Prospective Cohort Study

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Intra- and early postoperative predictors of delirium risk in cardiac surgery: results from the prospective observational FINDERI study

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Background: Postoperative delirium (POD) is a severe complication following cardiac surgery and is associated with increased morbidity and mortality. The impact of intra- and early postoperative factors on the occurrence of POD following cardiac surgery remains controversial. To close this gap, we investigated intra- and early postoperative factors and their predictive values for POD.
Methods: We performed a prospective observational study that aimed to FIND DElirium RIsk factors (FINDERI) for patients undergoing elective cardiac surgery. POD was assessed using the Confusion Assessment Method algorithm. Intra- and early postoperative factors were extracted from electronic medical records and reviewed by cardiac surgeons. To identify potential predictors of POD, we used univariate and multivariate logistic regression along with machine learning (ML) with ten-fold cross-validation.
Results: In our study cohort of 490 patients, 106 screened positive for POD (21.6%). In the multivariate analysis, we found a positive association between POD occurrence and age ($P < 0.001$), duration of surgery ($P = 0.027$), combined (versus isolated) surgical procedures ($P = 0.024$), opening of the cardiac chambers ($P = 0.046$), and ventilation time ($P < 0.001$). The ML-based decision tree identified a two level-algorithm including ventilation time and aortic cross-clamping time, with an AUC of 0.7116 ($P = 0.0002$) in the validation set. In the ML-based LASSO regression analysis, we identified ventilation time, administration of erythrocyte concentrates (EC), and usage of cardiopulmonary bypass (CPB) as predictors of POD, with an AUC of 0.7407 ($P < 0.0001$) in the validation set.
Conclusion: The results of this analysis highlight the associations between ventilation time, aortic cross-clamping time, administration of EC, and usage of CPB and POD. Additionally, they suggest that the optimization of surgical protocols has the potential to reduce POD risk in individuals undergoing cardiac surgery.

Keywords: cardiac surgery, early extubation, machine learning approach, postoperative delirium, prediction of postoperative delirium

Introduction

Postoperative delirium (POD) is a highly prevalent and potentially severe complication in all surgical disciplines[1–6], with an even higher impact on patients undergoing major surgery[3,6–9]. In patients undergoing cardiac surgery, the prevalence of POD has been reported between 3% and 55%, and when present, POD significantly affects length of stay (LOS) in hospital[3,8,10] and intensive care unit (ICU)[11,12], rates of postoperative complications, and mortality[4,5,13]. POD after cardiac surgery is associated with a 30-day mortality risk of up to 7% compared to 1% in individuals who do not develop delirium[14–16]. POD is known to be associated with non-modifiable predisposing factors, such as higher age, female sex, and other pre-existing

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HIGHLIGHTS

- This analysis highlights the associations between intra- and early postoperative factors and postoperative delirium following cardiac surgery.
- In machine learning-based approach (decision tree), ventilation time and aortic cross-clamping time were identified as predictors for postoperative delirium.
- Precise planning by cardiac surgeons and perioperative teams may influence the risk of postoperative delirium.
- These results may inform the development of perioperative delirium risk prediction tools and optimized delirium prevention strategies.

comorbidities (e.g. dementia, impaired cognitive function, or history of stroke)[8,10,11,13,17,18].

Identifying risk factors for POD has the potential to significantly alter the postoperative course of individuals undergoing cardiac surgery. Preventing POD is considered to be more effective than simply managing the symptoms of POD (e.g. agitation)[9,19,20]. Therefore, preoperative identification of precipitating factors of POD[13,21,22] may lead to more patient-tailored therapeutic approaches that may positively impact postoperative outcomes, including morbidity and mortality[4,5,13], and reduce the socioeconomic impact of POD[6]. However, more evidence is needed for early identification of predisposing and precipitating POD risk factors[3,21,23,24].

Though there is evidence that certain intraoperative factors (e.g. aortic cross-clamping time, transfusion requirements, or haemodilution)[7,8] increase POD risk, prior research focused primarily on preexisting factors[7,24]. In fact, two previous meta-analyses found a lack of evidence for the links between intraoperative factors, such as duration of cardiopulmonary bypass (CPB) or surgical procedures, and subsequent development of POD[13,25]. Due to these inconclusive findings, the authors of meta-analyses suggest additional research to better understand the relationships between intraoperative factors and POD incidence[3,4,21].

Accordingly, we designed the prospective FINd DElirium RIsk factors (FINDERI) observational study to identify risk factors for POD. To overcome the limitations of prior research, we analyzed a wider range of intraoperative factors as a part of a standardized surgical protocol. Furthermore, we included not only patients undergoing heart surgery via median sternotomy but also those undergoing open heart procedures using minimally invasive approaches such as minimally invasive mitral valve reconstruction (MIC-MVR), transapical aortic valve replacement (TAVR), or minimally invasive coronary bypass grafting (MIDCAB), to identify procedure-related risk factors for POD. In this study, we aimed to identify POD risk factors in patients following cardiac surgery using regression analysis and machine learning (ML)-based methods.

Methods

Recruitment and preoperative assessments of the patient cohort

The FINDERI (German Clinical Trials: DRKS00025095) study is a prospective, observational, interdisciplinary project performed in the Department of Cardiovascular and Thoracic Surgery at the University Medical Center Göttingen, Germany. A detailed study protocol was published previously[23]. Between February 2021 and October 2022, more than 800 patients aged 50 years or older were screened for the study. The study protocol was approved by the local ethics committee before start of the study on 16 February 2021 (#20/11/20). Informed consent was obtained by the study team after providing detailed study information and prior to baseline assessment. Inclusion and exclusion criteria can be seen in Fig. 1 showing the complete study design and the study program. To identify individuals with severe cognitive impairment (e.g. dementia or inability to follow the assessment instructions), cognitive assessments (e.g. Montreal Cognitive Assessment, Trail Making Test, and Six-item Cognitive Impairment Test) were performed. Preoperative data regarding cardiovascular comorbidities, such as coronary artery disease (CAD) including history of myocardial infarction), valve diseases and their severity, known heart failure, the presence of a pacemaker (PM) or implantable cardioverter defibrillator (ICD), history of aortic aneurysm or dissection, or atrial fibrillation, were collected. Other examined somatic factors were chronic obstructive pulmonary disease, renal insufficiency, recent dialysis, history of cancer in the last 5 years, thyroid diseases, type 2 diabetes, carotid artery stenosis, history of stroke, dementia, anxiety disorder, depression, substance use disorder, and Parkinson's disease. In this study, we followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement guidelines[26] and the Strengthening the Reporting of Cohort Studies in Surgery (STROCCS) guidelines[27].

Assessment of intraoperative and early postoperative data

Data from the standardized surgical protocol were collected from an electronic health system. To ensure high data quality, all study investigators were trained on surgical data collection using the quality and information management system (QIMS; terraconnect; V2.5 SP1, Germany) software program. QIMS is used for the electronic documentation of standardized surgical protocols, including intraoperative surgical data (e.g. duration of surgery, use and time of cardiopulmonary bypass [CPB], and intraoperative complications). Ventilation time was documented using the IntelliSpace Critical Care and Anesthesia (ICCA; Rev J.01; Philips, USA) system and was defined as the time between admission to the ICU and extubation. The FINDERI study investigators entered all variables into a secuTrial® database in compliance with good clinical practice. Blinded data reviews (without knowledge of the development of POD) were performed by cardiac surgeons (PI, MJS, MK, and HB) who were qualified to ensure high data quality.

Postoperative delirium screening

Screening for POD was performed twice daily (in the morning between 8 and 10 A.M. and evening between 4 and 6 P.M.) for five postoperative days after cardiac surgery following the published study protocol[23]. POD was assessed using the Confusion Assessment Method (CAM) for the ICU (CAM-ICU) and the I-CAM for the intermediate care unit and normal wards[17,28–32]. The Richmond Agitation Sedation Scale was used in the ICU to assess levels of sedation and agitation prior to CAM-ICU testing[33]. POD screening was performed by FINDERI investigators who were trained on the CAM algorithm, as well as the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), and the International Classification of Diseases, tenth Revision

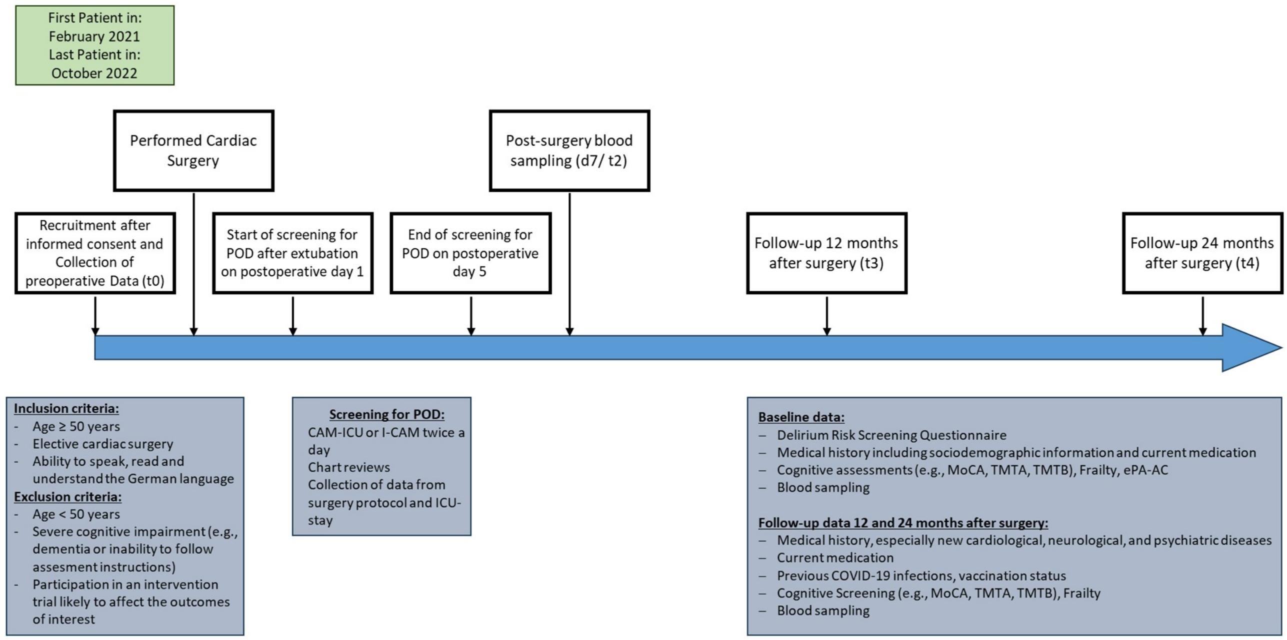

Figure 1. Flow diagram of the FINDERI study showing the study course and study visits. *Note.* t = time point of examination; POD = postoperative delirium; CAM-ICU = Confusion Assessment Method for intensive care unit; I-CAM = Confusion Assessment Method; ICU = intensive care unit; MoCA = Montreal Cognitive Assessment; TMTA = Trail Making Test Part A; TMTB = Trail Making Test Part B; ePA-AC = electronic care assessment acute care; COVID-19 = coronavirus disease 2019.

