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Predicting postoperative delirium after vascular surgical procedures

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Objective: The objective of this study was to determine the incidence of and specific preoperative and intraoperative risk factors for postoperative delirium (POD) in electively treated vascular surgery patients.

Methods: Between March 2010 and November 2013, all vascular surgery patients were included in a prospective database. Various preoperative, intraoperative, and postoperative risk factors were collected during hospitalization. The primary outcome variable was the incidence of POD. Secondary outcome variables were any surgical complication, hospital length of stay, and mortality.

Results: In total, 566 patients were prospectively evaluated; 463 patients were 60 years or older at the time of surgery and formed our study cohort. The median age was 72 years (interquartile range, 66-77), and 76.9% were male. Twenty-two patients (4.8%) developed POD. Factors that differed significantly by univariate analysis included current smoking ($P = .001$), increased comorbidity ($P = .001$), hypertension ($P = .003$), diabetes mellitus ($P = .001$), cognitive impairment ($P < .001$), open aortic surgery or amputation surgery ($P < .001$), elevated C-reactive protein level ($P < .001$), and blood loss ($P < .001$). Multivariate logistic regression analysis revealed preoperative cognitive impairment (odds ratio [OR], 16.4; 95% confidence interval [CI], 4.7-57.0), open aortic surgery or amputation surgery (OR, 14.0; 95% CI, 3.9-49.8), current smoking (OR, 10.5; 95% CI, 2.8-40.2), hypertension (OR, 7.6; 95% CI, 1.9-30.5) and age ≥ 80 years (OR, 7.3; 95% CI, 1.8-30.1) to be independent predictors of the occurrence of POD. The combination of these parameters allows us to predict delirium with a sensitivity of 86% and a specificity of 92%. The area under the curve of the corresponding receiver operating characteristics was 0.93. Delirium was associated with longer hospital length of stay ($P < .001$), more frequent and increased intensive care unit stays ($P = .008$ and $P = .003$, respectively), more surgical complications ($P < .001$), more postdischarge institutionalization ($P < .001$), and higher 1-year mortality rates ($P = .0026$).

Conclusions: In vascular surgery patients, preoperative cognitive impairment and open aortic or amputation surgery were highly significant risk factors for the occurrence of POD. In addition, POD was significantly associated with a higher mortality and more institutionalization. Patients with these risk factors should be considered for high-standard delirium care to improve these outcomes. (*J Vasc Surg* 2015;62:183-9.)

Postoperative delirium (POD), which is characterized by a disturbance of consciousness with reduced ability to focus, sustain, or shift attention is a common medical complication after surgery.¹ Symptoms of POD generally arise shortly after surgery and usually persist for a few days. In some cases, however, they can last up to several weeks.² POD is associated with longer intensive care unit (ICU) stay, longer hospital stay, higher hospital costs, increased postdischarge institutionalization, and increased 30-day mortality. Even long-term effects, such as persistent functional decline and death,

have been associated with POD.³ The incidence of POD after noncardiac surgery varies from 5.1% to 52.2%, with the highest incidences among elderly patients.⁴⁻⁹ With an aging population, the number of elderly patients undergoing surgery is growing, and this will continue to increase over time.¹⁰ Consequently, the incidence of POD will most likely increase in the coming years. Various studies focusing on POD demonstrated that vascular patients are at increased risk for development of POD compared with other surgical patients, particularly after open aortic surgery.^{4,5} Because of fluctuating symptoms, the presence of an acute confusional state may be unnoticed, leading to a delay in diagnosis and treatment. Also, clinical subtypes such as hypoactive delirium, which is more common in elderly patients and is associated with a worse prognosis, are frequently misconstrued.^{2,9,11} Because proactive geriatric consultation in combination with prophylactic low-dose haloperidol may reduce the incidence, severity, and duration of POD in high-risk postoperative patients, identifying those patients at risk is important.¹² Although the pathogenesis of POD remains poorly understood, it is considered a heterogeneous, multifactorial disorder with risk factors such as advanced age, preoperative cognitive impairment, cardiac surgery, and renal insufficiency.^{3,4,7,13-16} However, because of varying sample

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sizes and heterogeneity, it is still unclear which factors are the strongest predictors, particularly in a high-risk group such as vascular surgery patients.¹⁷

In 2010, a noninterventional, nonrandomized, single-arm prospective study was set up at our center to gain insight into the etiology of POD after vascular surgery. The aim of this study was to identify individual preoperative and intraoperative risk factors associated with POD after elective vascular surgery.

