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Preoperative Delirium Risk Screening in Patients Undergoing a Cardiac Surgery: Results from the Prospective Observational FINDERI Study

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ABSTRACT

Objective: *Postoperative delirium (POD) is a common complication of cardiac surgery that is associated with higher morbidity, longer hospital stay, cognitive decline, and mortality. Preoperative assessments may help to identify patients' POD risk. However, a standardized screening assessment for POD risk has not been established.* ***Design:*** *Prospective observational FINd DElirium RIsk factors*

Abbreviations: ASA, American Society of Anesthesiologists; AUC, area under the curve; CAM, Confusion Assessment Method; CSHA, Canadian Study of Health and Aging; DRKS, German Clinical Trials Register; DRSQ, Delirium Risk Screening Questionnaire; FAIR, Findability, Accessibility, Interoperability, and Reuse; GCP, Good Clinical Practice; ICU, intensive care unit; IMC, intermediate care unit; MoCA, Montreal Cognitive Assessment; OR, odd ratio; POD, Postoperative delirium; RASS, Richmond Agitation-Sedation Scale; ROC, receiver operating characteristics; SMI, subjective memory impairment; STROBE, The Strengthening the Reporting of Observational Studies in Epidemiology; TMTA, Trail Making Test A; TMTB, Trail Making Test B

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TRIAL REGISTRATION: Ethics approval for this study was obtained from the IRB of the University of Göttingen Medical Center. The investigators registered this study in the German Clinical Trials Register (DRKS; https://www.drks.de) (DRKS00025095) on April 19, 2021.

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(FINDERI) study. ***Participants:*** *Patients aged ≥50 years undergoing cardiac surgery.* ***Measurements:*** *The primary aim was to analyze the predictive value of the Delirium Risk Screening Questionnaire (DRSQ) prior to cardiac surgery. Secondary aims are to investigate cognitive, frailty, and geriatric assessments, and to use data-driven machine learning (ML) in predicting POD. Predictive properties were assessed using receiver operating characteristics analysis and multivariate approaches (regularized LASSO regression and decision trees).* ***Results:*** *We analyzed a data set of 504 patients (68.3 ± 8.2 years, 21.4% women) who underwent cardiac surgery. The incidence of POD was 21%. The preoperatively administered DRSQ showed an area under the curve (AUC) of 0.68 (95% CI 0.62, 0.73), and the predictive OR was 1.25 (95% CI 1.15, 1.35, p <0.001). Using a ML approach, a three-rule decision tree prediction model including DRSQ (score>7), Trail Making Test B (time>118), and Montreal Cognitive Assessment (score ≤ 22) was identified. The AUC of the three-rule decision tree on the training set was 0.69 (95% CI 0.63, 0.75) and 0.62 (95% CI 0.51, 0.73) on the validation set.* ***Conclusion:*** *Both the DRSQ and the three-rule decision tree might be helpful in predicting POD risk before cardiac surgery.* (Am J Geriatr Psychiatry 2024; 32:835−851)

Editorial accompaniment, please see page 852.

Highlights

- **What is the primary question addressed by this study?**
  Primary question addressed by study: We performed a prospective observational study to examine the ability of a delirium risk assessment tool (Delirium Risk Screening Questionnaire [DRSQ]) to predict postoperative delirium (POD) in patients undergoing cardiac surgery.
- **What is the main finding of this study?**
  Main finding of this study: POD is highly prevalent in patients after cardiac surgery (incidence of 21%). The DRSQ performed fairly well at identifying POD incidence and have the potential to be used clinically for predicting POD following cardiac surgery.
- **What is the meaning of the finding?**
  Meaning of the finding: The DRSQ has the potential to be used clinically for predicting POD following cardiac surgery that can be addressed before cardiac surgery in a POD prevention program.

INTRODUCTION

Postoperative delirium (POD) is characterized as an acute, rapidly occurring condition with fluctuating episodes of inattention, disorganized thinking, and altered level of consciousness.[1] POD is a common, potentially serious, but often unrecognized complication of cardiac surgery.[2−4] The incidence of POD during hospital stay is high, especially in elderly and critically ill adults, and it varies from 8% to 55% after cardiac surgery.[5−11] POD has been linked to longer hospital and intensive care unit (ICU) stay,[7,9,12,13] greater prevalence of falls,[12] greater likelihood of discharge to a nursing facility,[12,14] higher risk of hospital readmission,[15] and higher need for inpatient physical therapy and home health services after discharge.[12] Furthermore, POD is associated with higher risk of mortality,[16,17] decreased quality of life,[15] postoperative cognitive dysfunction, dementia,[14,15,18−22] and functional decline.[15,23] The increasing evidence for poor prognosis in patients with POD highlights the importance of both prevention and early recognition of POD in patients after cardiac surgery, as this has the potential to improve both short- and long-term outcomes.[15]

Assessment of risk for POD seems to be important for prevention and early treatment of POD[24] and might help to stratify patients at low, medium, and high POD risk.[25] Risk for POD is determined by

patient-related predisposing factors and treatment-associated precipitating factors.[26,27] Increasing age, pre-existing cognitive impairment, psychiatric disorders (e.g., depression), cerebrovascular disease (e.g., carotid artery stenosis), kidney failure, New York Heart Association (NYHA) functional class III or IV, low albumin, diabetes, and higher American Society of Anesthesiologists (ASA) score are consistent patient-related predisposing factors for POD.[10,28] Regarding treatment-associated factors, cardiopulmonary-bypass time, transfusion, postoperative atrial fibrillation, intraoperative pO2, pCO2, temperature, and hemodilution seem to increase the risk of POD.[11,29]

While the European Society of Anesthesiology (ESA) recommends preoperative evaluation of POD risk,[26] a standardized screening assessment for POD risk in patients undergoing cardiac surgery has not been established. Previous studies[6,24,30–32] investigated a variety of POD prediction scores, models, or checklists in patients undergoing cardiac or noncardiac surgery. For example, the DELIPRECAS prediction model[32] consisted of 4 preoperative risk factors (age >65 years, Mini-Mental State Examination [MMSE] score, insomnia needing medical treatment, and low physical activity). The PROPDESC score[30] estimates POD risk based on age, ASA, NYHA, operative risk, and short cognitive assessment using the attention and language portions of the Montreal Cognitive Assessment (MoCA). Further, a prediction rule of 4 preoperative characteristics (prior stroke or transient ischemic attack, MMSE score, abnormal serum albumin, and Geriatric Depression Scale) might be used to determine cardiac surgery patients´ risk for POD.[6] Lindroth et al.[24] developed a two-factor model consisting of the National Surgical Quality Improvement Program risk calculation for serious complication (NSQIP-SC) and the Trail Making Test B (TMTB) using advanced modeling techniques. In cardiac surgery, only a few studies have investigated a reliable and time-efficient risk screening instrument for POD risk that can be incorporated into the preoperative daily routine of cardiac surgery. Furthermore, previous studies investigating POD risk assessment tools have several limitations, including small numbers of participants,[6] mixed cohorts of cardiac- and non-cardiac surgery patients,[24,25,30] delirium diagnostic methods not using standardized screening tools such as Confusion Assessment Method-ICU (CAM-ICU),[33] or missing incorporation of patients´ comorbidities (e.g., prior stroke or previous delirium or substance use).[30]

