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Derivation and Validation of a Preoperative Prediction Rule for Delirium after Cardiac Surgery

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Abstract

Background—Delirium is a common outcome after cardiac surgery. Delirium prediction rules identify patients at risk for delirium who may benefit from targeted prevention strategies, early identification and treatment of underlying causes. The purpose of this prospective study was to develop a prediction rule for delirium in a cardiac surgery cohort and validate it in an independent cohort.

Methods and Results—Prospectively, cardiac surgery patients ≥60 years were enrolled in a derivation sample (n=122) and then a validation sample (n=109). Beginning on the second postoperative day, patients underwent a standardized daily delirium assessment and delirium was diagnosed according to the Confusion Assessment Method. Delirium occurred in 63 (52%) of the derivation cohort patients. Multivariable analysis identified four variables independently associated with delirium: prior stroke or transient ischemic attack (TIA), Mini Mental State Examination (MMSE) score, abnormal serum albumin, and the Geriatric Depression Scale (GDS). Points were assigned to each variable: MMSE ≤23 received 2 points; MMSE 24-27, GDS >4, prior stroke/TIA, and abnormal albumin received 1 point each. In the derivation sample, the cumulative incidence of delirium for point levels of 0, 1, 2, and ≥3 was 19%, 47%, 63%, and 86%, respectively (C-statistic 0.74). The corresponding incidence of delirium in the validation sample was 18%, 43%, 60%, and 87%, respectively (C-statistic 0.75).

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Short Commentary: Delirium is a common, morbid, and costly condition after cardiac surgery. This study developed and validated a prediction rule for postoperative delirium using four independent risk factors for delirium assessed before surgery: 1) prior stroke or transient ischemic attack, 2) impaired cognition, 3) abnormal serum albumin, and 4) depression. A risk stratification system assigned points to each risk factor: compared to no points, the presence of 1 point more than doubles the delirium risk, 2 points more than triples the delirium risk and the presence of 3 or more points more than quadruples delirium risk. This prediction rule provides clinicians a method to identify delirium risk prior to cardiac surgery. Clinically, patients who are stratified into moderate and high risk for delirium categories would benefit from frequent delirium screening and implementation of delirium prevention strategies. Importantly, this cardiac surgery delirium prediction rule provides a method to preoperatively stratify at-risk older patients for such interventions to ultimately reduce the morbidity, mortality, and cost of postoperative delirium.

Conclusion—Delirium occurs frequently after cardiac surgery. Using four preoperative characteristics, clinicians can determine cardiac surgery patients' risk for delirium. Patients at higher delirium risk could be candidates for close postoperative monitoring and interventions to prevent delirium.

Keywords

Delirium; Cardiac surgery; aged; cognition; prediction rule; depression

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Delirium, an acute alteration in attention and cognition, was first reported as a complication of cardiac surgery >40 years ago.[1] Since that time, advances in surgical and anesthesia practice have improved the efficiency and outcomes of cardiac surgery patients. However, delirium remains a frequent, but under-recognized, complication after cardiac surgery[2], which is associated with short term complications, such as mortality, morbidity, increased length of stay.[3-6] Moreover, while generally thought of as a short-term disorder of cognition, delirium can have long-term sequelae, including persistent cognitive deficits, loss of independence, functional decline, increased costs and increased mortality for up to 2 years.[3, 4] Importantly, delirium and its complications can be prevented in the surgical population.[6, 7]

Delirium prediction rules use cogent clinical items from the history, physical, and initial diagnostic tests to prospectively identify patients at high-risk for delirium.[8] Prediction rules also allow the patient and family to be better informed of risk, and targeting of surveillance and prevention efforts for delirium. Despite research identifying independent risk factors for delirium [2, 9], there is no validated preoperative prediction rule for delirium risk after cardiac surgery.

The objective of the current study is to develop and validate a clinical prediction rule, based on preoperative factors, for the development of delirium after cardiac surgery. We employ state-of-the-art methods, including rigorous prospective assessment of preoperative risk factors, comprehensive delirium detection methods, advanced statistical methods for identification of independent variables, and validation in an independent sample. We also examined the association of intraoperative variables with delirium, adjusted for preoperative risk. We believe that our results will aid clinicians caring for cardiac surgery patients and inform research studies to improve cognitive outcomes after cardiac surgery.