METHODS

Design of the study. Between March 2010 and November 2013, a total of 566 consecutive vascular surgery patients who were operated on in an elective setting were prospectively evaluated. Current literature has shown that patients older than 60 years are most at risk for the occurrence of POD.³ Because this study focuses primarily on independent risk factors for delirium, we limited the age of participants to ≥ 60 years. At the time of surgery, 463 patients (81.8%) were 60 years or older and were further assessed. Preoperative evaluation was performed by the anesthesiologist at the preoperative assessment clinic. All patients gave oral informed consent. For this study, the Medical Ethical Committee granted an official dispensation for the Dutch law regarding the patient-based medical research (WMO) obligation. Patient data were processed and electronically stored according to the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. Inclusion criteria were patients undergoing open or endovascular aortic repair, peripheral bypass surgery (including short jump graft in case of peripheral aneurysms and interventions on carotid, vertebral, and subclavian arteries), arteriovenous shunt surgery, percutaneous interventions, and different types of amputation surgery. Exclusion criteria were patients undergoing percutaneous interventions without placement of a stent, which was considered a minimally invasive intervention with no or very short hospital admission. Type of anesthesia, perioperative monitoring, and postoperative analgesia were at the discretion of the anesthesiologist. On the basis of anesthetic technique, patients were divided into general, regional, and local anesthesia groups. No further distinction was made between types of medication. Conscious sedation was not provided in the last two groups. Postoperatively, all patients who underwent open aortic repair were admitted to the ICU. They then were transferred to the surgical ward as soon as possible. After carotid interventions, patients were admitted to either the ICU or the recovery room for the first 24 hours. All other patients recovered on the surgical ward. Patients undergoing percutaneous interventions could be discharged home after 4 hours of strict bed rest if there were no signs of any complication. Missing data were complemented by review of the computerized hospital registry and charts. The primary outcome variable was the incidence of POD. Secondary outcome parameters were hospital length of stay, ICU admittance, ICU length of stay, type of care facility after discharge, and 1-year mortality.

POD. The method of POD assessment has been described previously by our group.¹⁸ In short, observation of patients during hospital admission was done by nurses specially trained to recognize behavioral changes related to delirium. The Delirium Observation Screening scale score was also obtained in all patients (surgical and nonsurgical) three times a day.¹⁹ With a Delirium Observation Screening scale score >3 , the geriatrician was consulted to confirm the diagnosis of POD according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, criteria.¹ Patients who developed delirium underwent a comprehensive physical examination with additional laboratory testing to identify a possible underlying cause for delirium, such as sepsis, electrolyte imbalance, or pharmacologic abnormalities, and were treated if necessary. According to the standardized hospital protocol, haloperidol was the medical treatment of choice for symptom control, supplemented by benzodiazepines if necessary.

Clinical data selection. Factors were selected on the basis of known risk factors for the occurrence of POD.¹⁷ Preoperative collected data included age, gender, body mass index (weight in kilograms/height in meters squared), American Society of Anesthesiologists (ASA) score, smoking status (current smokers and former smokers), and laboratory tests (level of hemoglobin and C-reactive protein [CRP]). Comorbidity, based on the previous medical history, was determined by the Charlson Comorbidity Index.²⁰ The Charlson Comorbidity Index is a weighted score that predicts the 1-year mortality of a patient based on coexisting medical conditions and age. Special attention was given to presence of hypertension, diabetes mellitus, cerebrovascular disease, chronic obstructive pulmonary disease, depression, cognitive impairment, and impaired renal function because these factors are known to increase the risk of POD.¹⁷ Renal function was expressed as the estimated glomerular filtration rate, with values $<60 \text{ mL/min} \times 1.73 \text{ m}^2$ indicating impaired renal function. As preoperative cognitive impairment and depression are known risk factors for POD, these were also measured with the Groningen Frailty Indicator (GFI) and further used for risk assessment for POD. The GFI is a simple questionnaire consisting of 15 items, classified in 8 separate groups, consistent with the domains of functioning. This questionnaire was routinely obtained in all vascular surgery patients at the outpatient clinic by specially trained nurses. The GFI has already been proven to predict POD after vascular surgery.¹⁸ Depression was scored on the basis of the 4-item psychosocial item; scores ≥ 1 were considered indicative for depression. Cognitive function was divided into current complaints about memory and history of POD. Cognitive impairment was determined by a score of ≥ 1 . Intraoperative predictors were type of surgery, type of anesthesia, duration of surgery, and estimated blood loss. Surgical complications were classified according to the Clavien-Dindo classification of surgical complications.^{21,22}