To extend the current scientific evidence and close the gap, we performed a prospective observational study to examine the ability of a delirium risk assessment tool (Delirium Risk Screening Questionnaire [DRSQ])—developed along the cluster-randomized PAWEL study[34]—to predict POD in patients undergoing cardiac surgery (primary aim). The DRSQ is completed preoperatively and assesses multiple POD risk factors (e.g., brief bedside cognitive and geriatric testing, comorbidities, functional status)[34] that might be helpful in preventing POD in patients at high risk. Our secondary aim was to analyze predictive values of different cognitive, frailty, and geriatric assessments and to use data-driven machine learning (LASSO regression and decision tree) to predict POD in patients undergoing cardiac surgery.

METHODS

Study Design

FINDERI[35] is a prospective, single-center, observational study. In total, over 500 patients aged 50 years or older undergoing an elective cardiac surgery were recruited between February 2021 and October 2022 at the Department of Cardiovascular and Thoracic Surgery of the University Medical Center Göttingen, Germany. Inclusion and exclusion criteria are summarized in Table 1. Informed consent was obtained by the study team after providing detailed study information and prior to baseline assessment. Initially, preoperative POD risk assessment, sociomedical history, cognitive, geriatric and frailty assessments were performed before cardiac surgery (t0). Furthermore, POD symptoms were assessed over the first five postoperative days (t1) after cardiac surgery. Ethical approval was obtained from the Ethics Committee of the University of Göttingen Medical Center (#20/11/20) on February 16, 2021. A detailed study protocol was published previously.[35] The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement and guidelines for reporting observational studies were followed.[36]

TABLE 1. Inclusion and Exclusion Criteria of the FINDERI Study

Inclusion criteria
Age ≥ 50 y
Hospitalized in the Department of Cardiovascular and Thoracic Surgery for an elective cardiac surgery
Ability to speak, read and understand German
Ability to provide informed consent
Exclusion criteria
Age < 50 y
Severe cognitive impairment (e.g., dementia or inability to follow the assessment instructions)
Communication difficulties (e.g., severe hearing loss, aphasia)
Participation in an intervention trial likely to affect the outcomes of interest

Preoperative Screening (t0)

The DRSQ (Table 2, Supplementary File S1) was adapted from the multicenter, stepped-wedge, cluster randomized PAWEL study [34] and used as an assessment of POD risk. The DRSQ consists of the following parts: A) PART I: Geriatric check[37,38] consists of five items (mobility, statutory level of independence, cognition, psychological symptoms, and previous hospital stay). Each item can be score with "yes" or "no." If patients have two or more answers with "yes," they are likely to be geriatric patients. In the validation studies,[37,38] the geriatric check was shown to be a useful and valid tool for the identification of geriatric inpatients of emergency departments and neurological wards. B) PART II: six-item Cognitive Impairment Test (6-CIT)[39–42] consists of the following items: orientation (year, months, time), memory and repetition, counting from 20 to 1 backwards, saying months of the year reverse. A score between 0 and 28 (rating correct answers = 0 points and incorrect answers with 2 −10 points) can be reached. Scores between 0 and 7 are considered normal; 8−9 as mild cognitive impairment, and 10−28 as cognitive impairment. The 6-CIT is a brief and simple test of cognition, which correlates with the MMSE and out-performs it in milder dementia.[39] Furthermore, the 6-CIT also has good diagnostic accuracy for delirium detection in emergency department.[41] C) PART III: General information (19 items) including results from A) and B), age > 80 years,[2,10,28,43] laboratory measurement[2,28,44] (i.e., creatinine > 1.00 mg/dL; CRP > 5 mg/L; hemoglobin <11.5 g/dL; protein <6.6g/dL; electrolytes out of the norm) that were measured as a part of routine preoperative care, and an ASA score ≥ 3.[28,43,45] The patient's current medications are also noted; however, particular attention is paid to the number of medications[44] and medications known to be associated with delirium.[44] Furthermore, preoperative diagnosis[28] of depression, stroke, or dementia, previous hospital stays within the last year, the patient's level of care, and whether the patient is a nursing home resident[28] were obtained. Study participants were asked about previous delirium/POD[43] and a recent increase in number of falls.[46–48] Another component of the assessment was the self-reported subjective memory impairment (SMI),[28] alcohol use,[49,50] and smoking status.[43] Finally, muscle strength [48] (i.e., the patient's handgrip strength) was measured by the Jamar® Hydraulic Hand Dynamometer.

Additionally, basic sociodemographic information and cardiac and non-cardiac comorbidities were collected. Frailty was assessed using the 7-point Clinical Frailty Scale of the Canadian Study of Health and Aging (CSHA Frailty Scale, 1-very fit up to 7-severely frail).[51] The patient's preoperative cognitive status was measured using MoCA,[52] the Trail Making Test A, and the Trail Making Test B (TMTA, TMTB).[53–56] The MoCA [52] is a 30-point brief cognitive screening tool with high sensitivity (0.90) and specificity (0.87) to detect patients with mild cognitive impairment. The TMT is a widely used neuropsychological instrument to assess the speed of cognitive processing, visuomotor tracking, divided attention, and cognitive flexibility.[53–56] TMTB had a specificity of 0.89, and a sensitivity of 0.63 for cognitive dysfunction, and 0.72 for dementia [53–56].

Postoperative Delirium Screening (t1)

After cardiac surgery, all study participants were assessed twice a day (in the morning between 8 and 10 A.M. and evening between 4 and 6 P.M.) using the CAM-ICU in the ICU and the I-CAM in the intermediate care unit or general unit. The screening of POD using the CAM-ICU and I-CAM was performed by trained study staff (doctoral students). These staff members received training on the use of the CAM-ICU and I-CAM, as well as on the DMS-5 and the International Classification of Diseases, Tenth Revision (ICD-10) diagnostic criteria of delirium, and they engaged in supervisory meetings (weekly or once in two weeks) with s senior consultation-liaison

TABLE 2. Delirium Risk Screening Questionnaire, Modified From the Multicenter, Cluster-Randomized PAWEL Trial [34])