Methods

Participants

From September 1, 2002 until October 31, 2004, we recruited 122 patients over age 60 years who were planning to undergo cardiac surgery at two academic medical centers and one Veterans Administration (VA) hospital for our derivation set. Subsequently, a validation set of 109 patients was recruited from November 1, 2004 until June 30, 2006 at one academic medical center and one VA hospital using identical criteria. Eligible cardiac procedures included coronary artery bypass graft (CABG), mitral or aortic valve replacement or repair (valve), and combined CABG-Valve. All patients provided written informed consent and the study was approved by the Institutional Review Board (IRB) at each institution. Exclusion criteria included living >60 miles from the study center, medical instability limiting preoperative assessment, emergency surgery, delirium before surgery, concurrent aortic or carotid surgical procedures, and non-English speaking.

Preoperative Assessment

Prior to surgery, all patients underwent extensive assessment with interviews and medical record review of demographics, behavioral factors, comorbidity, mental health, physical function, cognitive function, laboratory profile, and planned surgery. Participants provided information on age, sex, race, marital status, educational level and alcohol and tobacco exposure. The number of pack-years of tobacco use was calculated. Alcohol use was categorized according to drinks per week: non-users, users (≤7 drinks per week) and heavy users (>7 drinks per week). Body mass index (BMI), was calculated from the preoperative anesthesia assessment. Comorbidity information was collected from the medical record and supplemented with patient interview. We recorded the presence of hypertension, hyperlipidemia, diabetes, cancer, and a prior stroke, transient ischemic attack (TIA), or hemiparesis. Patients were interviewed using the Geriatric Depression Scale (GDS), an assessment of 15 symptoms of depression (range 0-15, 15=worst).[10] The patient's ability to function and care for themselves were assessed with the Activities of Daily Living (ADLs), a self-care scale(range 0-18, 0=worst)[11] and Instrumental Activities of Daily Living (IADLs), an independent task scale (range 0-21, 0=worst)[12]. American Society of Anesthesiologists class, a measure of preoperative illness[13], was recorded from the anesthesia record. The Mini Mental State Examination[14] (MMSE) was administered to all patients prior to surgery (range 0-30, 0=worst). The preoperative laboratory values most proximal to the operation that were recorded included: sodium, potassium, glucose, white blood cell count (WBC), hematocrit, blood urea nitrogen (BUN):creatinine ratio, and albumin. The type of surgery was included in our preoperative risk model, because the type of surgery (CABG±valve) is usually known preoperatively. Between catheterization and surgery, patients who remained in the hospital were considered urgent procedures and those who were discharged were considered elective procedures.

Delirium Assessment

A brief delirium assessment (<15 min) was performed preoperatively and daily during the postoperative period, beginning on day 2. Because of the intensive postoperative care required after the CABG procedure, patients were not assessed on the day of surgery or postoperative day 1. Delirium was assessed using the validated diagnostic algorithm of the Confusion Assessment Method (CAM)[15]. Prior to completing the CAM, a standardized mental status interview was conducted, which included the MMSE[14], digit span, the Delirium Symptom Interview (DSI)[16], and the Memorial Delirium Assessment Scale (MDAS)[17]. Digit span asks patients to repeat a series of digits forward and backward and is a test of working memory and attention. The DSI is a validated interview for eliciting 8 key symptoms of delirium. The MDAS is a validated severity scale for delirium (range 0-30, 30=worst). This combined assessment for delirium has been shown to be highly reliable (κ=0.95) when administered by trained, non-clinician interviewers.[18] In the event of an intubated patient, we assessed delirium using the CAM-ICU, a validated assessment for intubated patients, which uses the CAM diagnostic algorithm.[19] The daily assessment was augmented with medical record review for evidence of intervening delirium features.