Table I. Baseline characteristics and univariate analysis of possible risk factors for postoperative delirium (POD)

Parameter	Total (N = 463; 100%)	Delirium present (n = 22; 5%)	Delirium absent (n = 441; 95.2%)	P value ^a
Gender, male	356 (76.9)	20 (91)	336 (76)	.110
Age, years	72 (66-77)	70 (64-81)	72 (66-77)	.823
Age ≥80 years	74 (16.0)	7 (32)	67 (15)	.065
Body mass index, kg/m ² , mean ± SEM	27.3 ± 0.2	27.7 ± 0.8	27.3 ± 0.2	.705
Current smoking	138 (29.8)	15 (68)	123 (28)	.001
History of smoking	300 (64.8)	18 (82)	293 (66)	.210
ASA >2	299 (64.6)	17 (77)	282 (64)	.202
Comorbidity (CCI)	5 (4-7)	7 (6-8)	5 (4-7)	.001
Hypertension	237 (51.2)	18 (82)	219 (50)	.003
Diabetes	110 (23.8)	12 (55)	98 (22)	.001
Cerebrovascular disease	155 (33.5)	9 (41)	146 (33)	.449
Chronic obstructive pulmonary disease	48 (10.4)	5 (23)	73 (16)	.396
Depression	200 (43.2)	13 (59)	187 (42)	.083
Cognitive impairment	58 (12.5)	11 (50)	47 (11)	<.001
Impaired renal function	60 (13.0)	5 (23)	55 (13)	.186
Type of surgery (open aortic or amputation)	115 (24.8)	18 (82)	97 (22)	<.001
Type of anesthesia (general)	327 (74.1)	17 (77)	310 (70)	.493
Hemoglobin, mg/L, mean ± SEM	8.4 ± 0.1	7.9 ± 0.4	8.4 ± 0.1	.150
CRP, mg/L, mean ± SEM	12.4 ± 1.4	55.4 ± 19.4	10.3 ± 1.1	<.001
Duration of surgery, minutes, mean ± SEM	210.9 ± 5.2	242.8 ± 28.0	209.3 ± 5.2	.240
Intraoperative blood loss, mL, mean ± SEM	459.3 ± 42.7	1135.3 ± 377.2	425.6 ± 42.2	<.001

ASA, American Society of Anesthesiologists (classification system for assessing the fitness of patients before surgery; range, 1-5); CCI, Charlson Comorbidity Index (predicts 1-year mortality based on age and patient's comorbidities; range, 0-19); CRP, C-reactive protein; SEM, standard error of the mean. Data are presented as number or median (percentage or interquartile range).

^aP values < .05 were considered significant.

Statistical analysis. Categorical variables were analyzed by means of the χ^2 test or Fisher exact test and presented as numbers and percentages. Continuous variables were tested with the Student *t*-test for normal distribution and the Mann-Whitney *U* test for skewed distribution and presented as median and interquartile range (IQR). Multiple imputation was used for correction of missing data in univariate and multivariate logistic regression. To perform multiple imputation, we used the following predictors: gender, age, length, body weight, alcohol consumption, comorbidity, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, ASA score, type of intervention, hemoglobin level postoperatively, and CRP level postoperatively. For the imputed data, continuous variables were presented as mean ± standard error of the mean. A multivariate step forward logistic regression analysis was performed to determine all independent risk factors for POD. We used a probability for entry of $P < .10$ and a probability for removal of $P > .05$. This applied for known risk factors that did not reach significance in univariate significance. For the final model, significance was set at $P < .05$. Independent risk factors were presented as odds ratio and 95% confidence interval. All statistical analyses were done with the Statistical Package for the Social Sciences (SPSS 22.0; SPSS, Chicago, Ill).

