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Clinical Research

Clinical Predictors and Outcomes Associated with Postoperative Delirium Following Infrainguinal Bypass Surgery

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Background: Post-operative delirium (POD) is common yet often underdiagnosed following vascular surgery. Elderly patients with advanced peripheral artery disease may be at particular risk for POD yet understanding of the clinical predictors and impact of POD is incomplete. We sought to identify POD predictors and associated resource utilization after infrainguinal lower extremity bypass.
Methods: This single center retrospective analysis included all infrainguinal bypass cases performed for peripheral arterial disease from 2012–2020. The primary outcome was inpatient POD. Delirium sequelae were also evaluated. Key secondary outcomes were length of stay, nonhome discharge, readmission, 30-day amputation, post-operative myocardial infarction, mortality, and 2-year survival. Regression analysis was used to evaluate risk factors for delirium in addition to association with 2-year survival and amputation free survival.
Results: Among 420 subjects undergoing infrainguinal lower extremity bypass, 105 (25%) developed POD. Individuals with POD were older and more likely to have non-elective surgery ($P < 0.05$). On multivariable analysis, independent predictors of POD were age 60–89 years old, chronic limb threatening ischemia, female sex, and nonelective procedure. Consultations for POD took place for 25 cases (24%); 13 (52%) were with pharmacists, and only 4 (16%) resulted in recommendations. The average length of stay for those with POD was higher (17 days vs. 9 days; $P < 0.001$). POD was associated with increased non-home discharge (61.8% vs. 22.1%; $P < 0.001$), 30-day major amputation (6.7% vs. 1.6%; $P < 0.01$), 30-day post-operative myocardial infarction (11.4% vs. 4.1%; $P < 0.01$), and 90-day mortality (7.6% vs. 2.9%; $P = 0.03$). Survival at 2 years was lower in those with delirium (89% vs. 75%; $P < 0.001$). In a Cox proportional hazards model, delirium was independently associated with decreased survival (HR = 2.0; 95% CI = 1.15–3.38; $P = 0.014$) and decreased major-amputation free survival (HR = 1.9; 95% CI = 1.18–2.96; $P = 0.007$).
Conclusions: POD is common following infrainguinal lower extremity bypass and is associated with other adverse post-operative outcomes and increased resource utilization, including increased hospital length of stay, nonhome discharge, and worse 2-year survival. Future studies should evaluate the role of routine multidisciplinary care for high-risk patients to improve perioperative outcomes for vulnerable older adults undergoing infrainguinal lower extremity bypass.

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INTRODUCTION

In the United States, the population of adults 65 years and older is projected to nearly double by 2060 and age is an independent risk factor for the development of peripheral arterial disease (PAD).[1,2] Consequently, the number of patients requiring vascular surgery with its attendant physiologic demand is expected to grow. Patients requiring vascular surgery are some of the most complex and frail of any surgical population demonstrating the importance of better understanding the role of geriatric vulnerabilities in this population.[3,4]

One known complication following surgery in older adults with geriatric vulnerabilities is

post-operative delirium (POD) and has a reported incidence ranging from 5−39% following vascular surgery.[5] Delirium is defined as an acute, fluctuating disturbance in attention and awareness with associated cognitive dysfunction.[6] Despite standardized methods for delirium diagnosis, POD is commonly missed in up to 50% of hospitalized patients.[7] The fluctuating nature of delirium coupled with poor provider recognition and documentation, contribute to underdiagnosis.[7] Although, POD can affect all patients undergoing surgery, older adults are at elevated risk. A higher prevalence of comorbid conditions in older adults, including cognitive and sensory impairment, contributes to their elevated risk of POD.[5,8] Frailty, an age-related syndrome of decreased physiologic reserve, is associated with adverse post-operative outcomes, including POD.[9]

When uncontrolled, PAD can progress to chronic limb threatening ischemia (CLTI), which can be an indication for surgery. Major vascular surgery procedures such as lower extremity bypass (LEB) incur a high physiologic demand that can further exacerbate the risk of POD. This is particularly important because POD is known to be associated with increased rates of post-operative complications, nonhome discharge, and mortality across surgical specialties.[10] Whereas evidence has shown that patients undergoing major vascular surgery are at elevated risk for delirium,[8] its impact on perioperative outcomes and resource utilization after LEB is poorly described. We therefore sought to identify independent clinical predictors of POD and investigate its impact on resource utilization. We hypothesized that POD could be predicted and POD would be associated with increased healthcare resource utilization.