(ICD-10). In the FINDERI study, we used a modified version of CAM by adding psychomotor changes to the CAM algorithm (I-CAM)[17,30,31,34]. Since POD symptoms often occur at night, chart reviews were assessed by study investigators for the first 5 postoperative days. Finally, the FINDERI study investigators engaged in supervisory meetings (weekly or once in 2 weeks) with a senior consultation-liaison psychosomatic physician. A detailed CAM algorithm and description of a chart review of the FINDERI study were published previously[23,35].

Statistical approach

All statistical analyses were performed using R (R. Core Team, 2023, v. 4.3.1). Categorical variables are presented as absolute and relative frequencies (%). For continuous variables, the mean (M) and standard deviation (SD) were reported. To compare groups regarding the occurrence of POD, Pearson's chi-squared test was used for categorical variables and the Welch two-sample *t*-test for continuous variables. Differences were considered statistically significant at a two-sided P-value < 0.05. Univariate logistic regression was used to examine intraoperative and perioperative predictors of POD, with description of odds ratios (ORs) with 95% confidence intervals (CIs). We analyzed intraoperative and early postoperative factors, as well as several somatic key factors that are relevant for the surgical parameters and have been presented previously[35]. As duration of mechanical ventilation was not normally distributed, we performed a logarithmic transformation of these data.

For continuous variables (e.g. duration of surgery, ventilation time, or number of intraoperative blood transfusions), we also created receiver operating characteristic (ROC) curves using the R package *pROC*[36]. The area under the curve (AUC) is reported alongside 95% confidence intervals *(nparcomp)* and optimal cut-values determined by simultaneous maximization of sensitivity and specificity *(OptimalCutpoints)*[37,38]. Sensitivity, specificity, and positive and negative predictive values at the optimal cut-off-value were calculated using *epiR*.

Univariate regression was followed by multivariate regression analysis, which included all significant factors from the univariate regression analysis, with POD as the dependent variable. We entered the following factors as covariates into the multivariate regression analysis: age, duration of surgery, isolated vs. combined cardiac procedures, surgery with procedures other than valve surgery or coronary bypass grafting, surgery with opening of the cardiac chamber, CPB duration, aortic cross-clamping time, intraoperative administration of erythrocyte concentrates (EC) and thrombocyte concentrates (TC), development of intraoperative complications, and (log-transformed) duration of mechanical ventilation. To look for over-expression of statistical effects, we included the Akaike information criterion (AIC) and Bayesian information criterion (BIC) in the statistical analysis[39]. To investigate multicollinearity, we included the calculation of the variance inflation factor (VIF). Generally, a VIF above 5 indicates that multicollinearity might exist. When VIF is higher than 10, there is significant multicollinearity that needs to be considered. Though the VIF helps to determine the presence of multicollinearity, it cannot detect the explanatory variables causing multicollinearity[40].

Additionally, we used supervised ML, specifically regularized logistic regression using the least absolute shrinkage and selection operator (LASSO), which is implemented in *glmnet* and a decision tree *(rpart)*, to determine key predictors for the development of POD[37,38,41–43]. Input variables were all significant variables of the univariate regression, the use of CPB, CPB type, use of cardioplegic solution, aortic cross-clamping, and the number of administered EC and TC. The decision tree had a maximum depth of two and a minimal split requirement of 20 observations, as determined by the Gini index. Both ML-based approaches utilized ten-fold cross-validation for robust estimations. A dataset comprising 70% of the collected data was randomly selected as the training set, and the remaining 30% was used for validation[41]. Observations with missing values were removed from the multiple logistic regression models. Supplementary Digital Content, Table 1 (http://links.lww.com/JS9/D884) shows the number of observations used in the analysis.

Results

Basic characteristics of the FINDERI cohort

Demographics and comorbidities

The cohort for analysis included 504 patients (Fig. 2), of which 491 patients could be evaluated for the occurrence of POD. Statistical analysis was performed on 490 patients (Table 1A and 1B) due to missing assessment of POD in 13 patients and the exclusion of one patient who underwent pericardiectomy without any other cardiac surgical procedure due to recurring pericardial effusion. In the analyzed cohort of 490 patients, 106 patients (21.6%) developed POD after cardiac surgery defined by a positive score in CAM-ICU or I-CAM. Preoperative data showed that patients with POD were significantly older than those without POD (mean age with POD 71.02 ± 7.7 years vs. mean age without POD 67.6 ± 8.3 years; $P < 0.001$). Furthermore, patients with POD showed higher rates of heart failure ($P = 0.012$), higher severity of mitral valve disease, and a higher likelihood of PM or ICD ($P = 0.035$), heart valve disease ($P = 0.033$), and type 2 diabetes ($P = 0.001$) compared to patients without POD. A detailed analysis of preoperative somatic factors has been reported previously by Sadlonova *et al* 2023[35].

Regarding the surgical baseline data, patients with POD had longer surgeries ($P < 0.001$), more combined procedures ($P = 0.018$), more additional cardiac procedures besides valve or bypass surgery ($P = 0.032$), longer CPB duration ($P < 0.001$), longer aortic cross-clamping time ($P < 0.001$), higher likelihood of receiving EC ($P < 0.001$) and TC ($P = 0.007$), and longer intra- and postoperative ventilation times (log-transformed, $P < 0.001$). Finally, patients with POD had a higher incidence of complications ($P = 0.041$), longer ICU stay ($P < 0.001$), and longer hospital LOS ($P = 0.025$) compared to patients without POD.

Furthermore, there was no significant difference in POD occurrence between the patients with usage of CPB and the non-CPB group. However, the CPB patients were significantly younger ($P < 0.001$) and had lower rates of CAD ($P < 0.001$), tricuspid valve disease ($P = 0.049$), carotid artery stenosis ($P = 0.005$), peripheral artery disease ($P < 0.001$) as well as history of stroke ($P = 0.002$), and higher severity of mitral valve disease ($P = 0.024$) compared to the non-CPB group (for details see Supplementary Digital Content, Table 1A, http://links.lww.com/JS9/D884). Surgical study characteristics stratified by usage of CPB are presented in Supplementary Digital Content, Table 1B (http://links.lww.com/JS9/D885). Study characteristics stratified by surgical procedures are presented in Supplementary Digital Content, Table 1C (http://links.lww.com/JS9/D886). Finally, study characteristics in patients who underwent a valve surgery stratified by the surgical approach are presented in Supplementary Digital Content, Table 1D (http://links.lww.com/JS9/D887).

Univariate logistic analysis of intraoperative predictors for POD

In the first step, all included factors and the FINDERI cohort were analyzed using univariate logistic regression. The results of the univariate analysis are shown in Table 2. Extended data for other main and additional procedures, intraoperative complications, and reasons for surgical revision are provided in Supplementary Digital Content (Tables 2 http://links.lww.com/JS9/D888, 3 http://links.lww.com/JS9/D889, and 4 http://links.lww.com/JS9/D890).

In the second step, we performed a separate univariate logistic regression analysis for the CPB (on-pump) and non-CPB (off-pump) groups. For CPB patients, the analysis showed the same risk factors compared with the analysis of the complete FINDERI cohort (see Supplementary Digital Content, Table 5A, http://links.lww.com/JS9/D891). In the analysis of the off-pump data, there were no intra- or early postoperative factors associated with POD (see Supplementary Digital Content, Table 5B http://links.lww.com/JS9/D892).

Receiver operating characteristic (ROC) analysis of single intraoperative predictors for POD

Due to significant associations between POD and duration of surgery, duration of CPB, aortic cross-clamping time, duration of mechanical ventilation, and administration of ECs and TCs in the univariate analysis, we performed an ROC analysis for these factors to determine AUCs and optimal cut-off values. The AUCs were tested against the null hypothesis of being equal to 0.5.

The ROC analysis (Fig. 3) yielded an AUC of 0.6404 (95% CI: 0.576–0.6987; $P < 0.001$) for duration of surgery, an AUC of 0.665 (95% CI: 0.5976–0.7261; $P < 0.001$) for duration of CPB, and an AUC of 0.6489 (95% CI: 0.5816–0.7114; $P < 0.001$) for aortic cross-clamping time. Regarding the duration of surgery, we were able to determine an optimal cutoff value: 4.43 hours with a sensitivity of 60.4% and a specificity of 61.5%. For duration of CPB, the optimal cut-off value was 2.38 hours with a sensitivity of 62.2% and a specificity of 62.5%, and for aortic cross-clamping time, the optimal cut-off value was 1.567 hours with a sensitivity of 60.7% and a specificity of 59.6%. For the administration of ECs and TCs, there was no significant association between the number of given ECs and TCs and POD. The ROC analyses are shown in Supplementary Digital Content, Figure 1 (http://links.lww.com/JS9/D883). All ROC cut-off values, as well as sensitivity and specificity analyses, are shown in Supplementary Digital Content, Table 6 (http://links.lww.com/JS9/D893).