Operative Procedure

All patients underwent cardiac surgery (CABG, valve, or combined CABG-valve) under general anesthesia. The anesthesia protocol and operative procedure were performed in accordance with local hospital policies and protocols. The use of cardiopulmonary bypass, aortic cross clamp, high-dose heparin, apoprotinin, and hypothermia was at the discretion of the attending surgeon. Postoperative care, including pain control, was administered in accordance with local hospital policy and practice at each hospital. Intraoperative variables, including the use of cardiopulmonary bypass, were recorded from the operative, anesthesia, and perfusion records. Intraoperative variables were compared in those with and without delirium and adjusted for the preoperative prediction rule.

Statistics

Comparison of Derivation and Validation Cohorts—Preoperative characteristics of patients in the derivation cohort were compared to those in the validation cohort using a t-test for continuous variables and a Chi-square test for ordinal or dichotomous variables.

Derivation of Prediction Rule—We examined the distribution of all continuous variables. Variables with extremely skewed distributions were categorized according to clinically relevant cut-points if available, or at naturally occurring inflection points. There were few (n=6) patients with heavy alcohol use and alcohol use was dichotomized into users and non-users. IADLs and ADLs compared those with maximum numerical score to those with less than maximal score. The prevalence of individual laboratory abnormalities was low and we created a categorical variable, using the cut points from the Acute Physiology, Age, and Chronic Health Evaluation-III.[20] Albumin was categorized as an abnormal (≤3.5 or ≥4.5 g/dL) vs. normal value (3.6-4.4 g/dL) based on clinical cut points at our institution and a u-shaped bivariable relationship between albumin and delirium risk. BUN / Creatinine ratio ≥18 has been identified as an independent risk factor for delirium in medical patients[21] and this dichotomization was preserved. Normally-distributed, continuous variables (age, body mass index, MMSE) were maintained as continuous in the imputation, bootstrapping, and multivariable models, but were categorized for the final predictive model.

Preoperative characteristics of patients who developed delirium were compared to those who did not develop delirium using a t-test for continuous variables and a Chi-square test for ordinal or dichotomous variables. Variables with a bivariable relationship associated with a test statistic with a p-value ≤.10 were selected for inclusion in the multivariable analyses using imputation and bootstrapping.

Missing data among the predictor variables was handled using a multiple imputation procedure with 20 resampling replications, which generated an augmented data base with (122×20) 2440 observations with complete data.[22] To protect from overfitting the data and to limit chance associations in the derivation sample from influencing the development of the prediction rule, we used a bootstrap resampling procedure to determine the independent factors associated with delirium. We generated 100 bootstrap samples from the derivation cohort (each of n=122, drawn randomly with replacement from the augmented sample). With each bootstrap sample, we modeled the prediction of delirium given selected predictors using a backward stepwise logistic regression model, retaining parameters significant at the 0.05 level. Factors associated with delirium were defined as those variables returning regression coefficients significant at an alpha level of 0.05 in at least 50% of bootstrap samples. To finalize the prediction rule, the remaining continuous independent risk factors were categorized using clinically meaningful cut points.

Validation Sample and Model Performance—The clinical prediction rule was applied to the validation sample using multiple imputation procedures for missing data. We present the incidence of delirium with increasing clinical prediction rule points and risk ratio relative to the lowest risk group. Model performance in both cohorts was measured with the C-statistic. A sensitivity analysis examined the C-statistic excluding patients who did not have cardiopulmonary bypass (‘off-pump’).

Statement of Responsibility—The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Delirium developed in 52% (n=63/122) of the validation cohort and in 44% (n=48/109) of the derivation cohort. The peak incidence of delirium was on postoperative day 2 and it persisted for a median of 1 day (range 1-27 days). Patients with delirium were more likely to have a longer length of stay (10.2 ±6.3 vs. 7.5 ±3.8 days, p<.001) and to be discharged to a nursing home or rehabilitation hospital (73% vs. 27%, p<.001). Table 1 describes the baseline characteristics of the derivation (n=122) and validation cohorts (n=109). Typical of the cardiac surgery patients at our medical centers and nationwide, patients were of advanced age (73.7 ±6.7 years), mostly male (79%) and predominantly white (96%).[23] The derivation and validation cohorts were similar in their preoperative characteristics. However, the derivation cohort was slightly older, endorsed more depressive symptoms, had abnormal albumin more frequently, was more likely to undergo urgent surgery, and was more likely to have a CABG surgery. Five patients in the derivation and three patients in the validation cohort underwent ‘off-pump’ surgery.