PART I. Impairment preceding the current event/ illness (Geriatric Check)		
PART II. PART II: 6-item Cognitive Impairment Test (6-CIT)		
PART III. General information		
Likely to be a geriatric patient according to geriatric check	Yes	☐
6-CIT test result:	Yes	☐
Mild cognitive impairment Considerable cognitive impairment	Yes	☐☐[1]
Age > 80 y	Yes	☐
Laboratory measurements		
Increased creatinine levels	Yes	☐
Increased CRP levels	Yes	☐
Reduced Hb	Yes	☐
Electrolytes out of norm	Yes	☐
Reduced protein levels	Yes	☐
ASA ≥ 3	Yes	☐
More than 6 medications per day	Yes	☐
Medication with potential to cause delirium (see list; at least 1 of those)	Yes	☐
Dementia diagnosis	Yes	☐
Depression diagnosis	Yes	☐
Stroke diagnosis	Yes	☐
Parkinson's diagnosis	Yes	☐
Level of Care (German care level ≥ 1)	Yes	☐
Nursing home resident	Yes	☐
Did you suffer from delirium / acute confusion during another hospital stay?	Yes	☐
Did you trip or fall / nearly fall during the last few months?	Yes	☐
How many/Which alcoholic beverages do you consume per day on average?		
Wine/ beer/ other	More than 5	☐
Current smoking behavior:		
Daily	Correct	☐
Self-reported subjective memory impairment (SMI)		
Do you feel like your memory is declining? If so, does that significantly bother you?	Yes	☐
	Yes, it bothers me significantly	☐☐[1]
Manual force:		
< 20 kg for women	Yes	☐
< 32 kg for men		
	Sum of checked items:	

Notes. Evaluation (sum of checked items): < 2: no further measures necessary; 2-4: Further clarification concerning the risk for postoperative delirium if necessary, consult geriatrician/ neurologist; > 4: Note down and apply measures for further actions, suitable measures can also be found in the therapeutic concept. If existing, SOP's (Standard Operating Procedures) should be applied to guarantee an optimal support for patients at risk during their in-patient stay. [1]Counts as two checked items.

psychosomatic specialist (MS) from the Department of Cardiac Surgery after training had been completed.[57,58] The CAM[59–63] is a standardized, evidenced-based tool for delirium screening at the bedside. We used a modified form of the CAM algorithm; specifically, we used a short form of CAM[63,64] with adding psychomotor change to the CAM algorithm (I-CAM,[62] I represents the ICD-10) in the intermediate care unit or general unit involving the following features as worksheets for the raters: acute onset, inattention, disorganized thinking, altered level of consciousness,[63] and psychomotor change.[62] POD was present if the following aspects were present [63]: acute change or fluctuation and inattention and/either disorganized thinking or altered level of consciousness. The psychomotor change was used to support the above mentioned POD presence, and the POD subtype (e.g., hyperactive or hypoactive POD).[34,62] The administration of the short form of CAM typically takes 3 minutes.[59,63] The CAM-ICU is an adaptation of the CAM for critically ill patients on or off the ventilator. After monitoring the patients' level of consciousness by the Richmond Agitation-Sedation Scale (RASS) and ruling out coma, the four features of the CAM-ICU were completed. The CAM-ICU shows a high sensitivity of 0.95–1.00 and a specificity of 0.89–0.93 with inter-rater reliability ranging from 0.88 to 1.0.[59–62] The assessment of CAM-ICU typically takes 2–3 min.[61] The I-CAM has a high sensitivity of 0.77 in a cohort of geriatric patients with a high prevalence of dementia and a specificity of 0.96–1.00 with inter-rater reliability of 0.95.[59–62]

Statistical Analysis

The sample size of 500 patients was chosen specifically based on estimating the area under the curve (AUC) of the POD risk assessment for the occurrence of POD with a 95% confidence interval so that the 95% confidence interval has a width of approximately 0.05 points. For planning purposes, it was assumed that the incidence of POD would be 50% [6] and that there is a true AUC of 0.7. If 416 patients were analyzed, the 95% confidence interval extended approximately 0.025 points from the estimate. To compensate for possible dropouts (assumed dropout rate approx. 20%), the total sample size of 500 patients was necessary. The calculation was performed in nQuery.

All analyses were performed using the statistical programming environment R, version 4.2.2. For the description of the study sample, continuous variables are reported as mean values (M) and standard deviations (SD). Categorial variables are expressed as absolute or relative frequencies (%). Differences between patients with and without POD in categorical variables were tested with Pearson's Chi-squared tests. The differences in continuous variables were tested with Welch Two Sample t-test. Throughout, two-sided p-values smaller than 0.05 are interpreted as statistically significant. Initially, univariate consideration of the individual parameters (DRSQ, cognitive, geriatric and frailty assessments) was performed.

A receiver operating characteristics (ROC)-analysis was conducted to assess univariate prognostic properties of outcomes, and the associated AUC is reported with logit-transformed 95%-confidence intervals using a bootstrapped permutation approach and optimal cut-off points (simultaneous maximization of sensitivity and specificity, as well as according to Youden).[65,66] Furthermore, sensitivity, specificity, positive and negative predictive values for the optimal cut-off point are reported.[67] Odds-ratios are reported together with 95% confidence intervals (CI).

For multivariate consideration of predictive factors, machine learning (ML) methods for supervised learning were employed, specifically regularized LASSO logistic regression and classification decision trees with a maximum depth of four and a minimum of 30 observations for a split following the Gini index.[68,69] Candidate models were trained on a training data set (70% of the data collected chosen at random) using ten-fold cross-validation. The candidate models were validated on a validation set consisting of the remaining 30% of data collected.[70]

Data Management

All outcomes were entered into a Good Clinical Practice (GCP) compliant database (secuTrial), configured for the presented study. The configuration includes univariate checks for plausibility, such as range checks. Data were reviewed regularly for completeness by qualified personnel and locked after review. A blinded data review (without knowledge of the development of POD) to assess data quality was performed prior to database lock. An anonymized copy of the data set can be provided alongside the publication to ensure the reproducibility of results. The investigators follow the Findability, Accessibility, Interoperability, and Reuse (FAIR) Guiding Principles for scientific data management and stewardship.[71]