The ventilation time revealed an AUC of 0.7398 (95% CI: 0.6845–0.7882; $P < 0.001$; Fig. 4). Regarding the ventilation time, an optimal cut-off value of 13.75 hours with a sensitivity of 68.4% and a specificity of 69.5% was determined.

Multivariate logistic regression analysis of intraoperative predictors for POD

To rule out interactions between the significant intra- and early postoperative factors, we performed a multivariate logistic regression analysis (Table 3) with the following factors that were significantly associated with POD in the univariate analysis: age, duration of surgery, isolated vs. combined procedures, conducted additional procedure, opening of cardiac chamber(s), duration of CPB, aortic cross-clamping time, administration of ECs and TCs,

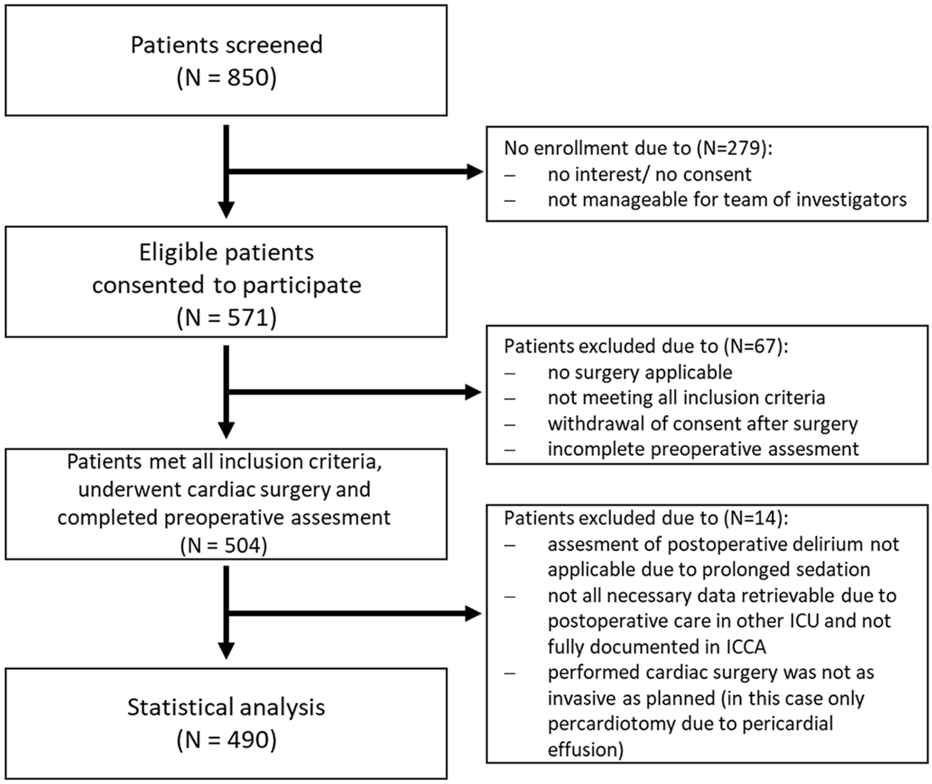

Figure 2. Flow chart of the prospective observational FINDERI study. *Note.* ICU = intensive care unit, ICCA = IntelliSpace Critical Care and Anesthesia (electronic clinical documentation system).

intraoperative complications, ventilation time (log-transformed), and the length of ICU stay. To investigate multicollinearity, we included the calculation of the VIF. The significant factors showed the following ORs: age (OR 1.07; 95% CI 1.04–1.11; $P < 0.001$), log duration of mechanical ventilation (OR 2.64; 95% CI 1.83–3.94; $P < 0.001$), duration of surgery (OR 1.46; 95% CI 1.04–2.04; $P = 0.027$), isolated versus combined procedure (OR 0.33; 95% CI 0.12–0.86; $P = 0.024$), and opening of cardiac chamber(s) (OR 2.22; 1.01–4.87; $P = 0.046$).

Machine learning approach to predict POD

Decision tree

To identify the best intra- and early postoperative predictors of POD, we performed an ML-based decision tree showing two important prediction rules. The rules for POD prediction were applied in the following sequence: (1) ventilation time ≥ 14 hours and (2) duration of aortic cross-clamping time ≥ 2.1 hours (Fig. 5A). The decision tree showed an AUC of 0.7021 (95% CI: 0.6329–0.7675; $P < 0.0001$) on the training set and 0.7116 (95% CI: 0.6167–0.7975; $P = 0.0002$) on the validation set (Fig. 5B and 5C).

LASSO

Using ML-based LASSO regression analysis, a non-zero regression coefficient estimate was observed for log-transformed ventilation time, administration of EC, and usage of CPB. The ROC analysis was used to assess the performance of the LASSO model in predicting POD, which demonstrated an AUC of 0.7852 (95% CI: 0.7207–0.8388, $P < 0.0001$) for the training set and an AUC of 0.7407 (95% CI: 0.6420–0.8199, $P < 0.0001$) for the validation set (Fig. 5B and 5C). The detailed data for the performance of LASSO regression and the decision tree are presented in Supplementary Digital Content, Table 7 (http://links.lww.com/JS9/D894; see also Tables 8A and 8B, http://links.lww.com/JS9/D895 and http://links.lww.com/JS9/D896, respectively).

Discussion

This prospective observational study of cardiac surgery patients identifies potentially modifiable intra- and postoperative factors that are associated with the occurrence of POD. This suggests that cardiac surgeons might predict the risk for POD and highlights potential factors that could be modified to reduce POD risk. The ML-based decision tree model, based on the ventilation time ≥14 hours and aortic cross-clamping time ≥ 2.1 hour, showed an AUC of 0.7116 in the validation set, while LASSO regression analysis yielded the highest accuracy for predicting POD with ventilation time, administration of EC, and usage of CPB, with an AUC of 0.7407 in the validation set. The presented analysis presents an easy-to-use model in a clinical context, without the necessity of calculating a score[2,21,24]. Therefore, including intra- and early postoperative factors in perioperative POD risk prediction models represents an important contribution to potentially influence the risk for POD in the field of cardiac surgery[21].

Table 1A

Somatic baseline characteristics of the FINDERI cohort stratified by POD

		Overall, *N* = 490	No POD, *N* = 384	POD, N = 106	
Characteristics	***N***	**Mean ± SD or *N* (%)**	**Mean ± SD or *N* (%)**	**Mean ± SD or *N* (%)**	***P*-value**
Sex	490				0.070
Male		385 (79%)	309 (80%)	76 (72%)	
Age [Y]	490	68.35 ± 8.29	67.61 ± 8.31	71.02 ± 7.71	**<0.001**
BMI [kg/m^2]	483	28.28 ± 4.62	28.30 ± 4.59	28.20 ± 4.75	0.851
Coronary artery disease	486	361 (74%)	279 (73%)	82 (78%)	0.377
History of myocardial infarction	485	124 (26%)	95 (25%)	29 (28%)	0.676
Heart failure	459	351 (76%)	267 (74%)	84 (87%)	**0.012**
Implanted PM or ICD	489				**0.035**
No		470 (96%)	372 (97%)	98 (92%)	
ICD		9 (1.8%)	4 (1.0%)	5 (4.7%)	
PM		10 (2.0%)	7 (1.8%)	3 (2.8%)	
Heart valve disease	488	309 (63%)	232 (61%)	77 (73%)	**0.033**
Aortic valve disease	308				0.271
No		106 (34%)	74 (32%)	32 (42%)	
Insufficiency		66 (21%)	48 (21%)	18 (23%)	
Stenosis		92 (30%)	75 (32%)	17 (22%)	
Combined		44 (14%)	34 (15%)	10 (13%)	
Severity of aortic valve disease	190				0.754
Mild		45 (24%)	33 (22%)	12 (28%)	
Moderate		34 (18%)	27 (18%)	7 (16%)	
Severe		111 (58%)	87 (59%)	24 (56%)	
Mitral valve disease	309				0.135
No		99 (32%)	80 (34%)	19 (25%)	
Insufficiency		199 (64%)	146 (63%)	53 (69%)	
Stenosis		5 (1.6%)	2 (0.9%)	3 (3.9%)	
Combined		6 (1.9%)	4 (1.7%)	2 (2.6%)	
Severity of mitral valve disease	203				**0.008**
Mild		105 (52%)	86 (57%)	19 (36%)	
Moderate		34 (17%)	19 (13%)	15 (28%)	
Severe		64 (32%)	45 (30%)	19 (36%)	
Tricuspid valve disease	307				0.391
No		212 (69%)	163 (71%)	49 (64%)	
Insufficiency		94 (31%)	66 (29%)	28 (36%)	
Stenosis		1 (0.3%)	1 (0.4%)	0 (0%)	
Severity of tricuspid valve disease	91				0.201
Mild		66 (73%)	48 (74%)	18 (69%)	
Moderate		16 (18%)	9 (14%)	7 (27%)	
Severe		9 (9.9%)	8 (12%)	1 (3.8%)	
Aortic aneurysm	487	37 (7.6%)	29 (7.6%)	8 (7.6%)	>0.999
History of aortic dissection	487	1 (0.2%)	1 (0.3%)	0 (0%)	>0.999
Carotid artery stenosis	478	67 (14%)	50 (13%)	17 (17%)	0.479
Atrial fibrillation	484	102 (21%)	73 (19%)	29 (28%)	0.074
History of endocarditis	483	7 (1.4%)	4 (1.1%)	3 (2.9%)	0.358
Peripheral arterial occlusive disease	486	58 (12%)	41 (11%)	17 (16%)	0.192
History of stroke	485	53 (11%)	38 (10.0%)	15 (14%)	0.266
Renal insufficiency	488	62 (13%)	45 (12%)	17 (16%)	0.296
Preoperative dialysis requirement	489	3 (0.6%)	3 (0.8%)	0 (0%)	0.833
Cancer (during the past 5 years)	487	42 (8.6%)	32 (8.4%)	10 (9.5%)	0.861
Thyroid diseases	487	85 (17%)	64 (17%)	21 (20%)	0.563
COPD	486	39 (8.0%)	31 (8.2%)	8 (7.5%)	0.998
Diabetes	489	148 (30%)	102 (27%)	46 (43%)	**0.001**
Depressive disorder	486	59 (12%)	41 (11%)	18 (17%)	0.109
Anxiety disorder	487	22 (4.5%)	19 (5.0%)	3 (2.9%)	0.509
Substance use disorder (drugs/alcohol)	484	16 (3.3%)	13 (3.4%)	3 (2.9%)	>0.999
Dementia	489	1 (0.2%)	0 (0%)	1 (0.9%)	0.491
Parkinson's disease	489	2 (0.4%)	0 (0%)	2 (1.9%)	0.067

POD, postoperative delirium; SD, standard deviation; Y, years; BMI, body mass index; PM, pacemaker; ICD, implantable cardioverter defibrillator; COPD, chronic obstructive pulmonary disease; *P*-value calculated by Pearsons chi-squared test and Welch two-sample *t*-test.