MATERIALS AND METHODS

Cohort

This was a single center retrospective analysis of unique cases treated at the University of California, San Francisco. Inclusion criteria were LEB for intermittent claudication or CLTI from 2012−2020. Cases were extracted from an electronic data warehouse with procedural, demographic, and outcome data audited by chart review. Preoperative diagnoses were identified using International Classification of Disease (ICD) codes. Frailty was defined using a previously described 11-item modified frailty index (mFI) score which was calculated by dividing the total number of included comorbidities by 11[11]; mFI scores $\geq$0.18 were considered frail. The optimal score cut-off was determined via Youden cutpoint estimation. The Committee on Human Research of the University of California, San Francisco approved this study (IRB 20−30112). Due to the observational nature of this study, participant consent was waived.

POD Identification

The primary outcome was POD, identified via a manual chart review method which has been validated against the Confusion Assessment Method (CAM) with 74% sensitivity and 83% specificity.[12] This method entailed screening all post-operative progress, nursing, and consult notes for evidence of an acute change in mental status; evidence of key words such as delirium, inattention, disorientation, confusion, hallucinations, and agitation aided in identification. During the study period, covering ward nurses performed routine shift Nu-DESC delirium assessments. Delirium timing was recorded, and only post-operative inpatient events were considered POD.

Outcomes

POD sequelae were characterized by evaluating the use of sitters, physical restraints, and reports of the subject pulling on equipment (not mutually exclusive). The use of consultation for POD was evaluated and classified by consultant specialty, indication for consultation, and the resulting recommendation(s) if any. Secondary outcomes included length of inpatient hospital stay, nonhome discharge (discharge to nursing facility or rehabilitation center), readmission at 30 days, major amputation at 30 days, postoperative myocardial infarction at 30 days, postoperative venous thromboembolism, mortality at 30 and 90 days, and survival at 2 years.

Statistical Methods

Continuous variables are reported as mean ± standard deviation (SD) and percentage. Bivariate analysis was performed: Student's *t*-test was used for normally distributed continuous variables, χ^2 analysis was used for counts, and Fisher's exact test for expected low cell counts as appropriate to the data. POD's association with 2-year survival was assessed using Kaplan-Meier analysis and multivariable Cox regression. A manual stepwise binary logistic regression identified independent predictors for POD. All variables with $P < 0.1$ on bivariate analysis were assessed for model inclusion; exit criterion was $P > 0.05$. All statistical analysis was performed on Stata (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

RESULTS

Study Population Demographics

During the study period, 420 subjects underwent LEB. The average age was 68.4 ± 12.6 and the majority of the population was male (63.6%). The majority of the cohort identified as White race (70.2%), 7.9% as Black race, 6.7% as Asian race and 10.2% as Hispanic/Latinx ethnicity. In addition, 48.2% of cases had diabetes mellitus, 17.1% had end stage renal disease, 89.8% were classified as frail, and 4% had a preoperative diagnosis of dementia (Table I).

Incidence and Predictors of POD

Within the 420 LEB cases 105 (25%) developed POD. On average, subjects with POD were older compared to subjects without POD (74.3 ± 10.0 vs. 66.5 ± 12.8; $P < 0.01$). After stratifying the cohort by age decade, we found the highest incidence of POD in the 80–89-year-old group (35.4%) (Table I). On bivariate analysis, POD was associated with female sex (32.7% vs. 20.6%, $P = 0.006$), Asian race (42.9% vs. 23.7%; $P = 0.024$), non-elective (urgent or emergent) surgery (33.0% vs. 18.7%; $P = 0.001$), CLTI (30.7% vs. 16.0%; $P < 0.001$), frailty (26.5% vs. 11.6%; $P = 0.033$), and those with preoperative dementia (53.0% vs. 23.8%; $P = 0.007$). Among those with preoperative dementia, median age was 76.0 (IQR = 71.2–81.6). Hispanic ethnicity was associated with decreased rates of POD (11.6% vs. 26.5%; $P = 0.033$) (Table I); however, Hispanic patients were younger (mean age 60.6 vs. 69.4; $P < 0.001$). On multivariable binary logistic regression for POD, independent risk factors were nonelective procedure, female sex, age, and CLTI as the indication for surgery (c-statistic = 0.72) (Table II).