The bivariable analysis comparing the risk factors in those with and without delirium in the derivation cohort is displayed in Table 2. Patients who developed delirium were significantly more likely to be older and tended to be female. Alcohol consumption was associated with a reduced delirium risk. Body mass index was significantly lower in patients with delirium. Patients with prior stroke/TIA were significantly more likely to develop delirium. Patients who developed delirium described significantly more depressive symptoms and had lower MMSE scores preoperatively. Suboptimal functional performance was not associated with delirium. In the laboratory profile, abnormal albumin was associated with increased incidence of delirium. Neither the urgency nor type of surgery was associated with delirium.

Table 3 presents the results of the multivariable model. Four variables were associated with delirium in at least 50% of bootstrap samples at an alpha level of 0.05 after backwards selection: MMSE, history of stroke/TIA, GDS, and abnormal albumin. These variables were selected for the development of the prediction rule. Based on the results of the multivariable modeling, a final prediction rule was developed using categorical versions of retained variables. Geriatric Depression Scale was dichotomized at >4 which has been shown to have good sensitivity (83-100%) and specificity (65-84%) for clinical depression.[24, 25] MMSE was categorized into established clinically important ranges for definitive impairment (≤23), mild impairment (24-27), and not impaired (28-30).[14, 26]

Clinical prediction rule points were assigned after standardization to the lowest regression coefficient. MMSE ≤23 was assigned 2 points. One point was assigned to MMSE 24-27, history of stroke/TIA, GDS >4, and abnormal albumin. Table 4 describes the performance of the clinical prediction rule in the derivation and validation cohorts. In both cohorts, there was increasing risk of postoperative delirium with increasing risk score, and the model predicted well in both the derivation (C-statistic =.74) and validation (C-statistic =.75) cohorts, with no degradation of model performance in the validation cohort. Excluding “off-pump” patients, the model C-statistic was 0.73 in the derivation cohort and 0.78 in the validation cohort. Additionally, delirium severity, as measured by MDAS, increased with increasing risk score. For point levels of 0, 1, 2, and ≥3, the mean MDAS score in the derivation cohort was 5, 7, 9, 11 (p<.01) and the validation cohort was 4, 7, 8, 9 (p<.001), respectively.

Intraoperative variables are presented in Table 5 comparing those with delirium and those without delirium. After adjustment for the clinical prediction rule, duration of anesthesia remained a significant predictor of delirium (RR 1.2, 95%CI 1.01, 1.4).

Discussion

In this prospective study of cardiac surgery patients delirium was extremely common. We identified four preoperative factors that were independently associated with postoperative delirium: impaired cognition, depressive symptoms, prior stroke or TIA, and abnormal albumin. With these factors, we developed a clinical prediction rule and validated this rule in a separate cohort. The rule performed well in both the derivation (C-statistic=0.74) and validation cohorts (C-statistic=0.75). When applying the risk stratification system, compared to no points, the presence of 1 point more than doubles the delirium risk, 2 points more than triples the delirium risk and the presence of 3 or more points more than quadruples delirium risk.

Our clinical prediction rule has face validity in that three of our risk factors, impaired cognition[27], prior stroke[28, 29], and depressive symptoms[30] have been identified in previous studies, but also adds substantial incremental value in that we have integrated these risk factors into a prediction rule that clinicians can use to stratify overall risk. Importantly, the identification of the additional risk factor of abnormal albumin extends the previous work. Albumin level is associated with operative mortality[31] and has been hypothesized to be an overall biomarker of frailty, nutritional, and functional abilities.[32, 33] In a non-cardiac surgery delirium prediction rule[34], low albumin was associated with delirium, but the high missing data rate precluded its inclusion in the modeling. Additionally, albumin plays an important role in intravascular volume status and drug binding. Thus, when recorded at the time of admission, low albumin may be a laboratory variable associated with lower functional level, as well as affecting hemodynamic shifts and pharmacokinetics of cognitively active drugs.