Statistically significant values are highlighted in bold.

Table 1B

Intraoperative and early postoperative baseline characteristics of the FINDERI cohort stratified by POD

	N	Overall, *N* = 490	No POD, *N* = 384	POD, *N* = 106	
Characteristics	***N***	**Mean ± SD or *N* (%)**	**Mean ± SD or *N* (%)**	**Mean ± SD or *N* (%)**	***P*-value**
Duration of surgery [h]	490	4.31 ± 1.29	4.17 ± 1.17	4.80 ± 1.54	**<0.001**
Procedure	490				**0.018**
Isolated		348 (71%)	283 (74%)	65 (61%)	
Combined		142 (29%)	101 (26%)	41 (39%)	
Surgery type	490				0.270
Isolated CABG		234 (48%)	192 (50%)	42 (40%)	
Isolated heart valve		108 (22%)	86 (22%)	22 (21%)	
Isolated other procedure		6 (1.2%)	5 (1.3%)	1 (0.9%)	
CABG and heart valve		48 (9.8%)	36 (9.4%)	12 (11%)	
CABG and other procedure		27 (5.5%)	18 (4.7%)	9 (8.5%)	
Heart valve and other procedure		53 (11%)	38 (9.9%)	15 (14%)	
CABG, heart valve and other procedure		14 (2.9%)	9 (2.3%)	5 (4.7%)	
CABG	490	323 (66%)	255 (66%)	68 (64%)	0.751
Heart valve surgery	490	223 (46%)	169 (44%)	54 (51%)	0.247
Type of surgical approach for heart valve surgery	222				0.056
Sternotomy		142 (64%)	105 (62%)	37 (70%)	
Partial sternotomy		28 (13%)	27 (16%)	1 (1.9%)	
Transapical TAVR		19 (8.6%)	13 (7.7%)	6 (11%)	
Minithoracotomy		33 (15%)	24 (14%)	9 (17%)	
Combined CABG and heart valve	490	48 (9.8%)	36 (9.4%)	12 (11%)	0.680
Additional procedure	490	100 (20%)	70 (18%)	30 (28%)	**0.032**
Heart chamber(s) opened	490	254 (52%)	190 (49%)	64 (60%)	0.060
Usage of cardiopulmonary bypass	490	417 (85%)	326 (85%)	91 (86%)	0.928
Cardiopulmonary bypass type	471				0.480
Conventional extracorporeal circulation		399 (85%)	310 (84%)	89 (88%)	
Minimal invasive extracorporeal circulation		17 (3.6%)	15 (4.1%)	2 (2.0%)	
Cardiopulmonary bypass duration [h]	413	2.46 ± 0.98	2.32 ± 0.85	2.97 ± 1.23	**<0.001**
Aortic cross-clamping	489	410 (84%)	320 (84%)	90 (85%)	0.852
Aortic cross-clamping time [h]	408	1.61 ± 0.69	1.52 ± 0.61	1.90 ± 0.86	**<0.001**
Usage of cardioplegia	490	411 (84%)	321 (84%)	90 (85%)	0.860
Selective head perfusion	488	3 (0.6%)	2 (0.5%)	1 (1.0%)	>0.999
Duration of selective head perfusion [min]	3	20.33 ± 5.03	20.00 ± 7.07	21.00 ± NA	
Circulatory arrest	487	3 (0.6%)	2 (0.5%)	1 (1.0%)	>0.999
Duration circulatory arrest [min]	3	23.33 ± 4.16	24.00 ± 5.66	22.00 ± NA	
Defibrillation	489	202 (41%)	156 (41%)	46 (43%)	0.703
EC administration	490	105 (21%)	67 (17%)	38 (36%)	**<0.001**
Number of EC administration	105	1.84 ± 1.13	1.82 ± 1.18	1.87 ± 1.04	0.831
TC administration	488	34 (7.0%)	20 (5.2%)	14 (13%)	**0.007**
Number of TC administration	34	1.91 ± 0.57	1.90 ± 0.64	1.93 ± 0.47	0.882
Other complications	490	25 (5.1%)	15 (3.9%)	10 (9.4%)	**0.041**
Ventilation time [h]	445	21.01 ± 58.70	15.38 ± 31.70	40.94 ± 108.04	0.023
Log ventilation time [h]	445	2.48 ± 0.82	2.35 ± 0.74	2.97 ± 0.90	**<0.001**
Surgical revision	490	18 (3.7%)	15 (3.9%)	3 (2.8%)	0.818
Length of ICU stay [days]	475	2.92 ± 3.81	2.31 ± 2.45	5.18 ± 6.30	**<0.001**
Length of hospital stay [days]	490	11.68 ± 8.18	11.17 ± 7.57	13.51 ± 9.89	**0.025**
In-hospital mortality	490	4 (0.8%)	2 (0.5%)	2 (1.9%)	0.439

POD, postoperative delirium; SD, standard deviation; h, hours; CABG, coronary artery bypass grafting; TAVR, transcatheter aortic valve replacement; min, minutes; NA, not applicable; EC, erythrocyte concentrate; TC, thrombocyte concentrate; ICU, intensive care unit; *P*-value calculated by Pearson's chi-squared test and Welch two-sample *t*-test.
Statistically significant values are highlighted in bold.

Intraoperative and postoperative risk factors for POD development

We explored the role of several intraoperative and early postoperative risk factors in prediction of POD that might be modifiable during or after cardiac surgery in a representative cohort. The prevalence of POD in our study (21.6%) is comparable to those reported in previous studies (3–55%)[3,5,8,10,12,44]. The variance in the reported occurrence of POD may be due to more specific cohorts of patients, applied diagnostic tools, or timing of data collection[2,6,7,45].

In the multivariate regression analysis, age, duration of surgery, combined versus isolated procedures, opening of cardiac chamber(s), and ventilation time were independently associated with POD occurrence. Surprisingly, intraoperative factors such as CPB time, administration of EC and TC, or occurrence of other complications were not significantly associated with POD in multivariate analysis.

Table 2

Univariate logistic regression of the FINDERI cohort: demographic, intraoperative, and early postoperative factors

Characteristics	*N*	OR	95% CI	*P*-value
Age [Y]	490	1.05	1.02, 1.08	**<0.001**
Duration of surgery [h]	490	1.46	1.23, 1.74	**<0.001**
Procedure	490			
Combined		1.77	1.12, 2.77	**0.014**
Surgery type	490			
CABG		—	—	
Heart valve		1.17	0.65, 2.06	0.594
Other procedures		0.91	0.05, 5.86	0.936
CABG and heart valve		1.52	0.71, 3.11	0.260
CABG and other procedures		2.29	0.92, 5.33	0.062
Heart valve and other procedure		1.80	0.89, 3.53	0.091
CABG, heart valve, and other procedures		2.54	0.75, 7.75	0.110
CABG	490			
Yes		0.91	0.58, 1.43	0.665
Heart valve surgery	490			
Yes		1.32	0.86, 2.04	0.205
Type of surgical approach for heart valve surgery	489			
Sternotomy		1.46	0.90, 2.35	0.126
Partial sternotomy		0.15	0.01, 0.75	0.068
Transapical TAVR		1.91	0.64, 5.08	0.211
Minithoracotomy		1.55	0.65, 3.43	0.297
Combined CABG and heart valve	490			
Yes		1.23	0.60, 2.40	0.551
Additional procedure	490			
Yes		1.77	1.07, 2.89	**0.024**
Heart chamber(s) opened	490			
Yes		1.56	1.01, 2.42	**0.048**
Usage of cardiopulmonary bypass	490			
Yes		1.08	0.60, 2.06	0.807
Cardiopulmonary bypass type	489			
Conventional extracorporeal circulation		1.11	0.61, 2.12	0.739
Minimal invasive extracorporeal circulation		0.52	0.08, 2.11	0.411
Cardiopulmonary bypass duration [h]	413	1.86	1.47, 2.37	**<0.001**
Aortic cross-clamping	489			
Yes		1.11	0.62, 2.07	0.737
Aortic cross-clamping time [h]	408	2.08	1.49, 2.95	**<0.001**
Usage of cardioplegia	490			
Yes		1.10	0.62, 2.06	0.745
Intraoperative defibrillation	489			
Yes		1.12	0.72, 1.72	0.622
EC administration	490			
Yes		2.64	1.64, 4.25	**<0.001**
Number of EC administration	105	1.04	0.71, 1.48	0.835
TC administration	488			
Yes		2.79	1.33, 5.70	**0.005**
Number of TC administration	34	1.09	0.30, 4.00	0.884
Other complications	490			
Yes		2.56	1.08, 5.82	**0.026**
Log ventilation time [h]	445	2.71	1.96, 3.87	**<0.001**

OR, odds ratio; CI, confidence interval; Y, years; h, hours; CABG, coronary artery bypass grafting; TAVR, transcatheter aortic valve replacement; EC, erythrocyte concentrate; TC, thrombocyte concentrate; ICU, intensive care unit. Statistically significant values are highlighted in bold.
Presented are odds ratio with a 95% confidence interval and the *P*-value.

