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Risk factors for postoperative delirium after colorectal operation

Frederik J. van der Sluis, MD,[a] Pieter L. Buisman,[a] Mark Meerdink, MD,[a] Wouter B. aan de Stegge, MD,[a] Boudewijn van Etten, MD, PhD,[b] Geertruida H. de Bock, PhD,[c] Barbara L. van Leeuwen, MD, PhD,[a] *and* **Robert A. Pol, MD, PhD,[a]** *Groningen, The Netherlands*

Background. *A clear understanding of risk factors for postoperative delirium helps in the selection of individuals who might benefit from targeted perioperative intervention. The aim of this study was to identify risk factors for postoperative delirium after colorectal operation for malignancy.*
Methods. *All consecutive patients who underwent elective or emergency operation because of malignancy of the colon, sigmoid, or rectum between 2009 and 2012 were included in this study. Potential risk factors for postoperative delirium were selected based on previous studies. These candidate factors were analyzed using univariate and multivariate logistic regression analysis. Based on this analysis, odds ratios and 95% confidence intervals were estimated.*
Results. *A total of 436 patients underwent an oncologic resection of the colon, sigmoid, or rectum. Postoperative delirium was observed in 45 (10.3%) patients. Patients with a delirium had a greater in-hospital mortality rate (8.9% vs 3.6%,* P *= .09), spent more days in the intensive care unit, and had a longer total hospital stay. Variables associated with postoperative delirium in univariate analyses were age, American Society of Anesthesiologists classification, blood transfusion, history of psychiatric disease, history of cerebrovascular disease, postoperative pain management, postoperative renal impairment, C-reactive protein levels, leukocyte blood count, and postoperative complications. Independent risk factors were history of psychiatric disease (odds ratio 8.38, 95% confidence interval: 1.50–46.82), age (odds ratio 4.01, 95% confidence interval; 1.55–10.37), and perioperative blood transfusion (odds ratio 2.37, 95% confidence interval; 1.11–5.06).*
Conclusion. *This study shows that postoperative delirium is a frequently encountered complication after colorectal operation. Three independent risk factors for postoperative delirium were identified (history of psychiatric disease, age, and perioperative transfusion) that may contribute to risk estimation in this patient population. (Surgery 2017;161:704-11.)*

From the Department of Surgical Oncology[a], Department of Colorectal Surgery[b], and Department of Epidemiology[c], University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Postoperative delirium (POD) is a common and important complication after operation. It is defined as an acutely altered and fluctuating mental status with features of inattention, disturbance, and an altered level of consciousness.[1]

The development of delirium during hospital admission is associated with functional decline, longer hospitalization and institutionalization, and increased mortality.[2,3] Although delirium may occur in patients of any age, it is particularly common among the elderly.[1] In the overall population of hospitalized patients, incidences ranging from 11% to 42% have been reported.[4] Among frail elderly patients, POD has a prevalence of up to 60% after major emergency operation.[5]

With the population aging at an unprecedented rate, the number of operative procedures on the elderly will continue to increase. Additionally, because of improvements in operative and anesthetic care and the development of less invasive

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Reprint requests: Frederik J. van der Sluis, MD, Department of Surgical Oncology, University Medical Center Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands. E-mail: f.j.van.der.sluis@isala.nl.

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operative techniques, more elderly patients are considered for major colorectal operation. The incidence of POD is therefore expected to increase in the coming decades.

Interventions aimed at reducing the prevalence of delirium in frail elderly patients have proven to be effective.[6] Whether using these preventative measures is effective in reducing POD in the overall population of elderly patients undergoing major operation remains to be determined. A recent study demonstrated no evident effect of structured perioperative measures on POD reduction after major operation for malignancy in the overall population of patients aged >65 years.[7]

Interventions aimed at reducing risk of POD, however, seem to be more effective when the risk of POD is >30%.[6] To take full advantage of available resources and employ a cost-effective strategy for POD prevention, interventions should be targeted at high-risk populations. A clear understanding of risk factors might help select individuals at increased risk for POD who might benefit from targeted perioperative intervention.

Risk factors and incidences of POD have been extensively studied in the field of cardiac and orthopedic surgery, yet only a few studies have assessed the incidence and risk factors of POD in the specific population of patients undergoing colorectal operations.[8-10] The aim of this study was to identify independent risk factors for POD in patients after colorectal operation because of a malignancy.