RESULTS

A total of 463 patients were included in this study. There were missing data for the following parameters: body mass index (4.5% missing), smoking status (2.8% and 1.9% missing), hemoglobin level (3.9% missing),

Table II. Risk of postoperative delirium (POD) compared with type of surgical procedure

Type of procedure	No. of patients (%)	POD		
		No.	Risk, %	95% CI
Open aortic surgery	73 (15.8)	11	15	8.6-25.0
Endovascular surgery	133 (28.7)	2	2	0.4-5.3
Peripheral bypass surgery	164 (35.4)	2	1	0.3-4.4
Arteriovenous shunt surgery	7 (1.5)	0	0	0-35.4
Percutaneous intervention	39 (8.4)	0	0	0-9.0
Amputation surgery	42 (9.1)	7	17	8.3-30.6
Miscellaneous	5 (1.1)	0	0	0-43.3
Total	463 (100)	22	5	3.2-7.1

CI, Confidence interval.

CRP level (34.8% missing), duration of surgery (9.7% missing), and amount of blood loss (31.5% missing). There was an unequal distribution in sex, with 356 men (76.9%) and 107 women (23.1%). Median age was 72 years (IQR, 66-77 years). The majority of patients were classified as ASA grade 2 (n = 163; 35.2%) and grade 3 (n = 283; 61.1%). There were no operative deaths. The characteristics of patients are summarized in Table I.

Predictors of delirium. Twenty-two patients (4.8%) with a median age of 70 years (IQR, 64-81 years) developed POD. The highest incidences were found in patients who had amputation surgery (16.7%) or open aortic surgery (15.1%). The lowest rates were found after endovascular surgery, peripheral bypass surgery, or percutaneous interventions (Table II). With univariate analyses, the following factors were associated with the occurrence of

Table III. Multivariate logistic regression analysis

Variable	β^a	OR	95% CI	P value ^b
Cognitive impairment (yes vs no) ^c	2.9	16.4	4.7-57.0	<.001
Type of procedure (open aortic surgery or amputation vs other)	2.7	14.0	3.9-49.8	<.001
Current smoking (yes vs no)	2.4	10.5	2.8-40.2	.001
Hypertension (yes vs no)	2.0	7.6	1.9-30.5	.004
Age \geq 80 years	2.0	7.3	1.8-30.1	.006
Maximal total score	12.0			

CI, Confidence interval; OR, odds ratio.

^aRegression coefficient.

^bP values < .05 were considered significant.

^cAs determined by a score of \geq 1 on the consistent item of the Groninger Frailty Indicator (GFI).

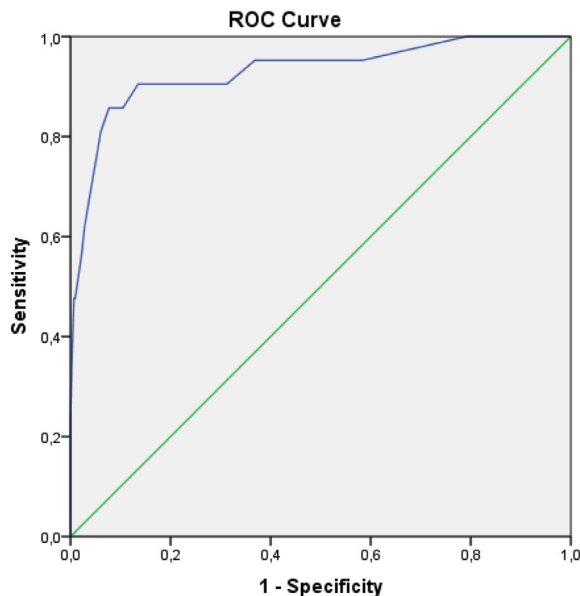


Fig. Receiver operating characteristic (ROC) curve for the final prediction model.

POD: current smoking, increased comorbidity, hypertension, diabetes mellitus, preoperative cognitive impairment, open aortic surgery or amputation surgery, elevated CRP level, and blood loss (Table I).

Multivariate analysis showed five independent risk factors for the occurrence of POD, including preoperative cognitive impairment, open aortic surgery or amputation surgery, current smoking, hypertension, and age \geq 80 years (Table III).

Score values were calculated by multiplying the coefficient β for the specific parameter by 1 (if present) or zero (if absent). Adding these values resulted in the total score. The maximal total score was 12.0.

In our cohort, the highest score of a single patient was 10. The median score was 2.4 (IQR, 2.0-4.4) in the non-POD group compared with 7.6 (IQR, 7.0-9.3) in patients with POD. Higher scores were associated with higher risks of POD.