Table 3

Multivariate logistic regression for significant intraoperative and early postoperative factors in univariate logistic regression

Characteristics	OR	95% CI	*P*-value	VIF
Age [Y]	1.07	1.04, 1.11	**<0.001**	1.2
Duration of surgery [h]	1.46	1.04, 2.04	**0.027**	3.0
Procedure				3.3
Combined	0.33	0.12, 0.86	**0.024**	
Additional procedure				2.3
Yes	1.82	0.76, 4.47	0.183	
Heart chamber(s) opened				2.4
Yes	2.22	1.01, 4.87	**0.046**	
Cardiopulmonary bypass duration [h]	0.99	0.59, 1.65	0.976	6.8
Aortic cross-clamping time [h]	0.94	0.48, 1.88	0.861	5.8
EC administration				1.2
Yes	1.22	0.66, 2.22	0.516	
TC administration				1.4
Yes	0.57	0.19, 1.55	0.282	
Other complications				1.1
Yes	1.30	0.43, 3.65	0.632	
Log ventilation time [h]	2.64	1.83, 3.94	**<0.001**	1.1
AIC		411		
BIC		460		

OR, odds ratio; CI, confidence interval; VIF, variance inflation factor; Y, years; h, hours; EC, erythrocyte concentrate; TC, thrombocyte concentrate; AIC, Akaike information criterion; BIC, Bayesian information criterion.
Statistically significant values are highlighted in bold. Presented are odds ratio with its 95% confidence interval and the *P*-value. In addition, we calculated the variance inflation factor.

Age remains one of the major non-modifiable predisposing risk factors for POD that has already been assessed and taken into account in preoperative assessment tools[13,18,21,46]. Similar to our results, previous studies have found associations between CPB time, combined versus isolated procedures, and the need for blood transfusion with POD[2,7,13]. Prolonged duration of surgery increases the risk of POD with an OR of 1.46. Additionally, combined surgical procedures were associated with an increased risk of POD with an OR of 1.77 in the univariate analysis. Therefore, especially in high-risk patients, cardiac surgeons may reduce surgical time and consider splitting combined surgical procedures in shorter isolated procedures like off-pump aortocoronary bypass surgery followed by an interventional transfemoral aortic valve replacement without using CPB, instead of one combined procedure of bypass surgery and aortic valve replacement with CPB. Longer duration of cardiac surgery, as required for complex or combined surgical procedures, is mostly associated with a longer duration of CPB, longer aortic cross-clamping time, and higher probability of transfusion of blood products, resulting in a higher probability of POD[2,7,12,47].

The link between intraoperative factors (e.g. aortic cross-clamping time) and POD may be caused by cerebral and systemic inflammatory response leading to glial cell injury and blood-brain barrier dysfunction due to the use of CPB, myocardial ischemia, hemodilution, and heparin/protamine complexes activating the complement system[2,48,49]. For example, systemic inflammatory response due to CPB leads to cytokine activation (e.g. interleukin-6), altering cerebral blood flow due to vasoconstriction, resulting in reduced microvascular circulation, followed by impairment of cerebral function in early postoperative stages[48–50]. Therefore, there are many triggers leading to an activation of inflammatory cascades in cardiac surgery and potentially causing POD[51–54]. An additional pathophysiological mechanism might be a fluid shift due to capillary leakage caused by inflammatory response resulting in cerebral edema[55–57]. Nevertheless, there has still been missing evidence with some reviews even refusing the thesis of an impact of CPB duration and other mentioned intraoperative risk factors on the occurrence of POD[8,11,13]. Reasons for the mixed evidence regarding intraoperative risk factors may be based on missing inclusion of key variables, selection bias, and detection bias in many studies. Bucerius *et al*[7]. concluded that some factors like duration of CPB or duration of surgery are related to increased surgical complexity, so that some factors might influence each other. For example, intermittent cerebral ischemia due to low-flow phases during CPB and longer surgery time might cause subclinical diffuse cerebral ischemia, resulting in functional cerebral alteration. Such low-flow situations might occur due to extensive vasodilation or low cardiac output after weaning from CPB.

In our cohort, opening of one or more cardiac chambers was a significant predictor of POD occurrence in the multivariate analysis. A high OR of 2.22 represents a clinically significant impact of the opening of a cardiac chamber on occurrence of POD. Even though this association has controversially been discussed in the literature with mixed evidence[2,13], the reason for a higher probability of POD after open-heart surgery could be diffused air embolism or embolism of microcalcifications, as well as microthrombi[58]. Most microembolisms are caused by atherosclerosis or atheromatosis correlating with age, aortic cannulation, and aortic cross-clamping[58]. Microembolisms (i.e. gaseous microemboli) may cause cerebral injury by altered cerebral microcirculation inducing inflammatory responses, potentially leading to POD[48,51,58].

Similar to other studies[3,10,25,59], prolonged ventilation time was most strongly associated with POD occurrence. Several mechanisms may help to explain the links between mechanical ventilation and POD. First, mechanical ventilation itself may lead to barotrauma of the lungs and dysregulation of the innate tract, causing inflammation and pulmonary dysfunction[60,61]. Alternatively, ventilation time may reflect intra- and postoperative complications that lead to increased lung injury and necessitate prolonged mechanical ventilation, subsequently increasing the risk of POD[18,51,59,60,62–64]. Finally, POD itself could be a cause for longer ventilation time, as confusion or reduced level of consciousness may make teams reluctant to extubate due to the absence of protective reflexes[65].

POD remains common after cardiac surgery and is associated with prolonged ICU stay, increased morbidity, and mortality. Therefore, modifiable intra- and early POD risk factors need to be addressed. Pre-, intra-, and early postoperative risk factors for POD may be optimized using protocols for Enhanced Recovery After Cardiac Surgery (ERACS). ERACS might reduce duration of surgery, surgical trauma, and the need for blood transfusion and suggest strategies for early extubation[66–68]. The data of this study suggest that early extubation plays a crucial role not only in ERACS protocols[69,70] but may also have the potential to reduce the probability of POD. While there is no durable definition of early extubation yet, the literature recognizes extubation until 6 or even 12 hours postoperatively as early extubation[66,69]. Some ERACS protocols even assume that immediate extubation after cardiac surgery improves patient outcomes, but data on whether it also influences the occurrence of POD are not yet available[66–68]. Additionally, the implementation of ERACS protocols may improve patient outcomes (e.g. length of ICU stay, postoperative complications, and readmission rate)[67-72].

Based on the presented results, we recommend evaluating the risk of POD in elderly patients and patients who require a combined procedure with a prolonged surgical time. These patients in particular may benefit from a modification of the surgical procedure (e.g. splitting surgical procedure and taking interventional procedures into account) and/or the implementation of an ERACS program.

Predictive value of intraoperative factors for POD occurrence

The impact of modifiable intra- and early postoperative factors on POD occurrence underlines the critical role of cardiac surgeons and the whole perioperative team in preventing POD. In our ML analysis, we investigated factors that can be influenced during and early after cardiac surgery, such as surgical planning (e.g. surgical approach and team and cardioplegia), re-evaluation of indications for surgery (off-pump, on-pump, minimally invasive, and no surgery), time point of extubation (OR, early on ICU, and next day), pain management, and sedation. The multivariate analysis showed that ventilation time had a major impact on POD development. In the ML-based LASSO regression analysis, a non-zero regression coefficient estimate was observed for log-transformed ventilation time, administration of EC, and usage of CPB, resulting in an AUC of 0.7852 for the training set and an AUC of 0.7407 for the validation set. Additionally, the ML-based decision tree model, based on the ventilation time $\geq$ 14 hours and aortic cross-clamping time $\geq$2.1 hour, showed an AUC of 0.7116 in the validation set. These results reinforce interdisciplinary concepts that focus on perioperative POD risk detection tools, shorter ventilation time, and less traumatic surgery (e.g. without aortic clamping or usage of CPB), potentially leading to lower POD prevalence in cardiac surgery.

Limitations

The FINDERI study has several strengths. First, we analyzed a representative sample of 490 patients undergoing cardiac surgery. Second, FINDERI is a prospective observational study with well-performed (standardized) POD screening and a detailed surgical protocol including various intraoperative factors. Third, we applied advanced ML-based approaches to identify intraoperative and early postoperative predictors that could be incorporated into perioperative POD risk detection tools. However, this study has several limitations. POD screening using the CAM algorithm (i.e. CAM-ICU or I-CAM) was applied twice a day after extubation only. Therefore, the POD screening did not encompass emergence POD, which typically manifests within minutes to hours after cardiac surgery. Although we intended to include all elective cardiac surgery patients, we were only able to include about half of the admitted elective patients in our department and excluded all patients undergoing urgent and emergent surgeries. In addition to the fact that all included patients underwent elective cardiac surgery, our study cohort was not as homogeneous as other studies in this field with regard to the performed surgical procedures[2,8]. On the one hand, we might have failed to identify special intraoperative risk factors that may only be present in some procedures or subgroups of patients undergoing cardiac surgery[3,10]. On the other hand, this heterogeneity is valuable and leads to identification of general risk factors for POD in cardiac surgery[2,7]. Additionally, this study was carried out at a single academic center, which may lead to an institutional bias. Therefore, our findings may not be applicable to other institutions performing cardiac surgery. Consistent with other studies, the