The cardiac surgery prediction rule for delirium may provide insights into our understanding of the pathophysiology of delirium. Several factors that we identified are potentially associated with central nervous system atherosclerotic disease (prior stroke/TIA, cognitive impairment, depression).[35] The two graded categories of cognitive function provides insight into the delirium risk of patients with milder degrees of cognitive impairment who do not meet the traditional dementia threshold (MMSE<24); this concept is consistent with the sub-dementia threshold frequently associated with vascular cognitive impairment. Further, there is an increasing literature on the association of vascular risk and depression.[36] Thus, atherosclerosis may be a common risk factor which can predispose patients to delirium.[9]

Our prediction rule conforms to a widely adopted approach for evaluating delirium risk, which considers predisposing factors (present prior to surgery) and precipitating factors (occur during and after surgery).[21, 34] Our overall goal was to develop a preoperative clinical prediction rule based on predisposing factors. However, we also analyzed the additive contribution of intraoperative precipitating factors. The finding that duration of anesthesia was associated with delirium after adjustment for the preoperative prediction rule, could represent worse underlying disease, more complex surgery, and/or additional exposure to anesthetics. We will consider intraoperative and postoperative precipitating factors for delirium in our future work to determine additional delirium prevention strategies. As based on previous studies, prevention of delirium in high risk patients would focus on environmental modifications, early mobilization, psychoactive medication reduction, and prevention of complications.[6, 7]

The rate of delirium in our study is at the higher end of published reports. There are several reasons for this. First, our study used state-of-the-art delirium detection methods including a standardized assessment which was delivered daily. This standardized delirium battery includes assessments for attention impairment which may not be identified in a routine clinical interview. The incidence of delirium after cardiac surgery varies widely (2-73%).[2] Studies utilizing a standardized battery[37, 38] have found a higher incidence of delirium than studies that assess delirium via chart review or nursing report.[39] Second, older age can be a risk factor for postoperative delirium[28-30, 34] and this study enrolled patients over age 60 resulting in a mean age of 73 years, which is older than other studies of delirium after cardiac surgery and reflects the trend toward operating on older patients.[23] Finally, we included patients regardless of preoperative cognitive function. Thus, we likely have patients with vascular cognitive impairment, mild cognitive impairment, and/or dementia, who are much more likely to develop delirium.

There are several strengths to this study that warrant mention. First, the study derived and validated the prediction rule in independent cohorts at more than one medical center. The study included patients undergoing elective or urgent cardiac surgical procedures. Emergency patients would likely have a higher delirium rate, but were not included because of an inability to obtain a preoperative baseline interview. Additionally, we aggressively identified and verified preoperative characteristics that were included in the model to ensure accurate risk factor identification. MMSE and GDS took about 15 minutes to administer before surgery and were performed by trained research assistants. Additionally, the model performed similarly after excluding “off-pump” patients. Finally, our analytic approach combined data augmentation via multiple imputation and bootstrap resampling procedures for deriving the independent predictors included in the clinical prediction rule. This advanced statistical methodology may provide more stable variables for prediction-validation rules by minimizing the impact of missing data, limiting model over-fitting, and is superior to listwise deletion or regression to the mean.[40, 41]

There are several limitations which need to be described. First, our population consisted of patients who were mostly white and well educated (>50% with education beyond high school) and recruited at academic medical centers in a single geographical region. MMSE performance may be improved with increased education, but in this study, education was not associated with delirium. This may limit generalizibility to less educated populations, but internal validity should not be challenged. There was variability in the derivation and validation cohorts specifically in characteristics which were included in the model such as age, GDS, and albumin. However, the differences in these variables in the validation cohort bias toward the null with respect to delirium risk (lower age, less depressive symptoms, higher incidence of normal albumin, etc), and yet, the overall model performance showed no degradation between the derivation and validation cohorts. We were unable to measure all preoperative characteristics, such as carotid stenosis, which may predispose to delirium.[9] Finally, the lowest risk in our prediction rule is 18-19%, which limits our ability to identify patients who might be excluded from interventions. The prediction rule performed better at predicting higher levels of delirium risk.