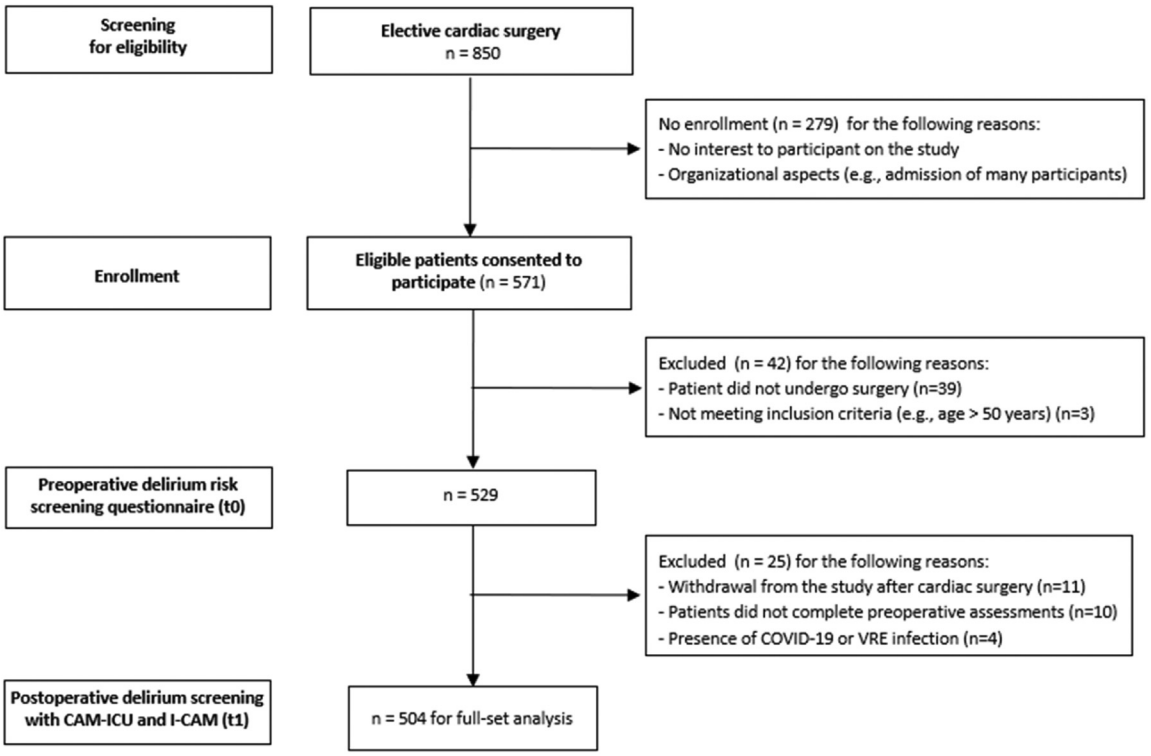
RESULTS

Participants

In total, 571 eligible patients consented to participate in this observational study. The flow chart (Fig. 1) shows the case number and the exclusion criteria from the analysis. Thirty-nine patients did not undergo a cardiac surgery for various reasons (e.g., frailty, discharge before surgery) during the observation period. Ten patients did not complete the preoperative assessments for various reasons (e.g., long duration of medical examination before surgery). Eleven patients withdrew the study consent. Four patients were isolated due to COVID-19 (n = 3) or Vancomycin-resistant Enterococci infection (n=1), and the raters were not able to perform the postoperative assessments. Three patients were removed due to age < 50 years (n=1) and participants who needed a healthcare power of attorney and were not able to provide informed consent (n=2). Ultimately, 504 patients were included in the full-analysis set.

Sociodemographic, clinical, and outcome variables are shown in Table 3. The total study sample had a mean age of 68.3 ± 8.2 years (21.4% women). Most study participants had an ASA score of 3. The most commonly performed surgery type was the coronary

FIGURE 1. Trial flow diagram



artery bypass graft (CABG) surgery; this was performed as a combined surgery (with a valve surgery) in 50 patients (9.9%). Overall, 85.3% of the study sample received cardiopulmonary bypass (CPB), and the surgery duration was 262.0 ± 83.8 minutes.

POD incidence in the study sample was 21.0% (n = 106, 95% CI 0.18, 0.25). Patients with POD were older, more often retired, and more likely to have heart failure, diabetes, a history of smoking, and a longer duration of surgery than patients without POD. Considering the preoperative assessments, patients with POD showed higher scores in DRSQ, 6-CIT, Geriatric Check Impairment Score and CSHA frailty score. They took longer to complete TMTA and TMTB, and they had lower MoCA scores than patients without POD.

Prediction Model of Delirium Risk Screening Questionnaire

Using ROC analysis (Fig. 2), we determined an AUC of 0.68 (95% CI 0.62, 0.73) for the DRSQ in predicting POD after cardiac surgery. In the univariate logistic regression analysis (Table 4), the predictive OR was 1.25 (95% CI 1.15, 1.35, p <0.001). The optimal cut-off value by simultaneous maximization of specificity and sensitivity was six, with sensitivity of 0.61 (95% CI 0.51, 0.71) and specificity of 0.67 (95% CI 0.62, 0.72) (Supplementary File S2a).

Prediction Model of Cognitive Assessments

In ROC analysis for MoCA (Fig. 3A), the AUC was 0.62 (95% CI 0.57, 0.68), and the predictive OR was 0.86 (95% CI 0.81, 0.92, p <0.001). Considering the ROC of the 6-CIT (Fig. 3B), the AUC was 0.61 (95% CI 0.54, 0.66). The predictive OR of the 6-CIT was 1.14 (95% CI 1.06, 1.12, p < 0.001). Considering TMTA (Fig. 3C), the AUC was 0.64 (95% CI 0.58, 0.70) and OR 1.01 (95% 1.01, 1.02). For TMTB (Fig. 3D), an AUC of 0.67 (95% CI 0.60, 0.72) and OR of 1.01 (95% CI 1.0, 1.0) were found. The optimal cut-off values of MoCA, 6-CIT, TMTA and TMTB by simultaneous

TABLE 3. Baseline Characteristics of the FINDERI Study Sample, Overall and Split up by POD