The corresponding receiver operating characteristic curve for our model is presented in Fig. The area under

the curve is 0.93 (95% confidence interval, 0.9-1.0). On the basis of this curve, a cutoff score of 6.0 was chosen as being at increased risk for POD; 51 patients had a score \geq 6.0, and 399 patients had a score <6.0. The corresponding sensitivity and specificity were 86% and 92%. Positive and negative predictive values were 35% and 99%, respectively.

To confirm our results, we performed a sensitivity analysis without CRP and blood loss on the original data, including only patients with complete data. We found no differences in the results obtained with the imputed data.

Outcome after POD. Median hospital length of stay was 6 days, with a significant difference between groups: 12 days in patients with POD compared with 5 days in the non-POD group. In the POD group, the number of patients admitted to the ICU was higher (50.0% vs 24.5%) and the length of ICU stay was longer (3 days vs 2 days). Furthermore, patients with POD had more surgical complications (other than POD) (100% vs 34.9%). Outcome after discharge was worse in patients with POD in terms of postdischarge institutionalization (45.5% vs 6.1%) and 1-year mortality rates (22.7% vs 7.5%; Table IV).

DISCUSSION

This study shows the predictive value of various preoperative and intraoperative risk factors for the development of POD after vascular surgery. Although previous studies have looked into predictive indicators for the development of POD, only a few prospective cohort studies focus on risk factors within a population of vascular surgery patients.^{6-8,13,15,23-26} We present one of the largest prospective cohorts focusing primarily on vascular surgery patients. On the basis of these results, a selective group of patients can be classified as high risk. It has already been proved that adherence to a nonpharmacologic multicomponent intervention strategy plays an important role in preventing delirium in patients considered susceptible for the development of delirium. Therefore, it might be expected that this group of patients may potentially benefit from active geriatric counseling.²⁷ We found a POD incidence of only 4.8%, a result much lower than expected. Compared with reported incidences after elective vascular surgery in the literature, varying from 14% to 39%, this is much lower.^{6-8,13,15,23-26}

Table IV. Outcome after vascular surgery

Outcome parameter	Total (N = 463)	Delirium present (n = 22)	Delirium absent (n = 441)	P value ^a
Hospital length of stay, days, median (IQR)	6 (4-8)	12 (9-21)	5 (4-8)	<.001
ICU admittance (No. of patients)	119 (25.7)	11 (50)	108 (25)	.008
ICU length of stay, days, median (IQR)	2 (2-3)	3 (2-4)	2 (2-3)	.003
Complications ^b	176 (38.0)	22 (100)	154 (35)	<.001
Postdischarge institutionalization	37 (8.0)	10 (45)	27 (6)	<.001
One-year mortality	38 (8.2)	5 (23)	33 (8)	.026

ICU, Intensive care unit; IQR, interquartile range.

Data are presented as number (%) unless otherwise indicated.

^aP values < .05 were considered significant.

^bPostoperative surgical complications other than delirium.

There are a number of reasons for this. First, a low incidence of POD is not entirely uncommon in high-risk patients. A recent study in frail elderly cancer patients undergoing surgery for a solid tumor reported an incidence of only 11.9%.²⁸ Two other large studies found similar low percentages of 9% and 8%, respectively.^{14,29} Second, we included patients undergoing various vascular surgery procedures. As a result, only 15% of interventions consisted of open aortic repair, whereas 30% consisted of endovascular procedures. These minimally invasive interventions are more often associated with a lower POD incidence. Various studies on outcome after endovascular aneurysm repair compared with open aneurysm repair report significantly lower rates of POD in favor of endovascular aneurysm repair.^{25,30,31} Finally, we included only patients subjected to elective procedures, whereas emergency surgery is a known risk factor for POD.¹⁶

In this study, we identified cognitive impairment, open aortic surgery or amputation surgery, current smoking, hypertension, and age ≥ 80 years as independent risk factors for the occurrence of POD. Various other studies, including a recent systematic review, also concluded that cognitive impairment is one of the strongest predictors for POD.^{3,4,15} It is suggested that changes in the brain's neurons or neurotransmitters lead to an increased risk of cognitive disruption in patients with preoperative cognitive impairment. Conflicting results have been published regarding the role of nicotine abuse in the development of POD.^{7,8} A direct neurotoxic effect in the brain and microvascular changes are thought to cause reduced executive function and cognitive reserve.^{32,33} Our findings, in which current smoking is a risk factor in contrast to history of smoking, could indicate a greater role for the first pathophysiologic pathway.

