**:901–906.
44 Wolinsky H, Katz D, Markle R, *et al.* Hydrolase activities in the rat aorta. IV. Relation between clearance rates of circulating 125I-labeled low-density lipoproteins and levels of tissue hydrolase activity. *Circ Res* 1980; **47**: 433–442.
45 Ait-Oufella H, Maury E, Lehoux S, *et al.* The endothelium: physiological functions and role in microcirculatory failure during severe sepsis. *Intensive Care Med* 2010; **36**:1286–1298.
46 Regan ER, Aird WC. Dynamical systems approach to endothelial heterogeneity. *Circ Res* 2012; **111**:110–130.
47 Song G-Y, Jung S-H, Kim K, *et al.* Endothelial activation and stress index (EASIX) is a reliable predictor for overall survival in patients with multiple myeloma. *BMC Cancer* 2020; **20**:803.
48 Pedraza A, Salas MQ, Rodriguez-Lobato LG, *et al.* Easix score correlates with endothelial dysfunction biomarkers and predicts risk of acute graft-versus-host disease after allogeneic transplantation. *Transplant Cell Ther* 2024; **30**:187 e1–e12.
49 Pérez-García F, Bailén R, Torres-Macho J, *et al.* Age-adjusted endothelial activation and stress index for coronavirus disease 2019 at admission is a reliable predictor for 28-day mortality in hospitalized patients with coronavirus disease 2019. *Front Med (Lausanne)* 2021; **8**:736028.
50 Go S-I, Park S, Kang MH, *et al.* Endothelial activation and stress index (EASIX) as a predictive biomarker in small cell lung cancer. *Cancer Biomark* 2022; **35**:217–225.
51 Gu JS, Ryu JW, Yu SH, *et al.* Prognostic value of the endothelial activation and stress index in patients with upper tract urothelial cancer undergoing radical nephroureterectomy. *Investig Clin Urol* 2022; **63**:623–630.
52 Kalicińska E, Biernat M, Rybka J, *et al.* Endothelial Activation and Stress Index (EASIX) as an early predictor for mortality and overall survival in hematological and non-hematological patients with COVID-19: multicenter cohort study. *J Clin Med* 2021; **10**:4373.
53 Korell F, Penack O, Mattie M, *et al.* EASIX and severe endothelial complications after CD19-directed CAR-T cell therapy – a cohort study. *Front Immunol* 2022; **13**:877477.
54 Park S, Go S-I, Lee G-W. The Endothelial Activation and Stress Index (EASIX) score is an independent prognostic factor in patients with diffuse large B-cell lymphoma. *BMC Cancer* 2022; **22**:816.
55 Melo Bezerra Cavalcante CT de, Castelo Branco KM, Pinto Júnior VC, *et al.* Syndecan-1 improves severe acute kidney injury prediction after pediatric cardiac surgery. *J Thorac Cardiovasc Surg* 2016; **152**:178–186. e2.
56 Sun T, Wang Y, Wu X, *et al.* Prognostic value of Syndecan-1 in the prediction of sepsis-related complications and mortality: a meta-analysis. *Front Public Health* 2022; **10**:870065.
57 Magoon R, Makhija N. Endothelial glycocalyx and cardiac surgery: newer insights. *J Cardiothorac Vasc Anesth* 2020; **34**:310–311.
58 Uchimido R, Schmidt EP, Shapiro NI. The glycocalyx: a novel diagnostic and therapeutic target in sepsis. *Crit Care* 2019; **23**:16.
59 Laufs U, La Fata V, Plutzky J, *et al.* Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors. *Circulation* 1998; **97**: 1129–1135.
60 Hernández-Perera O, Pérez-Sala D, Navarro-Antolín J, *et al.* Effects of the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors, atorvastatin and simvastatin, on the expression of endothelin-1 and endothelial nitric oxide synthase in vascular endothelial cells. *J Clin Invest* 1998; **101**: 2711–2719.
61 Zhou Y, Tai S, Zhang N, *et al.* Dapagliflozin prevents oxidative stress-induced endothelial dysfunction via sirtuin 1 activation. *Biomed Pharmacother* 2023; **165**:115213.
62 Salvatore T, Caturano A, Galiero R, *et al.* Cardiovascular benefits from gliflozins: effects on endothelial function. *Biomedicines* 2021; **9**: 1356.
63 Li S, Wu Y, Yu G, *et al.* Angiotensin II receptor blockers improve peripheral endothelial function: a meta-analysis of randomized controlled trials. *PLoS One* 2014; **9**:e90217.
64 Tiefenbacher CP, Friedrich S, Bleeke T, *et al.* ACE inhibitors and statins acutely improve endothelial dysfunction of human coronary arterioles. *Am J Physiol Heart Circ Physiol* 2004; **286**:H1425–H1432.
65 Shahin Y, Khan JA, Samuel N, *et al.* Angiotensin converting enzyme inhibitors effect on endothelial dysfunction: a meta-analysis of randomised controlled trials. *Atherosclerosis* 2011; **216**:7–16.
66 Lüscher TF, Yang Z. Calcium antagonists and ACE inhibitors. Effect on endothelium and vascular smooth muscle. *Drugs* 1993; **46** (Suppl 2): 121–132.
67 Li T, Liu X, Zhao Z, *et al.* Sulodexide recovers endothelial function through reconstructing glycocalyx in the balloon-injury rat carotid artery model. *Oncotarget* 2017; **8**:91350–91361.
68 Sosińska P, Baum E, Maćkowiak B, *et al.* Sulodexide reduces the proinflammatory effect of serum from patients with peripheral artery disease in human arterial endothelial cells. *Cell Physiol Biochem* 2016; **40**: 1005–1012.
69 Raffetto JD, Calanni F, Mattana P, *et al.* Sulodexide promotes arterial relaxation via endothelium-dependent nitric oxide-mediated pathway. *Biochem Pharmacol* 2019; **166**:347–356.
70 Cospite M, Ferrara F, Cospite V, *et al.* Sulodexide and the microcirculatory component in microphlebopathies. *Curr Med Res Opin* 1992; **13**: 56–60.
71 Pabst C, Schreck N, Benner A, *et al.* Statin-based endothelial prophylaxis and outcome after allogeneic stem cell transplantation. *Eur J Clin Invest* 2023; **53**:e13883.