	Total sample		Patients without POD		Patients with POD		
	N	Mean ± SD or N (%)	N	Mean ± SD or N (%)	N	Mean ± SD or N (%)	p
Age (years)	504	68.3 ± 8.2	385	67.6 ± 8.3	106	71.0 ± 7.7	<0.001
Women	504	108 (21.4%)	385	76 (19.7%)	106	30 (28.3%)	0.078
Demographic characteristics							
Married or in relationship	500	384 (76.8%)	383	297 (77.5%)	104	77 (74.0%)	0.110
Migration background	500	32 (6.4%)	383	23 (6.0%)	104	9 (8.7%)	0.500
Retired	500	350 (70.0%)	383	258 (67.4%)	104	82 (78.8%)	0.002
Comorbidities							
Coronary heart disease	504	368 (73.0%)	385	279 (72.5%)	106	82 (77.3%)	0.600
Heart valve disease	504	318 (63.1%)	385	232 (60.3%)	106	77 (72.6%)	0.056
Heart failure	500	365 (73.0%)	382	268 (70.2%)	104	84 (80.8%)	0.027
NYHA I	362	32 (8.8%)	266	28 (10.5%)	83	4 (4.8%)	0.300
NYHA II		144 (39.8%)		108 (40.6%)		29 (34.9%)	
NYHA III		173 (47.8%)		121 (45.5%)		46 (55.4%)	
NYHA IV		13 (3.6%)		9 (3.4%)		4 (4.9%)	
Atrial fibrillation	503	105 (20.9%)	384	73 (19.0%)	106	29 (27.4%)	0.094
Aortic aneurysm	503	40 (8.0%)	384	29 (7.6%)	106	8 (7.5%)	0.600
Carotis artery stenosis	503	69 (13.7%)	384	50 (13.0%)	106	17 (16.0%)	0.300
History of stroke	503	54 (10.7%)	384	38 (9.9%)	106	15 (14.2%)	0.200
Renal insufficiency	503	64 (12.7%)	384	46 (12.0%)	106	17 (16.0%)	0.085
Diabetes mellitus type 2	503	150 (29.8%)	384	102 (26.6%)	106	46 (43.4%)	0.001
Smoking	501	78 (15.5%)	384	62 (16.1%)	104	14 (13.5%)	0.300
History of smoking	501	300 (59.9%)	384	222 (57.8%)	104	71 (68.2%)	0.023
Depressive disorder	503	61 (12.1%)	384	41 (10.7%)	106	18 (17.0%)	0.200
Anxiety disorder	503	23 (4.6%)	384	19 (4.9%)	106	3 (2.8%)	0.400
ASA (0-5)							0.110
ASA 0	499	8 (1.6%)	381	5 (%)	105	3 (2.9%)	
ASA 1		4 (0.8%)		4 (%)		0 (0%)	
ASA 2		40 (7.9%)		25 (7.9%)		14 (13.3%)	
ASA 3		419 (83.1%)		327 (78.5%)		83 (79.0%)	
ASA 4		28 (5.6%)		20 (13.6%)		5 (4.8%)	
Cardiac surgery							
CABG	504	329 (65.3%)	385	255 (66.2%)	106	68 (64.2%)	0.800
Heart valve surgery	504	230 (45.%)	385	169 (43.9%)	106	54 (50.9%)	0.200
Combined CABG and heart valve	504	50 (9.9%)	385	36 (9.4%)	106	12 (11.3%)	0.700
Cardiopulmonary bypass	504	430 (85.3%)	382	326 (87.4%)	106	91 (85.8%)	0.900
Surgery duration (min)	504	262.0 ± 83.8	385	249.6 ± 70.7	106	288.2 ± 92.6	<0.001
Preoperative assessments							
Delirium Risk Screening Questionnaire (0-27)	503	5.2 ± 2.6	384	4.8 ± 2.6	106	6.5 ± 2.6	<0.001
6-Item Cognitive Impairment Test (0-28)	500	2.9 ± 3.0	383	2.7 ± 2.8	104	3.9 ± 3.4	<0.001
Impairment Score (0-5)	500	1.0 ± 1.1	383	0.9 ± 1.1	104	1.3 ± 1.2	0.002
MoCA (0-30)	499	23.8 ± 3.6	382	24.3 ± 3.4	104	22.3 ± 4.1	<0.001
TMTA time (s)	486	63.4 ± 32.2	375	60.0 ± 30.6	98	75.9 ± 36.2	<0.001
TMTB time (s)	453	143.2 ± 80.7	359	134.8 ± 72.8	82	178.8±104.2	<0.001
CSHA (1-7)	498	3.1 ± 1.0	381	3.0 ± 0.9	104	3.5 ± 1.0	<0.001

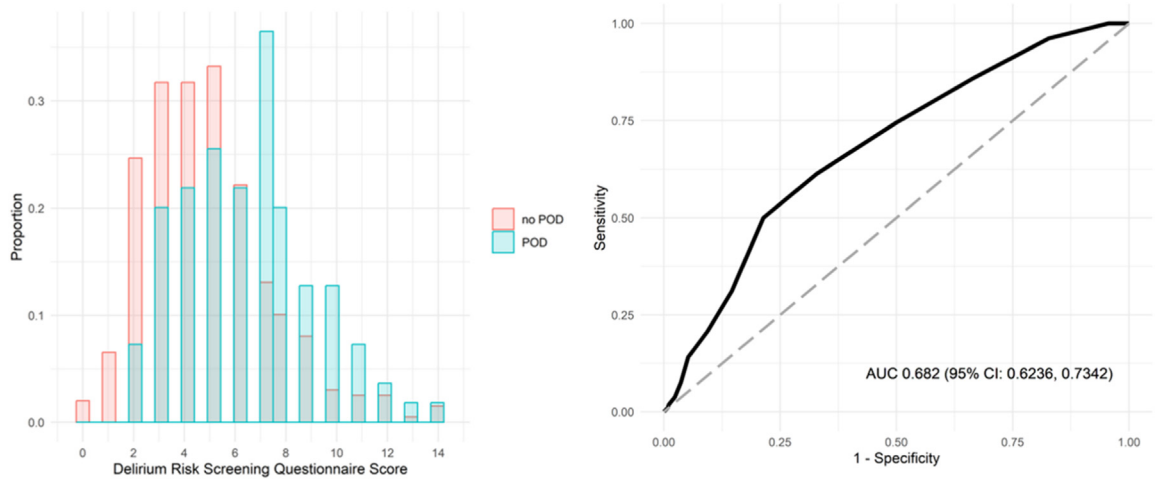
Note. ASA: American Society of Anesthesiologists; CBAG: coronary bypass artery grafting; CSHA: Clinical Frailty Scale of the Canadian Study of Health and Aging; MoCA: Montreal Cognitive Assessment; NYHA = New York Heart Association; TMTA: Trail Making Test A; TMTB: Trail Making Test A; POD: postoperative delirium. Differences in categorical variables were tested with Pearson's Chi-squared tests. Differences in continuous variables were tested with Welch Two Sample t-test.

maximization of specificity and sensitivity are presented in Supplementary File S2b-e.

Prediction Model of Geriatric and Frailty Assessments

In ROC analysis for the Geriatric Check (Fig. 4A), the AUC was 0.60 (95% CI 0.55, 0.66), and the predictive OR was 1.35 (95% CI 1.12, 1.61, p <0.001). Considering the CSHA frailty score (Fig. 4B), the AUC was 0.63 (95% CI 0.57, 0.69), and the predictive OR was 1.60 (95% CI 1.29, 2.01, p <0.001). The optimal cut-off values of the Geriatric Check and CSHA Frailty Score by simultaneous maximization of specificity and sensitivity are presented in Supplementary File S2f-g.

FIGURE 2. ROC of Delirium Risk Screening Questionnaire in predicting POD *Note.* AUC = area under the curve; CI: confidence interval; POD: postoperative delirium; ROC: receiver operating characteristics.