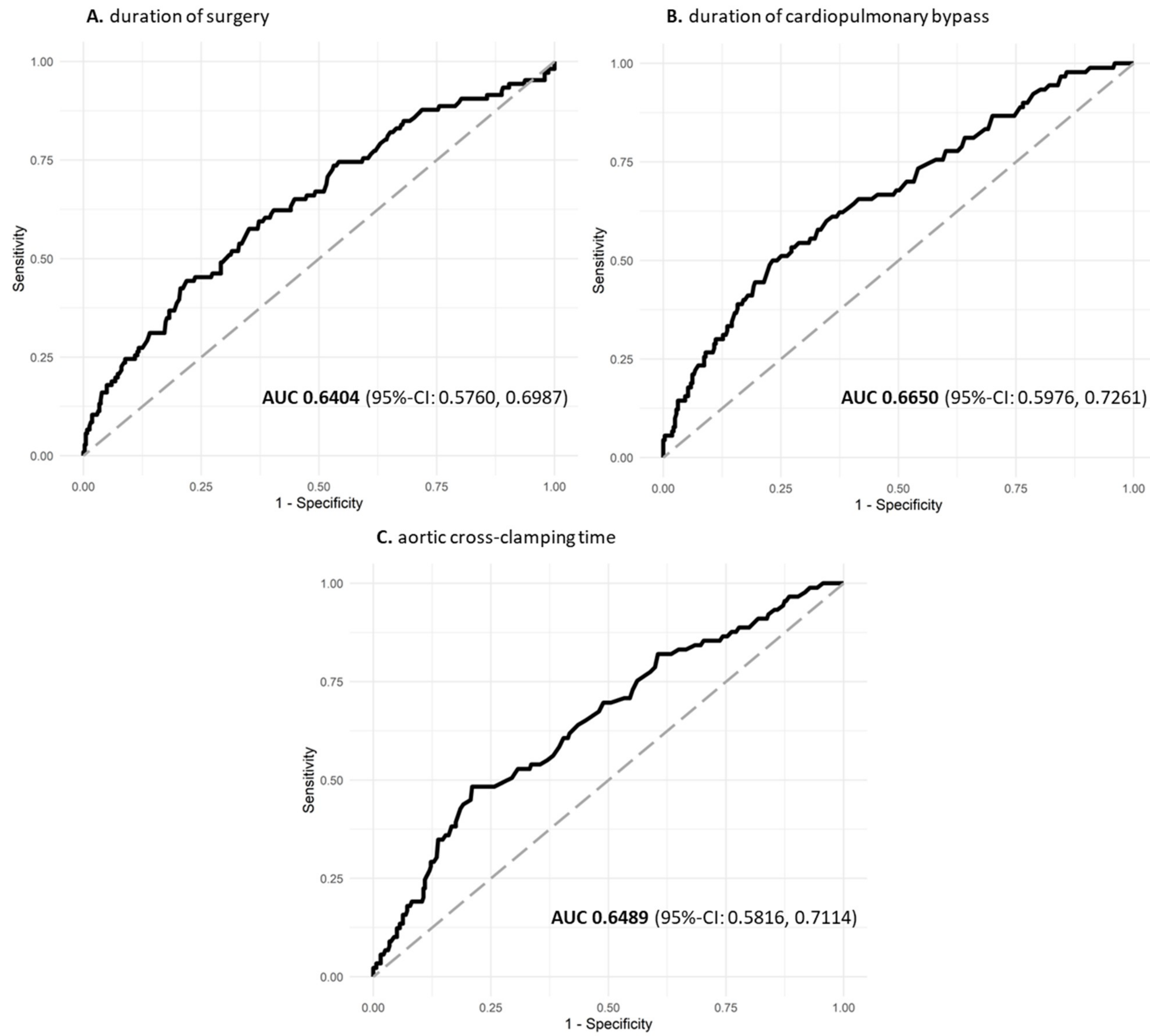

Figure 3. ROC analysis for intraoperative durations (duration of surgery, duration of cardiopulmonary bypass, and aortic cross-clamping time) in predicting POD. A: ROC analysis for duration of surgery. B: ROC analysis for duration of cardiopulmonary bypass. C: ROC analysis for aortic cross-clamping time. *Note.* ROC = receiver operating characteristics; POD = postoperative delirium; AUC = area under the curve; CI = confidence interval. AUC are reported for all ROCs below the curve.

majority of the included patients undergoing cardiac surgery were male. Extensive research should be conducted with special focus on gender equality and gender-related issues in surgical studies. In addition to this, we were unable to include all potential confounders (e.g. preoperative psychological status, impact of surgical and ICU teams, and stressors in the ICU) that influence the impact of intra- and early postoperative factors on POD. For example, we did not describe and control for protocols for perioperative patients' management, general anesthesia, postoperative sedation, or weaning criteria. In the multivariate logistic regression analysis, the VIF for CPB and ischemic time was above 5 (6.8 and 5.8, respectively). Generally, a VIF above 5 indicates that multicollinearity might exist, potentially leading to imprecise conclusions in terms of statistical significance of these factors. These limitations underline the need for further research to enhance the predictive accuracy for POD in terms of intra- and early postoperative factors. In the future, larger studies with heterogeneous study populations and well-defined data acquisition are required to allow for subgroup analyses. Finally, multicenter prospective observational studies should be carried out to identify more generalizable POD risk factors. The presented risk factors for developing POD are also partially limited to the field of cardiac surgery, due to surgical techniques or usage of medical products only used in the field of cardiac surgery (e.g. widespread use of CPB or aortic cross-clamping, and usage of cardioplegia). Other risk factors, especially those regarding mechanical ventilation, may be applicable for other fields of major surgeries with general anesthesia as well. Therefore, the findings of duration of mechanical ventilation being a risk factor of developing POD are consistent with similar studies in other surgical specialties.

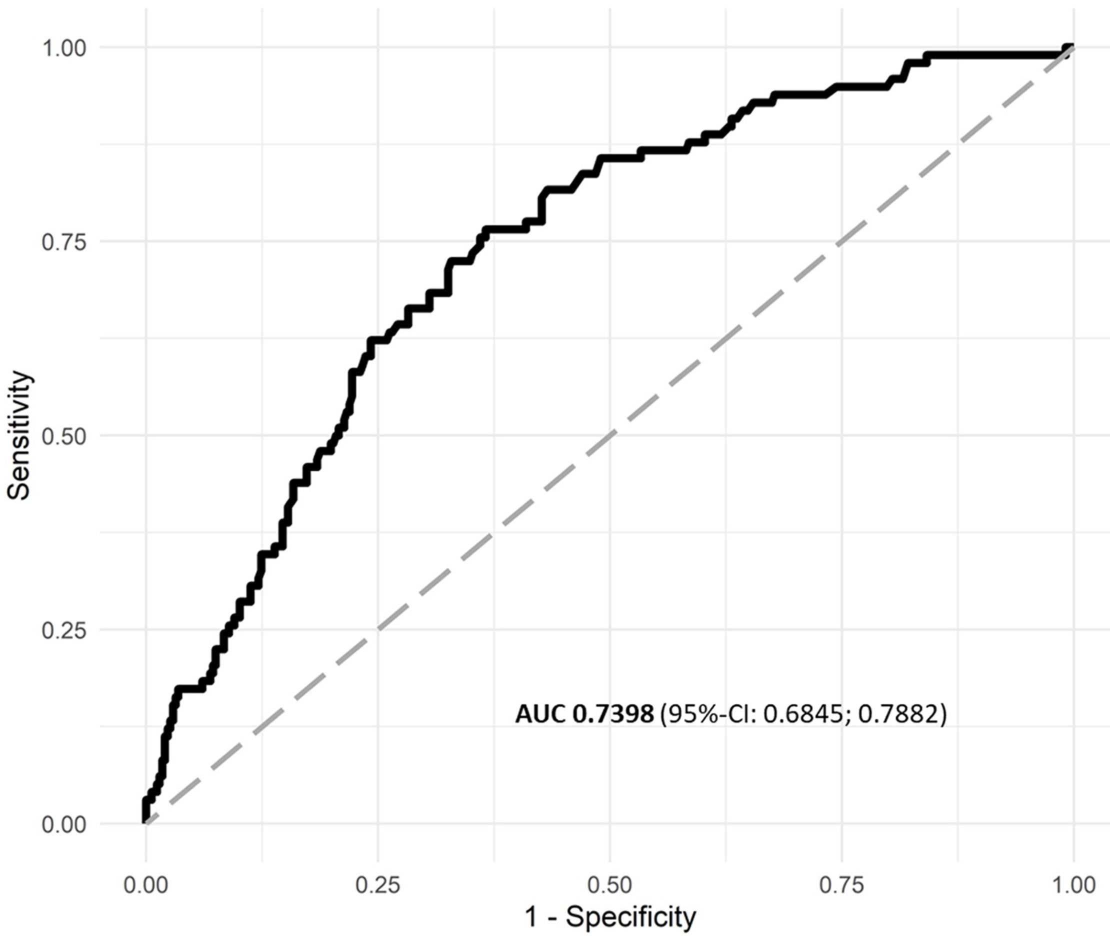

Figure 4. ROC analysis for ventilation time in predicting POD. *Note.* ROC = receiver operating characteristics; POD = postoperative delirium; AUC = area under the curve; CI = confidence interval. AUC is reported below the ROC curve.

Conclusions

In summary, we found further evidence for intra- and early postoperative risk factors for development of POD, a life-threatening complication after cardiac surgery. ML-based approaches (i.e. decision trees or LASSO regression) provided additional tools for risk prediction of POD. The identified intra- and early postoperative risk factors, especially ventilation time, aortic cross-clamping time, and duration of surgery, can be influenced by cardiac surgeons and perioperative teams. Future studies are needed to confirm these associations and to investigate whether optimized surgical planning and performance (e.g. reducing surgical time or/and avoiding CPB by splitting combined cardiac surgery into an interventional procedure and a shorter surgical procedure without CPB), reduction of ventilation time, and ERACS may help to reduce POD occurrence.

Ethics approval

The study protocol was approved by the Ethics Committee of the University of Göttingen Medical Center on 16 February 2021 (#20/11/20).

Consent

Written informed consent was obtained from each participant before any trial-related procedures were performed, and the patients received a copy of the signed and dated written consent form.

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Author contributions

Conceptualization, M.S., J.W., H.B., C.A.F.v.A., N.H., H.E., T. A., I.K.; investigation, M.S., C.A.F.v.A., J.W., H.B.; methodology, project administration, data curation, M.S., C.A.F.v.A., H.