Outcomes and Interventions Associated with POD

Within the group who developed POD, 32% required a sitter, 16% physical restraints, 25% pulled out equipment, and 24% had a specialist consultation for delirium (Table III). Most consults (52%) were to pharmacy, of which only 4 (31%) resulted in a recommendation all only addressing medication changes. Consults to the pain medicine service (24%) and psychiatry (24%) always resulted in a recommendation for a medication change. Furthermore, psychiatry recommended environmental interventions in 67% of their consults in contrast to pharmacy and the pain medicine service that did not comment on environment in any of their consultations (Table IV).

On bivariate analysis, POD was associated with longer inpatient length of stay (17 days vs. 9 days; $P < 0.01$), non-home discharge (62% vs. 22%; $P < 0.01$), increased rate of major amputation at 30 days (6.7% vs. 1.6%; $P = 0.007$), post-operative myocardial infarction at 30 days (6.7% vs. 1.6%; $P = 0.007$) and mortality at 90 days (7.6% vs. 2.9%; $P = 0.03$) (Table V). On Kaplan-Meier analysis, POD was associated with decreased 2-year survival (75% vs. 89%; $P < 0.001$) (Fig. 1). Additionally, POD was associated with decreased major amputation free survival at 2 years (64.8% vs. 83.2%; $P < 0.001$) (Fig. 2). On multivariable Cox regression for 2-year survival, delirium was independently associated with worse survival (Hazards Ratio = 2.0; 95% confidence interval:1.15–3.38; $P = 0.014$) after adjusting for operative indication, elective status, race, age, and preoperative MI diagnosis. Furthermore, delirium was independently associated with worse major amputation free survival (Hazards Ratio = 1.9; 95% CI:1.18–2.96; $P = 0.007$) after adjusting for age, race, sex, ethnicity, elective status, operative indication, frailty, preoperative coronary artery disease, preoperative dementia, and preoperative end-stage renal disease diagnosis.

DISCUSSION

In this retrospective study at a single tertiary care center, POD after infrainguinal LEB was identified in a quarter of cases and was associated with increased resource utilization and worse 2-year

Table I. Study population demographics and post-operative delirium incidence

Category	Total (%)[a]	Delirium (%)[b]	*P*-value
Infrainguinal LEB[c]	420 (100)	105 (25)	
Age	68.4 (SD 12.6)	74.3 (SD 10.0)	<0.001
Age Group			<0.001
<60	91 (21.7)	9 (9.9)	
60−69	127 (30.2)	27 (21.3)	
70−79	126 (30.0)	35 (27.8)	
80−89	68 (16.2)	31 (45.6)	
≥90	8 (1.9)	3 (37.5)	
Sex			0.006
Female	153 (36.4)	50 (32.7)	
Male	267 (63.6)	55 (20.6)	
Race			
White			0.33
Yes	295 (70.2)	70 (23.7)	
No	125 (31.3)	35 (28.0)	
Black			0.464
Yes	33 (7.9)	10 (30.3)	
No	387 (92.1)	95 (24.5)	
Asian			0.024
Yes	28 (6.7)	12 (42.9)	
No	392 (93.3)	93 (23.7)	
Other			0.427
Yes	64 (15.2)	13 (20.3)	
No	356 (84.8)	92 (25.8)	
Hispanic			0.033
Yes	43 (10.2)	5 (11.6)	
No	377 (89.8)	100 (26.5)	
Urgency			0.001
Elective	235 (56.0)	44 (18.7)	
Urgent/Emergent	185 (44.0)	61 (33.0)	
CLTI[d]			<0.001
Yes	257 (61.2)	79 (30.7)	
No	163 (38.8)	26 (16.0)	
Coronary Artery Disease			0.183
Yes	161 (38.3)	46 (28.6)	
No	259 (61.7)	59 (22.8)	
COPD			0.94
Yes	71 (16.9)	18 (25.4)	
No	349 (83.1)	87 (24.9)	
Diabetes Mellitus			0.09
Yes	202 (48.1)	58 (28.7)	
No	218 (51.9)	47 (21.6)	
End Stage Renal Disease			0.07
Yes	72 (17.1)	24 (33.3)	
No	348 (82.9)	81 (23.3)	
Smoking			0.41
Yes	146 (34.8)	33 (22.6)	
No	274 (65.2)	72 (26.2)	
Preoperative Statin			0.885
Yes	342 (81.4)	86 (25.2)	
No	78 (18.6)	19 (24.4)	
Preoperative Dementia			0.007
Yes	17 (4.0)	9 (53.0)	
No	403 (96.0)	96 (23.8)	