Multivariate Logistic Regression and ML Approach of Preoperative Assessments

The regularized LASSO multivariate regression was performed on a subset of clinically relevant preoperative variables (DRSQ, 6-CIT, MoCA, TMTA, TMTB, Geriatric Check Impairment Score, CSHA frailty score). Non-zero regression coefficient estimates were found for DRSQ and MoCA, while other variables were estimated to have no additional predictive properties. The predictive OR for DRSQ was 1.20 (95% CI 1.10, 1.31, p <0.001). The OR for MoCA was 0.90 (95% CI 0.85, 0.96, p = 0.002). The AUC, using the predictive probability of POD, on the training set was 0.74 (95% CI 0.67, 0.79, p <0.001) and 0.64 (95% CI 0.52, 0.74, p = 0.02) on the validation set (Table 5, Fig. 5). Sensitivity and specificity at optimal cut-points were 71.6% and 72.48%, respectively, for the training set, and 60% and 62.2%, respectively, for the validation set (Supplementary File S3a-b).

A decision tree was calculated using the same subset of clinically relevant variables as for the regularized LASSO multivariate regression. The decision tree revealed a classification algorithm using DRSQ, TMTB and MoCA scores. The AUC using predictive probability of POD on the training set was 0.69 (95% CI 0.63, 0.75) and 0.62 (95% CI 0.51, 0.73) on the validation set (Table 5, Fig. 5). Sensitivity and Specificity at optimal cut-points were 44.74% and 88.81%, respectively, for the training set, and 26.7% and 90.6%, respectively, for the validation set Supplementary File S3c-d). Of this tree, a subset for classification was identified to be more suited for clinical practice. The identified tree consisted of using three judgement rules for the prediction of POD: DRSQ (score > 7), TMTB (time > 118), and MoCA (score ≤ 22) (Fig. 6). The accuracy rate of the sub tree was 81.6%. The sensitivity, specificity, positive predictive value, and negative predictive value were 16.7%, 98.2%, 71.4%, and 82.1%, respectively (Table 5).

TABLE 4. Univariate Logistic Regression Analysis of Preoperative Assessments

Characteristic	N	OR	95% CI	p-Value
Delirium Risk Screening Questionnaire	490	1.25	1.15, 1.35	<0.001
MoCA	486	0.86	0.81, 0.92	<0.001
6-Item Cognitive Impairment Test	487	1.14	1.06, 1.22	<0.001
CSHA	485	1.60	1.29, 2.01	<0.001
Impairment Score	487	1.35	1.12, 1.61	0.001
TMTA time (seconds)	473	1.01	1.01, 1.02	<0.001
TMTB time (seconds)	441	1.01	1.00, 1.01	<0.001

Note. CI: confidence interval; CSHA: Clinical Frailty Scale of the Canadian Study of Health and Aging; MoCA: Montreal Cognitive Assessment; OR: odds ratio; TMTA: Trail Making Test A; TMTB: Trail Making Test A.

FIGURE 3. ROCs of cognitive assessments (MoCA, 6-CIT, TMTA, TMTB) in predicting POD ***Note.*** **6-CIT = 6-Item Cognitive Impairment Test; AUC: area under the curve; CI: confidence interval; MoCA: Montreal Cognitive Assessment; POD: postoperative delirium; ROC: receiver operating characteristics; TMTA: Trail Making Test A; TMTB: Trail Making Test A.**

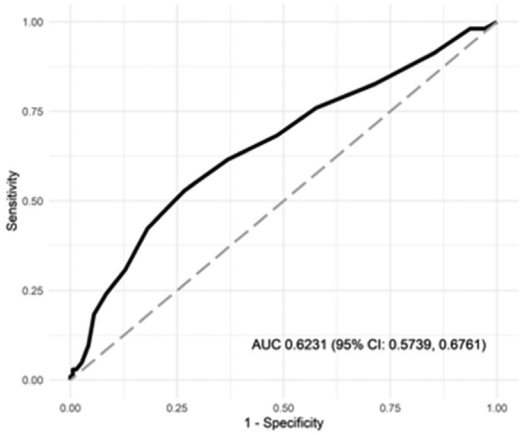


Figure 3a. MoCA

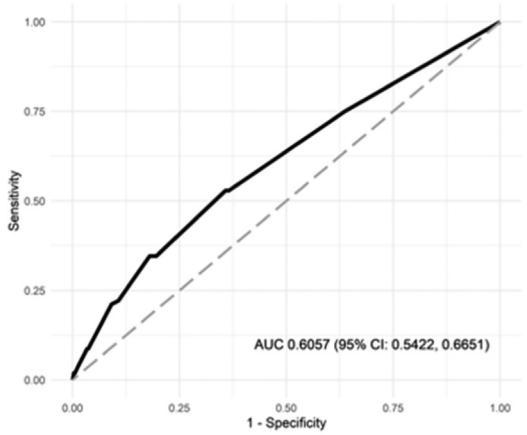


Figure 3b. 6-CIT

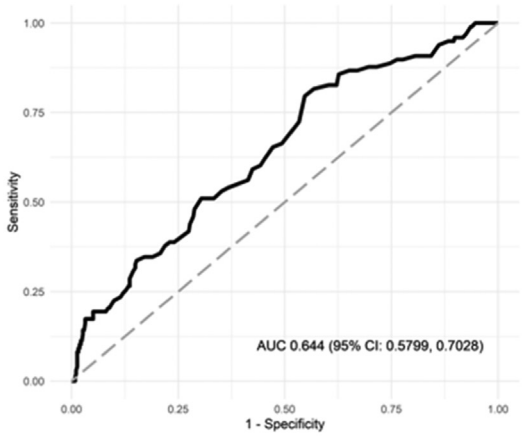


Figure 3c. TMTA

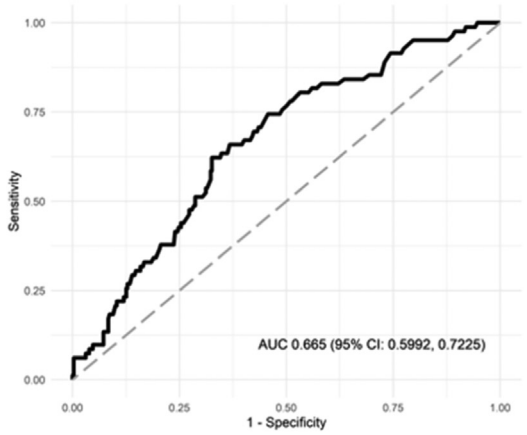


Figure 3d. TMTB

DISCUSSION

In this prospective observational study, of 504 patients undergoing cardiac surgery, we found that the incidence of POD was 21.0%. Both the DRSQ and a ML-driven, three-rule decision tree prediction model (consisting of the DRSQ, TMTB, and MoCA) performed fairly well at identifying POD incidence and have the potential to be used clinically for predicting POD following cardiac surgery.