This study identified four cogent risk factors for delirium: MMSE, prior stroke or TIA, depression, and abnormal albumin. Delirium risk more than quadruples moving from the lowest to highest risk levels. Clinically, patients who are stratified into moderate and high risk for delirium categories would benefit from frequent delirium screening and implementation of delirium prevention strategies. Importantly, this cardiac surgery delirium prediction rule provides a method to preoperatively stratify at-risk older patients for such interventions to ultimately reduce the morbidity, mortality, and cost of postoperative delirium.

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Table 1

Characteristics of the Derivation and Validation Cohorts

Characteristic	Derivation Cohort (n= 122)	Validation Cohort (n=109)	p-value
Age (years)	74.7 (6.3)	72.6 (7.1)	.02
Female sex n (%)	25 (20%)	29 (27%)	.27
Non-white n (%)	2 (2%)	6 (5%)	.11
Education			
<High School	19 (17%)	18 (15%)	.52
High School	44 (36%)	32 (29%)	
>High School	59 (49%)	58 (53%)	
Unmarried n (%)	38 (32%)	46 (42%)	.12
Tobacco Exposure			
None	29 (26%)	33 (31%)	.28
1-30 pack-years	48 (42%)	34 (32%)	
>=30 pack years	36 (31%)	39 (38%)	
Alcohol User	66 (58%)	58 (54%)	.53
Body mass index (kg/m^2)	28.3 (5.6)	29.0 (5.6)	.36
Hypertension	99 (81%)	97 (90%)	.11
Hyperlipidemia	84 (70%)	90 (83%)	.02
Diabetes	56 (47%)	41 (38%)	.18
Stroke/Transient Ischemic Attack	26 (22%)	16 (15%)	.18
Cancer	9 (8%)	15 (14%)	.12
Geriatric Depression Scale	3.3 (3.0)	2.3 (2.1)	.005
Instrumental Activities of Daily Living <21	57 (49%)	54 (50%)	.90
Activities of Daily Living <18	10 (9%)	1 (1%)	.01
ASA Class[†]			
2	2 (2%)	0 (0%)	.33
3	21 (18%)	16 (15%)	
4	97 (81%)	93 (85%)	
Mini Mental State Examination	26.9 (2.6)	26.8 (2.7)	.74
Albumin (g/dL)			
3.6-4.4	61 (64%)	75 (80%)	.02
≤3.5 or ≥4.5	34 (36%)	19 (20%)	
Hematocrit (%)	37.0 (4.5)	36.2 (5.0)	.25
Abnormal Laboratory Values[*]	24 (20%)	21 (19%)	.89
Urea nitrogen : creatinine ≥18	81 (69%)	67 (62%)	.30
Urgent Surgery	96 (79%)	75 (69%)	.09
Elective Surgery	26 (21%)	34 (31%)	
Type of Surgery			
CABG[‡]	103 (84%)	77 (71%)	.01
Valve +/- CABG	19 (16%)	32 (29%)	

[*] Abnormal electrolytes values: sodium <135 or >154(mg/dL); glucose <60 or >200(mg/dL); white blood cell count <3.0 or >20 (×1000/mcL)