(*Continued*)

Table I. Continued

Category	Total (%)[a]	Delirium (%)[b]	*P*-value
Frail			0.033
Yes	377 (89.8)	100 (26.5)	
No	43 (10.2)	5 (11.6)	

Chronic Obstructive Pulmonary Disease.
[a]Column percentage.
[b]Row percentage.
[c]Lower Extremity Bypass.
[d]Chronic Limb Threatening Ischemia.

Table II. Binary logistic regression model predicting delirium incidence

Variable	Odds ratio	95% CI	*P*-value
Age (Reference <60 years)			
60–69 years old	2.30	1.08–4.89	0.031
70–79 years old	2.88	1.38–6.01	0.005
80–89 years old	5.92	2.67–13.11	<0.001
Female Sex (reference Male sex)	1.73	1.08–2.79	0.024
Non-Elective Procedure	2.15	1.33–3.47	0.002
CLTI[a]	1.92	1.12–3.26	0.017
C-Statistic = 0.72			

[a]Chronic Limb Threatening Ischemia–reference group intermittent claudication.

Table III. Characterization of delirium sequelae

Delirium sequelae	Number of patients with delirium (%)
Sitter	34 (32)
Restraints	17 (16)
Pulled Out Equipment	26 (25)
Consults for Delirium	25 (24)

survival. After adjusting for demographic variables and medical, POD was independently associated with twice the hazards for death over 2-years. This study highlights the importance of identifying and addressing delirium after LEB given the significant associations with worse outcomes and underscores the need to identify patients at increased risk and develop better prevention and treatment strategies.

Our study's estimate of POD incidence falls within the range of 24–43% reported in subjects 65 and older undergoing LEB for CLTI.[13–15] In our study, delirium was most common in older subjects and age was an independent predictor of delirium. With increasing age, physiologic reserve decreases along with structural changes to the brain like cerebral atrophy predisposing older adults to delirium.[16,17] Furthermore, endothelial dysfunction, a fundamental pathophysiologic mechanism behind atherosclerosis and PAD also predisposes individuals to delirium.[18,19] Given the high risk for POD, older patients with atherosclerotic disease and PAD may benefit from preoperative screening for delirium risk.

Our finding that other delirium predictors in our study included non-elective surgery, CLTI, and female sex aligns with results from previous studies. In a recent systematic review, emergency surgery was an independent intraoperative risk factor for development of POD in patients undergoing vascular surgery.[8] Nonelective cases may be associated with pain, inflammation and/or infection which have been found to increase the risk of inpatient delirium.[20,21] CLTI, previously reported as an independent risk factor for POD,[5,14] is associated with systemic atherosclerotic disease, which contributes to accelerated cognitive decline.[22,23] Cognitive impairment is a known risk factor for POD.[5,24,25] However, in our study, preoperative cognitive impairment did not remain statistically significant on multivariable analysis, although this may be secondary to a type II error. Cognitive impairment is frequently unrecognized and poorly