MATERIALS AND METHODS

Population. All consecutive patients aged >40 years who underwent either elective or emergency colorectal resection for malignancy between 2009 and 2012 at University Medical Center Groningen, the Netherlands, were included in this study. University Medical Center Groningen is a tertiary referral center serving a population of approximately 1 million in the northern part of the Netherlands. As this was an observational study, and patient data were stored in a hospital database from which data could not be reduced to individual patients, the study received ethical review board approval. Patient data were processed and stored according to the Declaration of Helsinki—ethical principles for medical research involving human subjects.

Collected data. During the study period, patient data were collected prospectively and stored anonymously in an electronic database. Stored data consisted of patient demographics, procedure details, and candidate risk factors. Parameters considered as potential risk factors were identified based on study results published previously.[8-15]

Candidate risk factors were perioperative blood transfusion (defined as transfusion during the week prior to operation or during postoperative hospital stay), decreased postoperative hemoglobin level, emergency operation (operation required and undertaken within 24 hours of acute admission), duration of anesthesia, postoperative pain management (defined as either epidural analgesia or opioid analgesia, including patient-controlled intravenous analgesia), Charlson comorbidity index,[16] American Society of Anesthesiologists (ASA) classification,[17] alcohol abuse (self-reported consumption of >4 units daily average), history of psychiatric disease (mental disorder documented preoperatively by psychiatrist), dementia or early signs of dementia, history of cerebrovascular disease (documented cerebrovascular accident or transient ischemic attack), chronic preoperative use of analgesics, elevated preoperative blood urea nitrogen (>7.5 mmol/L according to local laboratory reference range), postoperative renal impairment defined as glomerular filtration rate <45 mL/min $\times$ 1.73 m^2 (lowest value measured until the third postoperative day), postoperative C-reactive protein (CRP) levels (greatest value measured until the fourth postoperative day, mg/L), postoperative leukocyte count (greatest value measured until the fourth postoperative day, 10^9/L), and postoperative complications (most serious complication during hospital admission according to the Clavien-Dindo classification of surgical complications other than POD).

Postoperative CRP levels were dichotomized according to what was assumed to be a normal postoperative response (CRP <150 mg/L) and an elevated postoperative response (CRP ≥150 mg/L). The same was done for postoperative leukocyte blood count (normal <15.0 $\times$ 10^9/L, elevated ≥15.0 $\times$ 10^9/L) and decreased postoperative hemoglobin level (<2 mmol/L, >2 mmol/L decrease).

The primary outcome variable was POD, defined as a postoperative disturbance of consciousness with reduced ability to focus, sustain, or shift attention during the concerning hospital admission. Three times a day delirium observation screening (DOS) scores[18] were obtained from all patients. In patients observed to have a DOS score of 3 and greater, the geriatrician was consulted to confirm the POD diagnosis according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition criteria.[19]

Patients who developed POD 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 when necessary. According to the standardized hospital protocol, haloperidol was the medical treatment of choice for symptom control, supplemented by benzodiazepines when necessary. Secondary outcome variables were hospital length of stay (HLOS), admittance to the intensive care unit (ICU), duration of stay on the ICU, and 1-year mortality.

Statistical analysis. Univariate analysis was performed to identify potential risk factors for the primary outcome variable POD. Continuous variables were categorized into subgroups representing strata of increased risk for POD. Subgroups were compared using the unadjusted odds ratio (OR). The group representing the lowest risk for POD was considered to be the reference group (OR = 1). After univariate analysis, a multiple logistic regression analysis was performed linking the explanatory variables to the primary outcome variable. Parameters with a P value $< .10$ in univariate analysis were considered for multivariate analysis.

For 4 parameters, missing data were observed: leukocyte count (13.9%), postoperative glomerular filtration rate (6.8%), postoperative hemoglobin levels (4.3%), and CRP (19.4%). Missing value analysis was conducted by performing Little's missing completely at random test to identify potential patterns in missing data that might bias the analysis. Because the missing completely at random test was not significant (χ^2 = 62.14, DF = 55, Sig = 0.24), it was concluded that the data were missing at random, and a multiple missing value imputation technique was applied. The robustness of our findings and the validity of the data imputation technique were tested by conducting a sensitivity analysis of our primary results using only patients with complete data.

The Statistical Package for the Social Sciences (SPSS version 20.0; IBM Corp, Armonk, NY) was used for all calculations.