The incidence of POD with 21% was comparable with several studies investigating POD in patients undergoing cardiac surgery.[25,30,31] Other studies showed a slightly lower POD incidence of 16%–17% in patients who underwent cardiac surgery.[5,32,72] In contrast, there are studies reporting higher POD incidence ranging from 34 to 52%.[6,50] The differences might be caused by patient characteristics (e.g., type of surgery, age, comorbidities), methodological approaches in the studies (e.g., different detection of POD) or a broad variety of pre-existing and precipitating POD risk factors. Additionally, our method of training the study or clinical staff might also have led to differences in POD incidence.[57,58] For example, a study comparing nurse ratings for delirium using

FIGURE 4. ROCs of geriatric and frailty assessments (Geriatric Check and CSHA Frailty Score) in predicting POD *Note.* AUC = area under the curve; CI: confidence interval; CSHA: Clinical Frailty Scale of the Canadian Study of Health and Aging; POD: postoperative delirium; ROC: receiver operating characteristics.

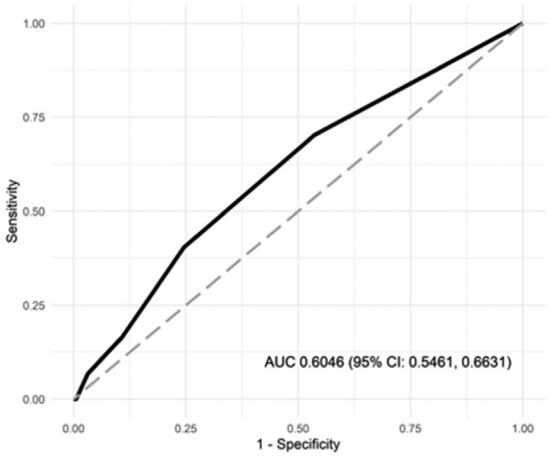


Figure 4a. Geriatric Check

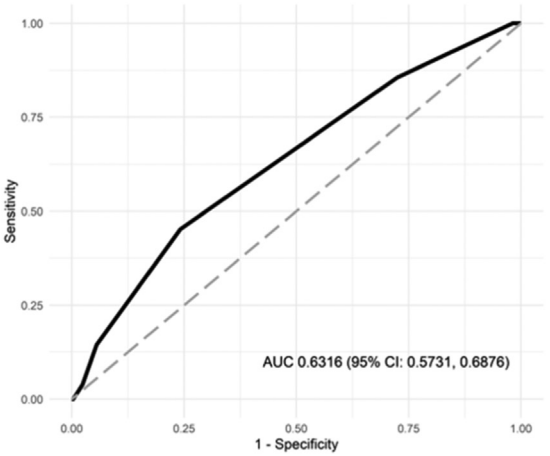


Figure 4b. CSHA Frailty Score

CAM based on routine clinical observations with researcher ratings based on cognitive testing showed that nurses often missed delirium when present.[58] There were four independent risk factors for under-recognition by nurses: hypoactive delirium, age 80 years or older, vision impairment, and dementia.[58] Therefore, a standardized training program for POD recognition might lead to high quality delirium assessments, especially for standardization of research methodology in multicenter studies.[57]

Nevertheless, the incidence of POD after cardiac surgery is high, and its occurrence is associated with serious adverse outcomes, and up to $64,000 addition health costs per patient with delirium per year (ranging from $38 to $152 billion/per year).[73] An estimated 30%−40% of cases of delirium are preventable,[74] and identification of POD risk factors and prevention of POD may be the most effective strategy for minimizing the occurrence and clinical consequences of POD.

The presented DRSQ showed acceptable performance in predicting POD after cardiac surgery. The estimated time of the questionnaire performance is 6 −7 minutes. The questionnaire combines different risk factors: cognition (subjective and objective), geriatric assessment, comorbidities, history of delirium, laboratory measurements (routine measurements), and functional measurement of muscle strength with hand grip. It allows for the assessment of important pre-existing POD risk factors.[26,27] Considering Prediction model Risk Of Bias ASsessment Tool (PROBAST) criteria,[75] this screening tool might have the potential to be integrated into electronic health record (EHR) system for delirium risk screening with minimal cost burden (e.g., Jamar Hydraulic Hand Dynamometer). In the decision tree, a three-rule algorithm with an accuracy of 81.6% was identified. However, the disadvantage of this algorithm is the time performance of all assessments (DRSQ, TMTB, MoCA) of around 15 minutes. Previous studies investigated different prediction models for POD following cardiac surgery as well. For example, the PROPDESC (age, ASA, NYHA, operative risk, short MoCA assessment) score in cardiac and non-cardiac patients[30] and DELIPRECAS (age, MMSE, insomnia needing medical treatment, low physical activity) model in patients undergoing cardiac surgery[32] showed a promising performance with AUC of 0.73 and 0.79, respectively in the validation cohort. Another prediction model in cardiac surgery consisting of MMSE, Geriatric Depression Scale, prior stroke/transient ischemic attack, and abnormal serum albumin showed an AUC of 0.6.[72] The PROPDESC score[30] seems to a good and easily implemented prediction model into the daily routine of cardiac surgery. However, this

TABLE 5. Model Performances in POD Prediction in Training and Validation for Regularized LASSO Multivariate Regression and Decision Tree

	AUC	AUC.lower 95%-CI	AUC.upper 95%-CI	AUC p value	Accuracy	Accuracy.lower 95%-CI	Accuracy.upper 95%-CI	Sensitivity	Specificity	PPV	NPV
LASSO: Training	0.7410	0.6730	0.7997	<0.0001	0.2330	0.1891	0.2817	0.8395	0.0426	0.2159	0.4583
LASSO: Validation	0.6403	0.5234	0.7415	0.02	0.8026	0.7304	0.8627	0.1200	0.9370	0.2727	0.8440
Decision Tree: Training	0.6905	0.6293	0.7513	<0.0001	0.7994	0.7531	0.8405	0.1184	0.9925	0.8182	0.7988
Decision Tree: Validation	0.6219	0.5085	0.7323	0.037	0.8163	0.7441	0.8753	0.1667	0.9829	0.7143	0.8214

Note. AUC = are under the curve; CI = confidence interval (logit-transformed, permutation based); LASSO = least absolute shrinkage and selection operator; ML = machine learning; POD = postoperative delirium; PPV = positive predictive value; NPV = negative predictive value.

score was validated retrospectively in a cohort derived from the same hospital, which may have led to overfitting in the validation cohort. Furthermore, the study included cardiac and non-cardiac surgical patients. The strength of the DELIPRECAS prediction model[32] is the multicenter character of the validation. The disadvantage of the DELIPRECAS prediction model[32] might be considered the use of MMSE due to its estimated assessment duration up to 10 minutes. In Delphi trial,[76] the AUC of the best prediction model in the validation cohort was 0.94. However, Delphi trial[76] conducted a complex ML algorithms and involved data that are not available prior to surgery. The advantage of the DRSQ of the FINDERI prospective observational study might be the preoperative screening of multiple characteristics (e.g., cognition, geriatric assessment, muscle strength, laboratory measurements, medication) that could be use in multimodal POD prevention programs such as modified Hospital Elder Life Program (mHELP)[77] or AKTIVER ([“More Active”]: Alltags- und Kognitions-Training & Interdisziplinarität verbessert Ergebnis und mindert das Risiko [“everyday skills and cognition training and interdisciplinarity improves outcome and mitigates risk”]).[78] Additionally, the preoperatively identified patients characteristics (e.g., cognitive impairment, frailty, decreased protein) could also be addressed in a multimodal prehabilitation program prior to cardiac surgery (e.g., Prehabilitation in older patients prior to elective cardiac procedures [PRECOVERY][79]) to potentially reduce postoperative complications.