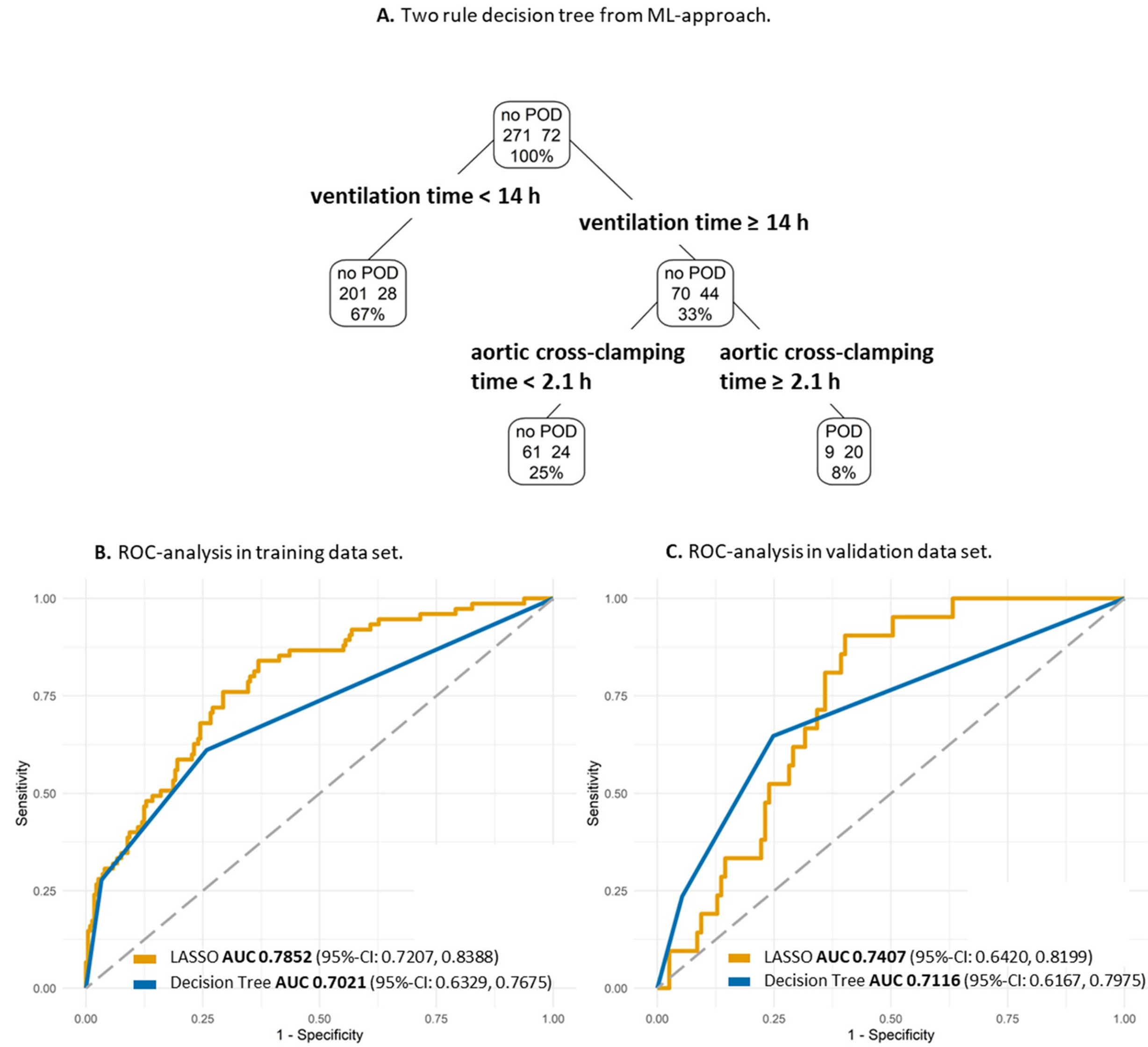

Figure 5. Two-rule decision tree from the ML approach and ROC analysis for decision tree and LASSO regression. A: Two-rule decision tree from the ML approach. B: ROC analysis in the training dataset. C: ROC analysis in the validation dataset. *Note.* ML = machine learning; ROC = receiver operating characteristics; LASSO = least absolute shrinkage and selection operation; AUC = area under the curve; POD = postoperative delirium; h = hours; CI = confidence interval. AUC are reported for all ROCs below the curve.

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Conflicts of interest disclosure

C.M.C. received funding from the National Heart, Lung, and Blood Institute (grant R01HL155301) and stipends from Elsevier for editorial work for General Hospital Psychiatry. J.W. has served on scientific advisory boards for Abbot, Biogen, Boehringer-Ingelheim, Eli Lilly, F. Hoffmann-La Roche, Immunogenetics, MSD SHARP & DOHME, and has also received honorarium for lectures sponsored by Eli Lilly, Pfizer, Janssen, MSD SHARP & DOHME, Amgen, Roche Pharma, Actelion Pharmaceuticals, Guangzhou Glorylen Medical Technology Co. (China), and Beijing Yibai Science and Technology Ltd. C.A.F.v.A. has received honoraria from serving on the scientific advisory board of Biogen, Roche, Lilly, and Dr. Willmar Schwabe GmbH &Co. C.A.F.v.A. has also received funding for travel and speaker honoraria from Biogen, Roche diagnostics AG, Novo Nordisk, MedTrixGmbH, Landesvereinigung für Gesundheit und Akademie für Sozialmedizin Niedersachsen e.V., Medical Tribune Verlagsgesellschaft mbH, Novartis, FomF GmbH, Paracelsus–Kliniken Deutschland, Schön Klinik Bad Aibling and Dr. Willmar Schwabe GmbH &Co. P.T.I., M.S., M.J.S., M.K., C.E., M.H., M.F.S., C.D., T.A., N.H., S.H., H.E., I.K., and H.B. report no competing interests..

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Data availability statement

The FINDERI dataset generated and/or analyzed for the present article is available upon request from the corresponding author (P.T.I.) and the study statisticians (C.D., T.A.).

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References

[1] Anderson BJ, Chesley CF, Theodore M, *et al*. Incidence, risk factors, and clinical implications of post-operative delirium in lung transplant recipients. J Heart Lung Transplant 2018;37:755–62.
[2] Andrási TB, Talipov I, Dinges G, Arndt C, Rastan AJ. Risk factors for postoperative delirium after cardiac surgical procedures with cardioplegic arrest. Eur J Cardiothorac Surg 2022;62:ezab570.
[3] Chen H, Mo L, Hu H, Ou Y, Luo J. Risk factors of postoperative delirium after cardiac surgery: a meta-analysis. J Cardiothorac Surg 2021;16:113.
[4] Witlox J, Eurelings LSM, de JJFM, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. JAMA 2010;304:443–51.
[5] Visser L, Prent A, Banning LBD, van Leeuwen BL, Zeebregts CJ, Pol RA. Risk factors for delirium after vascular surgery: a systematic review and meta-analysis. Ann Vasc Surg 2021;76:500–13.
[6] Rengel KF, Pandharipande PP, Hughes CG. Postoperative delirium. Presse Med 2018;47:e53–e64.
[7] Bucerius J, Gummert JF, Borger MA, *et al*. Predictors of delirium after cardiac surgery delirium: effect of beating-heart (off-pump) surgery. J Thorac Cardiovasc Surg 2004;127:57–64.
[8] Gosselt AN, Slooter AJ, Boere PR, Zaal IJ. Risk factors for delirium after on-pump cardiac surgery: a systematic review. Crit Care 2015;19:346.
[9] Janssen TL, Steyerberg EW, Faes MC, *et al*. Risk factors for postoperative delirium after elective major abdominal surgery in elderly patients: a cohort study. Int J Surg 2019;71:29–35.
[10] Koster S, Hensens AG, Schuurmans MJ, van der Palen J. Risk factors of delirium after cardiac surgery: a systematic review. Eur J Cardiovasc Nurs 2011;10:197–204.
[11] Staveski SL, Pickler RH, Khoury PR, *et al*. Prevalence of ICU delirium in postoperative pediatric cardiac surgery patients. Pediatr Crit Care Med 2021;22:68–78.
[12] Sugimura Y, Sipahi NF, Mehdiani A, *et al*. Risk and consequences of postoperative delirium in cardiac surgery. Thorac Cardiovasc Surg 2020;68:417–24.
[13] Burkhart CS, Dell-Kuster S, Gamberini M, *et al*. Modifiable and nonmodifiable risk factors for postoperative delirium after cardiac surgery with cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2010;24:555–59.
[14] Jin Z, Hu J, Ma D. Postoperative delirium: perioperative assessment, risk reduction, and management. Br J Anaesth 2020;125:492–504.
[15] Maniar HS, Lindman BR, Escallier K, *et al*. Delirium after surgical and transcatheter aortic valve replacement is associated with increased mortality. J Thorac Cardiovasc Surg 2016;151:815–823.e2.
[16] Ma X, Chu H, Han K, *et al*. Postoperative delirium after transcatheter aortic valve replacement: an updated systematic review and meta-analysis. J Am Geriatr Soc 2023;71:646–60.
[17] Thomas C, Kreisel SH, Oster P, Driessen M, Arolt V, Inouye SK. Diagnosing delirium in older hospitalized adults with dementia: adapting the confusion assessment method to international classification of diseases, tenth revision, diagnostic criteria. J Am Geriatr Soc 2012;60:1471–77.
[18] Ormseth CH, LaHue SC, Oldham MA, Josephson SA, Whitaker E, Douglas VC. Predisposing and precipitating factors associated with delirium: a systematic review. JAMA Network Open 2023;6:e2249950.
[19] Inouye SK. Delirium in hospitalized older patients. Clin Geriatr Med 1998;14:745–64.
[20] Sadlonova M, Duque L, Smith D, *et al*. Pharmacologic treatment of delirium symptoms: a systematic review. Gen Hosp Psychiatry 2022;79:60–75.
[21] Cai S, Li J, Gao J, Pan W, Zhang Y. Prediction models for postoperative delirium after cardiac surgery: systematic review and critical appraisal. Int J Nurs Stud 2022;136:104340.
[22] Krzych LJ, Wybraniec MT, Krupka-Matuszczyk I, Skrzypek M, Bochenek AA. Delirium Screening in Cardiac Surgery (DESCARD): a useful tool for nonpsychiatrists. Can J Cardiol 2014;30:932–39.
[23] Sadlonova M, Vogelgsang J, Lange C, *et al*. Identification of risk factors for delirium, cognitive decline, and dementia after cardiac surgery (FINDERI-find delirium risk factors): a study protocol of a prospective observational study. BMC Cardiovasc Disord 2022;22:299.
[24] Koster S, Oosterveld FGJ, Hensens AG, Wijma A, van der Palen J. Delirium after cardiac surgery and predictive validity of a risk checklist. Ann Thorac Surg 2008;86:1883–87.
[25] Vasilevskis EE, Han JH, Hughes CG, Ely EW. Epidemiology and risk factors for delirium across hospital settings. Best Pract Res Clin Anaesthesiol 2012;26:277–87.
[26] von EE, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg 2014;12:1495–99.
[27] Rashid R, Sohrabi C, Kerwan A, *et al*. The STROCSS 2024 guideline: strengthening the reporting of cohort, cross-sectional, and case-control studies in surgery. Int J Surg 2024;110:3151–65.
[28] Green JR, Smith J, Teale E, *et al*. Use of the confusion assessment method in multicentre delirium trials: training and standardisation. BMC Geriatr 2019;19:107.
[29] Inouye SK, Foreman MD, Mion LC, Katz KH, Cooney LM. Nurses' recognition of delirium and its symptoms: comparison of nurse and researcher ratings. Arch Intern Med 2001;161:2467–73.
[30] Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med 1990;113:941–48.
[31] Inouye SK, Kosar CM, Tommet D, *et al*. The CAM-S: development and validation of a new scoring system for delirium severity in 2 cohorts. Ann Intern Med 2014;160:526–33.
[32] Inouye SK, Leo-Summers L, Zhang Y, Bogardus ST, Leslie DL, Agostini JV. A chart-based method for identification of delirium: validation compared with interviewer ratings using the confusion assessment method. J Am Geriatr Soc 2005;53:312–18.
[33] Ely EW, Truman B, Shintani A, *et al*. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). JAMA 2003;289:2983–91.