We found the highest POD incidence after open aortic surgery and amputation surgery (15.1% and 16.7%, respectively), a result that has been published previously.⁴ The extent of the procedure in conjunction with greater amounts of blood loss, an increased inflammatory response, and oxidative stress may offer a possible explanation for this increased risk of POD after open aortic surgery. This pathophysiologic process may also apply to amputation surgery, although this cannot be ascertained on the basis of our data.

Conditions that indicate vascular damage or increase vascular risk are thought to be associated with POD,

and this is consistent with our finding in which atherosclerosis was determined as a risk factor for POD.^{5,17,34} The Leiden 85-plus study assessed the relationship of generalized atherosclerosis and cognitive decline in a community-dwelling elderly population and demonstrated that in old age, generalized atherosclerosis is indeed associated with cognitive decline.³⁵ Although in this study there were more men than women suffering from POD (5.6% vs 1.9%), this difference did not reach statistical significance. Although conflicting results are reported, studies that did find a positive association between male sex and POD suggest that the increased cardiovascular risk profile in men is a possible explanation for the sexual differences in POD.^{14,36}

Outcome after surgery was significantly worse in patients suffering from POD in terms of complications, hospital length of stay, ICU admission, ICU length of stay, and institutionalization after discharge. These findings are consistent with the literature.³ Since cause and effect can easily intersect in POD, we are reluctant to make assumptions about the role of POD on outcome after surgery. However, on the basis of these outcomes, it is reasonable to conclude that there is a strong correlation. Although not an end point in this study, we know from both the literature and our own experiences that many patients do not fully recover cognitively after an episode of delirium.³⁷ When this is taken into account, the question of whether POD is actually a result of any other complication or a precipitating factor seems less important from a clinical perspective.

There are several drawbacks in this study that need to be addressed. Because of the low incidence of POD, the problem of underfitting occurred in our multivariate analysis.³⁸ This enables the possibility that important risk factors are unjustly excluded from our prediction model. Despite this, when our model is used, a significant group of high-risk patients can still be identified who will be able to benefit.

Because of missing data, we relied on the method of imputing data regarding CRP level and amount of blood loss. Although this is a statistically validated method leading to reliable outcomes, there is a possibility that this might have led to an underestimation of the role for those particular variables.

We would also have preferred to split our cohort in multiple subgroups to validate our model. Because the POD incidence was lower than expected, this method would have then led to unreliable outcomes. The cutoff score of 6.0 was arbitrarily chosen as a threshold for high-risk patients with concomitant specificity and sensitivity of 92% and 86% and a negative predictive value of 99%. In contrast to those high percentages, the positive predictive value was only 35%. This results in a substantial amount of patients who are wrongly regarded as high risk. Given the importance of POD on outcome after surgery and the minimal negative effects of high-standard delirium care, we considered this an appropriate tradeoff. In addition, other models designed to predict POD in various groups of patients show similar results, implicating the difficulty with regard to predicting POD. Depression is assumed to be a risk factor for POD, but our results could not confirm this assumption.⁷ Although the Hamilton Depression Scale is a conventional tool to score for depression, we chose to use the consistent items of the GFI.³⁹ Because previous studies by our group did find a relation between depression and POD, we do not think using another screening tool would have altered those results as different tools have also led to conflicting results.^{18,40,41} To confirm our results, we started an internal and external validation for our model, from which we hope to present the results in the coming years.

CONCLUSIONS

This prospective study supports the conventional conception that POD is a multifactorial disease. Cognitive impairment, open aortic surgery or amputation surgery, smoking, hypertension, and age ≥ 80 years were identified as independent risk factors. Postoperative outcome was significantly worse in delirious patients in terms of hospital length of stay, mortality, and more institutionalization, making it a serious complication after surgery. Patients who have the above-mentioned risk factors should be considered for high-standard delirium care.

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AUTHOR CONTRIBUTIONS

Conception and design: LV, RP

Analysis and interpretation: LV, BL, GI, RP

Data collection: LV, AP

Writing the article: LV, RP

Critical revision of the article: LV, AP, MvdL, BL, GI, CZ, RP

Final approval of the article: LV, AP, MvdL, BL, GI, CZ, RP

Statistical analysis: LV, RP

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Overall responsibility: RP

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