The FINDERI study has several strengths. The multicomponent DRSQ has the potential to identify patients at risk of developing POD after cardiac surgery. In addition, the study utilizes the highest standards for delirium detection, including the CAM-ICU and I-CAM. Finally, the study analyzes a broad and representative sample in cardiac surgery. However, this study has several limitations. Firstly, to use the decision tree, assessors would need training in DRSQ and cognitive assessments (e.g., MoCA, TMTA, TMTB), and different institutions/users may lead to inconsistent results/risk of bias. Secondly, the time duration of the assessment and decision tree rules may be a burden for clinical implementation. Thirdly, the study was performed in a single academic center that might have led to institutional bias, and the results might to be generalizable to patients

FIGURE 5. Combined ROCs of the ML approach *Note*. ROC: receiver operating characteristics; LASSO: least absolute shrinkage and selection operator; ML: machine learning.

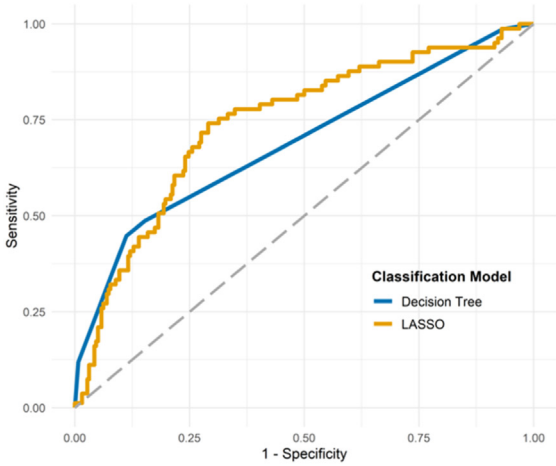


Figure 5a. Combined ROC of the ML approach (training)

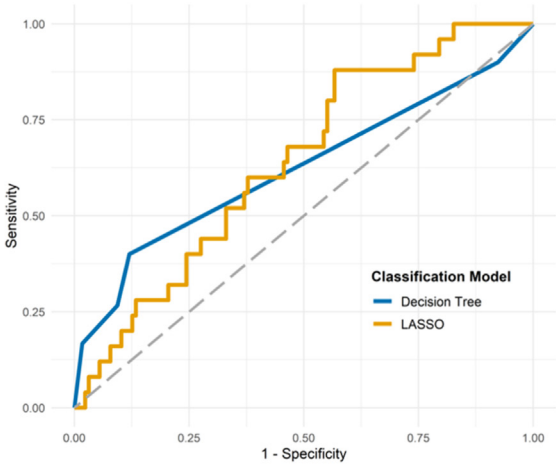
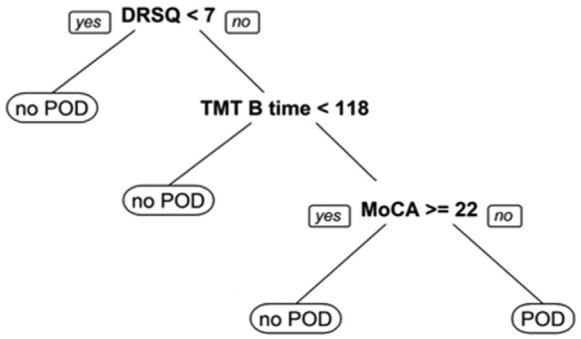


Figure 5b. Combined ROC of the ML approach (test/validation)

undergoing a cardiac surgery in other institutions. Fourthly, further research will be needed to replicate our findings, to compare the results to the other tools (i.e., DELIPRECAS, PROPDESC score), and to assess the clinical benefits of the assessment tool in a larger multicenter, prospective, observational study.

In summary, we found that the incidence of POD in patients who underwent a cardiac surgery was 21%. Both the DRSQ and a ML-driven, three-rule decision tree prediction model (consisting of the DRSQ, TMTB, and MoCA) performed fairly well at identifying POD incidence. POD is highly prevalent in patients after cardiac surgery, and it is associated with serious adverse outcomes as well as high healthcare costs. Therefore, it is clinically important to identify patients with increased risk of POD prior to cardiac surgery. DRSQ and three-rule decision tree prediction model have the potential to be used clinically for predicting POD following cardiac surgery that can be addressed before cardiac surgery in a POD prevention program (e.g., AKTIVER or mHELP).

FIGURE 6. Decision three with three-rule approach in detection of patients at POD risk *Note*. DRSQ: Delirium Risk Screening Questionnaire; MoCA: Montreal Cognitive Assessment; POD: postoperative delirium; TMTB: Trail Making Test B.



ETHICS APPROVAL AND CONSENTS TO PARTICIPATE

The study protocol was approved by the Ethics Committee of the University of Göttingen Medical Center on February 16, 2021 (#20/11/20). Written informed consent is obtained from each participant before any trial-related procedures are performed and patients receive a copy of the signed and dated written consent form.

AUTHOR CONTRIBUTIONS

Conceptualization, MS, NH, HE, TA, MC, IK, JW, HB, CAFvA,; investigation, MS, JS, AW, FEB, JE;

methodology, project administration, data curation, MS, CAFvA, HB, JW, NH, HE, CD, TA; statistical analyzes, CD, TA, MS, CMC; writing—original draft, MS, CMC, CD, TA; writing—review & editing, NH, SH, JW, HB, CAFvA, funding acquisition, MC, MS; supervision MS, HB, CAFvA, JW, NH, HE. All authors have read and approved the final manuscript.

DATA STATEMENT

The FINDERI dataset generated and/or analyzed for the present article is available upon request to the corresponding author. The investigators follow the FAIR Principles for scientific data management and stewardship.

DISCLOSURES

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CMC has received stipends from Elsevier for editorial work for General Hospital Psychiatry. JW has served at scientific advisory boards for Abbot, Biogen, Boehringer-Ingelheim, Eli Lilly, F. Hoffmann-La Roche, Immunogenetics, MSD SHARP & DOHME, he 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), Beijing Yibai Science and Technology Ltd. CAFvA has received honoraria from serving on the scientific advisory board of Biogen, Roche, Lilly and Dr. Willmar Schwabe GmbH &Co. CAFvA 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. MS, NH, HE, CD, TA, MC, SH, AW, JS, FEB, JE, IG, HB report no competing interests.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.jagp.2023.12.017.

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