Table IV. Delirium consultants and recommendation characterization

Service	Total (%)	Recommendation (%)	Medication change (%)	Environment change (%)
Pharmacy	13 (52)	4 (30.8)	4 (100)	0
Pain Medicine	6 (24)	6 (100)	6 (100)	0
Psychiatry	6 (24)	6 (100)	6 (100)	4 (66.7)

coded potentially contributing to the low frequency in our study population.[26] CLTI contributes to functional impairment, predisposing patients to POD.[25] In our 80–89-year-old subjects who had CLTI or nonelective surgery, POD incidence was 51% and 54% respectively, suggesting an increased need for preventative measures in these groups. An unexpected finding was that female sex was independently associated with increased odds of delirium on multivariable analysis. A prior study found that male sex was a risk factor for hyperactive delirium following hip replacement.[27] Our finding may be a result of differences in patient demographics between LEB and hip fracture patients, differences in screening practices, and inclusion of hypoactive delirium in our study, which is more common in female patients.[28]

Using the 11-item mFI score, frailty was not an independent predictor of POD. On bivariate analysis, frailty was associated with POD; after accounting for age, this association did not persist. Cognitive impairment, a component of frailty and known predictor of POD, shares a high collinearity with age, which may account for the association between frailty and POD on bivariate analysis. It remains unclear if it is the components of frailty or the overall phenotype of frailty that predicts POD. Additionally, our study lacked a direct measurement of patient function. Other frailty scores that directly measure patient function or are designed for individual assessment have been shown to be associated with POD.[13,29]

Consultation for delirium was requested in 24% of POD cases. Pharmacists were consulted the most often, but less than a third recommended any medication changes. Pain medicine and psychiatric providers recommended changes to pain management or discontinuation of deliriogenic medications in all their consults. Additionally, psychiatrist consultants provided nonpharmacologic environmental interventions such as removal of tethers to encourage mobilization, exposure to daylight to promote sleep-wake cycle, frequent reorientation, and stimulation with TV/activities. At our institution, inpatient geriatric consultation was available only after 2018, but even when they were available, no geriatric consultations were performed. Interestingly, proactive geriatrics consultation reduced delirium incidence by one-third and severe delirium by one-half in hip fracture patients 65 years and older.[30] These consultations included assessment and recommendations regarding oxygen, fluid electrolyte balance, pain control, elimination of unnecessary medications, bowel and bladder function, nutritional intake, early mobilization, post-operative complications, environmental stimuli, and treatment of agitation.[30] With a focus on multicomponent interventions such as frequent reorientation, mobilization, sensory aids, promotion of sleep, improved nutrition status, and reducing polypharmacy, geriatric consultations may provide essential guidance to reduce the incidence and detrimental effects of delirium.[30] The specific benefit of geriatric consultation should therefore be studied in vascular surgery patients.

Our study found that POD is associated with increased resource utilization and adverse post-operative outcomes following LEB. This is consistent with previous studies in aortic surgery and lower extremity major amputation that demonstrated an increased length of stay in patients with POD.[31–33] A study of delirium after vascular surgery, including peripheral bypass, found that POD was associated with nonhome discharge and mortality, which concurs with our findings.[34] In addition, a study of open and endovascular procedures for lower extremity PAD found that POD was associated with worse 2-year amputation free survival.[35] In the ICU, delirium has been associated with a significant increase in costs, even after controlling for length of stay and illness severity.[36] To help relieve the burden that POD places on resource utilization, patients undergoing LEB may benefit from increased preoperative risk screening. Risk factors identified in our study can help to identify high risk populations who could benefit from comprehensive geriatric assessment which has been shown to reduce the risk of POD.[37]

Our study should be considered in the context of its limitations. This analysis is from a single tertiary care center and therefore the study population