†ASA American Society of Anesthesiology

‡CABG-Coronary Artery Bypass Graft

Table 2

Prediction Cohort: Independent Risk Factors for Delirium

Risk Factor	Delirium Mean (SD) n/N (%) (n=63)	No Delirium Mean (SD) n/N (%) (n=59)	Crude p-values	Risk Ratio (95%CI)*	Entered into stepwise model
Mean Age (years)	75.8 (6.5)	73.5 (5.9)	.04	1.2 (0.9, 1.6)*	Yes
Female sex	17 (27%)	8 (14%)	.07	1.4 (1.0, 2.0)	Yes
White	61 (97%)	59 (100%)	.17		
Education					
>High School	27 (43%)	32 (55%)	.39	Referent	
High School	26 (41%)	18 (31%)		1.3 (0.9, 1.9)	
<High School	10 (16%)	8 (14%)		1.2 (0.7, 2.0)	
Unmarried	23 (37%)	15 (24%)	.11	1.8 (0.9, 1.9)	
Tobacco Exposure					
None	16 (27%)	13 (24%)	.30	Referent	
1-30 pack-years	28 (47%)	20 (37%)		1.1 (0,7, 1.6)	
>=30 pack years	15 (25%)	21 (39%)		0.8 (0.5, 1.3)	
Alcohol Use	28 (47%)	38 (69%)	.02	0.6 (0.4, 0.9)	Yes
Mean BMI	27.3 (5.7)	29.4 (5.3)	.04	0.8 (0.6, 1.1)*	Yes
Hypertension	51 (84%)	48 (81%)	.75	1.1 (0.7, 1.8)	
Hyperlipidemia	44 (72%)	40 (68%)	.60	1.1 (0.7, 1.7)	
Diabetes	28 (46%)	28 (50%)	.86	1.0 (0.7, 1.4)	
Stroke/TIA	19 (31%)	7 (12%)	.01	1.6 (1.2, 2.3)	Yes
Cancer history	3 (5%)	6 (10%)	.28	0.6 (0.2, 1.6)	
Geriatric Depression Scale	4.0 (3.3)	2.6 (2.6)	.02	1.2 (1.0, 1.5)*	Yes
Instrumental Activities of Daily Living <21	33 (55%)	24 (43%)	.19	1.2 (0.9, 1.8)	
Activities of Daily Living <18	7 (12%)	3 (5%)	.23	1.4 (0.9, 2.2)	
ASA Class† 4	49 (80%)	48 (81%)	.89	0.9 (0.6, 1.5)	
Mini Mental State Examination	26.1 (2.9)	27.7 (2.1)	<.001	0.8 (0.6, 1.0)*	Yes
Abnormal Albumin‡	22 (43%)	11 (25%)	.06	1.4 (1.0, 2.0)	Yes
Hematocrit (%)	36.5 (4.7)	37.4 (4.2)	.25	0.9 (0.7, 1.2)	
Abnormal Laboratory Values§	13 (21%)	11 (19%)	.86	1.0 (0.7, 1.6)	
Urea nitrogen : creatinine ≥18	43 (70%)	38 (67%)	.65	1.0 (0.7, 1.5)	

Risk Factor	Delirium Mean (SD) n/N (%) (n=63)	No Delirium Mean (SD) n/N (%) (n=59)	Crude p-values	Risk Ratio (95%CI)*	Entered into stepwise model
Urgent Surgery	52 (83%)	44 (75%)	.28	1.3 (0.8, 2.1)	
Valve Surgery (±CABG)	9 (14%)	10 (17%)	.69	0.9 (0.5, 1.5)	

* For continuous variables, the risk ratio is expressed as the risk per standard deviation increase

† ASA-American Society of Anesthesiology;

‡ Abnormal Albumin ≤3.5 or ≥4.5g/dL

§ Abnormal electrolytes values: sodium <135 or >154(mg/dL); glucose <60 or >200(mg/dL); white blood cell count <3.0 or >20(×1000/mcL)

// CABG-Coronary Artery Bypass Graft

Table 3

Predictors of Delirium in Derivation Cohort. Results of multivariate modeling with bootstrap resampling.

Variable	Bootstrapping Selection*	Included in Prediction Rule
Mini Mental State Examination	87	Yes
Prior Stroke /TIA†	70	Yes
Abnormal Albumin‡	58	Yes
Geriatric Depression Scale	52	Yes
Body Mass Index	35	No
Age	32	No
Alcohol use	31	No
Female Sex	15	No

*Bootstrapping selection is the number of times in 100 replications a variable was retained in the final backwards stepwise selected model at an alpha level of 0.05. Bootstrap replications were drawn from augmented data set derived using multiple imputation.