[34] Ely EW, Margolin R, Francis J, *et al*. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med 2001;29:1370–79.
[35] Sadlonova M, Hansen N, Esselmann H, *et al*. Preoperative delirium risk screening in patients undergoing a cardiac surgery: results from the prospective observational FINDERI study. Am J Geriatr Psychiatry 2024;32:835–51. doi:10.1016/j.jagp.2023.12.017
[36] Robin X, Turck N, Hainard A, *et al*. pROC: an open-source package for R and S+ to analyze and compare ROC curves. BMC Bioinf 2011;12:77.
[37] Konietschke F, Placzek M, Schaarschmidt F, Hothorn LA. nparcomp: an R software package for nonparametric multiple comparisons and simultaneous confidence intervals. J Stat Soft 2015;64:1–7.
[38] López-Ratón M, Rodríguez-Álvarez MX, Suárez CC, Sampedro FG. OptimalCutpoints: an R package for selecting optimal cutpoints in diagnostic tests. J Stat Soft 2014;61:1–36.
[39] Dziak JJ, Coffman DL, Lanza ST, Li R, Jermiin LS. Sensitivity and specificity of information criteria. Brief Bioinform 2020;21:553–65.
[40] Kim JH. Multicollinearity and misleading statistical results. Korean J Anesthesiol 2019;72:558–69.
[41] Kuhn M. Building predictive models in R using the caret package. J Stat Soft 2008;28:1–26.
[42] Friedman J, Hastie T, Tibshirani R. Regularization paths for generalized linear models via coordinate descent. J Stat Soft 2010;33:1.
[43] Therneau T, Atkinson B. CRAN: Contributed Packages, 1999.
[44] Mariscalco G, Cottini M, Zanobini M, *et al*. Preoperative statin therapy is not associated with a decrease in the incidence of delirium after cardiac operations. Ann Thorac Surg 2012;93:1439–47.
[45] Kazmierski J, Kowman M, Banach M, *et al*. Incidence and predictors of delirium after cardiac surgery: results from the IPDACS study. J Psychosom Res 2010;69:179–85.
[46] Janssen TL, Alberts AR, Hooft L, Mattace-Raso F, Mosk CA, van der Laan L. Prevention of postoperative delirium in elderly patients planned for elective surgery: systematic review and meta-analysis. Clin Interv Aging 2019;14:1095–117.
[47] Raats JW, Steunenberg SL, de LDC, van der Laan L. Risk factors of post-operative delirium after elective vascular surgery in the elderly: a systematic review. Int J Surg 2016;35:1–6.
[48] Vasunilashorn SM, Ngo L, Inouye SK, *et al*. Cytokines and postoperative delirium in older patients undergoing major elective surgery. J Gerontol A Biol Sci Med Sci 2015;70:1289–95.
[49] Reinsfelt B, Ricksten S-E, Zetterberg H, Blennow K, Fredén-Lindqvist J, Westerlind A. Cerebrospinal fluid markers of brain injury, inflammation, and blood-brain barrier dysfunction in cardiac surgery. Ann Thorac Surg 2012;94:549–55.
[50] Muszynski JA, Spinella PC, Cholette JM, *et al*. Transfusion-related immunomodulation: review of the literature and implications for pediatric critical illness. Transfusion 2017;57:195–206.
[51] Simone MJ, Tan ZS. The role of inflammation in the pathogenesis of delirium and dementia in older adults: a review. CNS Neurosci Ther 2011;17:506–13.
[52] Körber MI, Schäfer M, Vimalathasan R, *et al*. Periinterventional inflammation and blood transfusions predict postprocedural delirium after percutaneous repair of mitral and tricuspid valves. Clin Res Cardiol 2021;110:1921–29.
[53] Xiao MZ, Liu CX, Zhou LG, Yang Y, Wang Y. Postoperative delirium, neuroinflammation, and influencing factors of postoperative delirium: a review. Medicine (Baltimore) 2023;102:e32991.
[54] Berger M, Terrando N, Smith SK, Browndyke JN, Newman MF, Mathew JP. Neurocognitive function after cardiac surgery: from phenotypes to mechanisms. Anesthesiology 2018;129:829–51.
[55] Newman MF, Mathew JP, Grocott HP, *et al*. Central nervous system injury associated with cardiac surgery. Lancet 2006;368:694–703.
[56] Ottens TH, Hendrikse J, Slooter AJC, van Herwerden LA, Dieleman JM, van Dijk D. Low incidence of early postoperative cerebral edema after coronary artery bypass grafting. J Cardiothorac Vasc Anesth 2015;29:632–36.
[57] van Harten AE, Scheeren TWL, Absalom AR. A review of postoperative cognitive dysfunction and neuroinflammation associated with cardiac surgery and anaesthesia. Anaesthesia 2012;67:280–93.
[58] Eifert S, Reichenspurner H, Pfefferkorn T, *et al*. Neurological and neuropsychological examination and outcome after use of an intra-aortic filter device during cardiac surgery. Perfusion 2003;18:55–60.
[59] Chen N, Mo YC, Xu M, *et al*. Risk factors for postoperative delirium in elderly patients undergoing heart valve surgery with cardiopulmonary bypass. J Cardiothorac Surg 2024;19:106.
[60] Schechter MA, Shah AA, Englum BR, *et al*. Prolonged postoperative respiratory support after proximal thoracic aortic surgery: is deep hypothermic circulatory arrest a risk factor? J Crit Care 2016;31:125–29.
[61] Kuchnicka K, Maciejewski D. Ventilator-associated lung injury. Anaesthesiol Intensive Ther 2013;45:164–70.
[62] Koch C, Li L, Figueroa P, Mihaljevic T, Svensson L, Blackstone EH. Transfusion and pulmonary morbidity after cardiac surgery. Ann Thorac Surg 2009;88:1410–18.
[63] Michaud L, Dureau P, Kerleroux B, *et al*. Development and validation of a predictive score for prolonged mechanical ventilation after cardiac surgery. J Cardiothorac Vasc Anesth 2022;36:825–32.
[64] Deininger MM, Schnitzler S, Benstoem C, *et al*. Standardized pharmacological management of delirium after on-pump cardiac surgery reduces ICU stay and ventilation in a retrospective pre-post study. Sci Rep 2023;13:3741.
[65] Stransky M, Schmidt C, Ganslmeier P, *et al*. Hypoactive delirium after cardiac surgery as an independent risk factor for prolonged mechanical ventilation. J Cardiothorac Vasc Anesth 2011;25:968–74.
[66] Mertes P-M, Kindo M, Amour J, *et al*. Guidelines on enhanced recovery after cardiac surgery under cardiopulmonary bypass or off-pump. Anaesth Crit Care Pain Med 2022;41:101059.
[67] Schneider C, Marguerite S, Ramlugun D, *et al*. Enhanced recovery after surgery program for patients undergoing isolated elective coronary artery bypass surgery improves postoperative outcomes. J Thorac Cardiovasc Surg 2024;168:597–607.e2.
[68] Giger A, Schneider C, Marguerite S, *et al*. An enhanced recovery programme significantly improves postoperative outcomes after surgical aortic valve replacement. Eur J Cardiothorac Surg 2023;63:ezad125.
[69] Akhtar MI, Sharif H, Hamid M, Samad K, Khan FH. Fast track extubation in adult patients on pump open heart surgery at a tertiary care hospital. J Ayub Med Coll Abbottabad 2016;28:639–43.
[70] Guller U, Anstrom KJ, Holman WL, Allman RM, Sansom M, Peterson ED. Outcomes of early extubation after bypass surgery in the elderly. Ann Thorac Surg 2004;77:781–88.
[71] Ender J, Borger MA, Scholz M, *et al*. Cardiac surgery fast-track treatment in a postanesthetic care unit: six-month results of the Leipzig fast-track concept. Anesthesiology 2008;109:61–66.
[72] Camp SL, Stamou SC, Stiegel RM, *et al*. Can timing of tracheal extubation predict improved outcomes after cardiac surgery? HSR Proc Intensive Care Cardiovasc Anesth 2009;1:39–47.