Table V. Post-operative outcomes by delirium status

Outcome	Total (%)	Delirium (%)	No delirium (%)	*P*-value
Length of Stay	10.8 (SD 12.6)	16.7 (SD 20.6)	8.8 (SD 7.5)	<0.001
Non-Home Discharge	131 (32.0)	63 (61.8)	68 (22.1)	<0.001
Readmission 30 days	86 (20.5)	25 (29.1)	61 (70.9)	0.955
Major Amputation 30 days	12 (2.9)	7 (6.7)	5 (1.6)	0.013
Post-operative MI[a] 30 days	25 (6.0)	12 (11.4)	13 (4.1)	0.006
Mortality 30 days	5 (1.2)	3 (60)	2 (40)	0.07
Mortality 90 days	17 (4.1)	8 (7.6)	9 (2.9)	0.033
Venous Thromboembolism	6 (1.4)	3 (2.9)	3 (1.0)	0.351

[a]Myocardial Infarction.

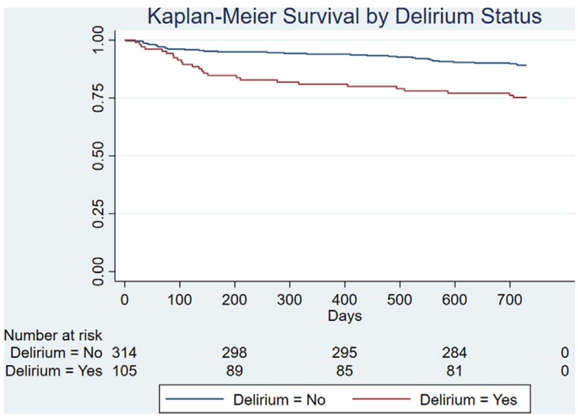

Fig. 1. Survival Analysis by Delirium Status. Kaplan Meier analysis demonstrated a significant difference in survival (79% vs. 89%; $P < 0.001$) at 2 years between those with delirium and those without delirium.

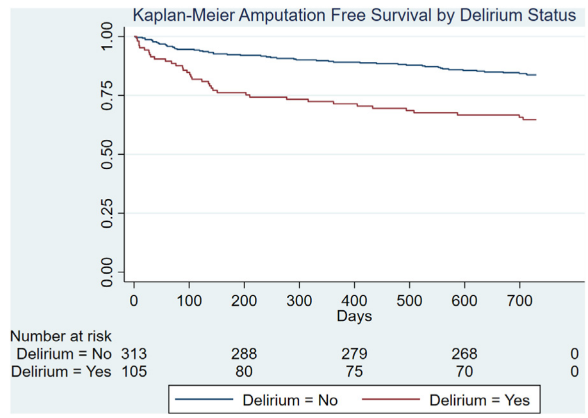

Fig. 2. Major Amputation Free Survival by Delirium Status. Kaplan Meier analysis demonstrated a significant difference in amputation free survival (64.8% vs. 83.2%; $P < 0.001$) at 2 years between those with delirium and those without delirium.

may not be representative of the general population in the United States. In addition, this was a retrospective analysis, so we cannot infer causality regarding delirium's relationship with post-operative outcomes. Moreover, there was limited data on other comorbidities such as functional status and current smoking status that may also contribute to delirium incidence. This data could be important since previous studies have shown functional status, substance abuse, and current smoking status to be independent predictors of POD.[34,38] There was also limited data on post-operative analgesia and infectious complications that may also contribute to delirium incidence and worse outcomes. A focus for future study is the effect of a delirium care bundle, which incorporates specific interventions aimed at reducing delirium incidence such as limiting the use of opioid medications. Finally, delirium was identified by manual chart review using a validated method but may inaccurately identify delirium.[12] Despite these limitations, this study identifies delirium predictors and describes the impact that POD may have on postoperative outcomes; this work can inspire the design of interventions to minimize adverse outcomes in vulnerable patients.

CONCLUSION

POD is a serious, yet common and often unrecognized complication associated with downstream hospital resource utilization. In this single center retrospective study, POD following LEB was found following 25% of cases and was associated with increased resource utilization and worse 2-year survival. Our findings indicate that individuals undergoing LEB are particularly vulnerable to POD, and that more research is warranted on how to prevent and mitigate delirium, including whether pre-operative geriatric assessment and peri-operative delirium prevention strategies can decrease the risk of POD after LEB.

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