†TIA-transient Ischemic attack

‡Abnormal albumin (≤3.5 or ≥4.5g/dL)

Table 4

Performance of the Predictive Model in the Two Cohorts

Risk Group	Prediction Rule Points	Delirium Rate	Risk Ratio (95% CI)	C-Statistic
Derivation Cohort (n=122)				0.74
	0	5/25 (19%)	Referent	
	1	20/44 (47%)	2.4 (1.9, 3.0)	
	2	23/36 (63%)	3.2 (2.6, 4.0)	
	≥3	15/18 (86%)	4.4 (3.5, 5.6)	
Validation Cohort (n=109)				0.75
	0	5/29 (18%)	Referent	
	1	21/48 (43%)	2.4 (2.0, 3.0)	
	2	13/22 (60%)	3.4 (2.7, 4.2)	
	≥3	9/10 (87%)	4.9 (3.8, 6.2)	

Table 5

Impact of prediction rule on intraoperative factors

Variable	No Delirium Mean(SD) n/N (%)	Delirium Mean(SD) n/N (%)	Crude p-value	Crude RR* (95%CI)	Adjusted RR† (95%CI)
# anastamoses	2.9 (1.0)	3.0 (0.9)	.86	1.0 (0.8, 1.2)	1.1 (0.9, 1.3)
Initial Pulse	67 (11)	67 (12)	.80	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)
Initial systolic blood pressure (mmHg)	141 (27)	150 (24)	.01	1.2 (1.0, 1.4)	1.1, (0.9, 1.4)
Surgery time (hr)	3.8 (1.1)	4.2 (1.1)	.01	1.2 (1.0, 1.4)	1.2 (0.98, 1.4)
Anaesthesia time (hr)	5.1 (1.2)	5.6 (1.2)	.002	1.2 (1.0, 1.5)	1.2 (1.01, 1.4)
Time of bypass (hr)	1.5 (0.5)	1.7 (0.6)	.004	1.2 (1.0, 1.4)	1.2 (0.99, 1,4)
Intraoperative fluid (L)	3.3 (1.0)	3.6 (1.5)	.06	1.1 (0.9, 1.4)	1.1 (0.9, 1.3)
Urine output (mL)	847 (450)	849 (611)	.98	1.0 (0.8, 1.2)	1.0 (0.9, 1.2)
Lowest BP during bypass (mmHg)	52 (11)	51 (8)	.61	1.0 (0.9, 1.2)	1.0 (0.8, 1.2)
Single cross clamp	100/115 (87%)	95/108 (88%)	.34	1.0 (0.7, 1.4)	1.0 (0.8, 1.2)
Cross clamp time (hr)	1.1 (0.4)	1.3 (0.5)	.008	1.2 (1.0, 1.4)	1.2 (0.99, 1.4)
Lowest temperature (°C)	33.1 (1.9)	33.1 (1.8)	.76	1.0 (0.8, 1.2)	1.0 (0.9, 1,2)
Highest pH	7.44 (0.06)	7.45 (0.05)	.28	1.1 (0.9, 1.3)	1.0 (0.8, 1.2)
Lowest pH	7.36 (0.05)	7.35 (0.07)	.69	1.0 (0,8, 1.2)	1.0 (0.8, 1.2)
Highest pCO2 (mmHg)	47 (6)	47 (8)	.99	1.0 (0.8, 1.2)	1.0 (0.9, 1.2)
Lowest pCO2 (mmHg)	37 (5)	36 (5)	.09	0.9 (0.7, 1.1)	1.0 (0.8, 1.2)
Cell saver	89/120 (74%)	77/109 (71%)	.36	0.9 (0.6, 1.4)	0.9 (0,6, 1.4)
Moderate – severe ascending aortic plaque‡	36/90 (40%)	34/82 (41%)	.85	1.0 (0.7, 1.6)	0.9 (0.6, 1.4)
Intraoperative complications	11/120 (9%)	8/111 (7%)	0.29	0.9 (0.4, 1.8)	0.8 (0.4, 1.7)

* For continuous variables, the risk ratio is expressed as the risk per standard deviation increase.

† Adjusted for the prediction rule

‡ Aortic plaque was assessed with intraoperative transesophageal echocardiogram