Table I. Patient and disease characteristics

Total no. of patients	N = *436*
Sex (male)	246 (56.4)
Age (y)	
40–69	266 (61.0)
70–79	124 (28.4)
>80	46 (10.6)
Charlson comorbidity index	
0–1	347 (79.6)
2–3	72 (16.5)
4–5	14 (3.3)
6–7	2 (0.5)
8	1 (0.2)
ASA classification	
1	57 (13.1)
2	235 (53.9)
3	136 (31.2)
4	8 (1.8)
Emergency operation	
No	380 (87.2)
Yes	56 (12.8)
Neoadjuvant therapy	
No	269 (61.7)
Yes	167 (38.3)
Recurrent disease	
No	407 (93.3)
Yes	29 (6.7)
Transfusion	
No	281 (64.4)
Yes	155 (35.6)
Procedure	
Partial colectomy*	191 (43.8)
Total colectomy	12 (2.8)
Anterior resection	73 (16.7)
Abdominoperineal resection	78 (17.9)
Total pelvic exenteration	31 (7.1)
HIPEC	51 (11.7)
Cancer stage†	
I	77 (17.7)
II	119 (27.3)
III	88 (20.2)
IV	152 (34.9)

*Including right and left hemicolectomy, transversectomy, and sigmoid resection.
†Tumor staging according to the American Join Committee on Cancer/ Union for International Cancer Control.
Values in parentheses are percentages unless indicated otherwise.

RESULTS

Patient characteristics. Between January 2009 and December 2012, a total of 436 patients underwent an oncologic resection of the colon, sigmoid, or rectum. The patient characteristics are summarized in Table I. Median age was 67 years (range, 40–90). The majority of patients (N = 380, 87%) were operated on electively for a primary malignancy of the colon or rectum. In most cases, the tumor was an adenocarcinoma (93.5%). Procedures performed ranged from (partial) resection of the colon or rectum to combined resections with hyperthermic intraperitoneal chemotherapy.

Patient outcomes. Overall in-hospital mortality was 4.1% (n = 18). The primary outcome variable, POD, was observed in 45 patients (10.3%). In this patient group, in-hospital mortality was 8.9%, greater than the 3.6% observed in the non-POD group (P = .09). After 1 year, 82.6% of patients (n = 360) were still alive (66% were patients who had POD). During hospital admission 38% (n = 165) of patients were admitted to the ICU for ≥1 day (range, 1–50, median 1). Median HLOS was 11 days (range, 2–256). Patients with POD spent more days on the ICU (median 0 vs 1 day) and had a longer total HLOS (median 10 vs 19 days).

Identification of risk factors for POD. Table II summarizes the unadjusted OR of parameters that were associated with POD. Type of operation was not associated with POD except for patients who underwent a hyperthermic intraperitoneal chemotherapy procedure who had a 2-fold increase in risk for developing POD. In 4 patients, early signs of dementia were suspected and documented. None of these patients developed POD.

Variables included as potential risk factors ($P < .1$) for POD in multivariate analyses were age, ASA classification, blood transfusion, history of psychiatric disease, history of cerebrovascular disease, postoperative pain management, postoperative renal impairment, CRP levels, leukocyte blood count, and postoperative complications. Adjusted ORs were calculated for these variables (Table III). Age, history of psychiatric disease, and transfusion were found to be strong independent risk factors for the occurrence of POD. The strongest independent risk factor for POD was found to be a history of psychiatric disease (OR 8.38, 95% confidence interval [CI], 1.50–46.82). In 7 out of 8 cases, a history of psychiatric disease consisted of ≥1 episode of depression.

For age, the adjusted OR for postoperative delirium was 4.01 (95% CI, 1.55–10.37) in patients in the highest age group compared with the baseline group. In the group of patients that received perioperative blood transfusion, the OR to develop POD was 2.37 (95% CI, 1.11–5.06) compared with those who did not receive transfusion. When corrected for the occurrence of serious/major complications, increased levels of CRP and leukocyte blood count demonstrated a significant decrease in ORs compared with univariate analyses. Although not significant in multivariate analyses ($P > .05$), history of cerebrovascular disease and perioperative pain management also appeared to be related to POD.

Sensitivity analysis. Repeating the analysis by using only cases with complete data yielded comparable results. Greater age, perioperative blood transfusion, and a history of psychiatric disease were independent risk factors for the occurrence of POD (OR 3.88, 95% CI, 1.49–10.08; OR 2.20, 95% CI, 1.02–4.75; and OR 7.66, 95% CI, 1.40–42.10, respectively).

DISCUSSION

In the present study, 10% of patients undergoing operation for colorectal cancer developed delirium during the postoperative period. Postoperative mortality was found to be greater in patients that developed POD. In-hospital mortality was 8.9% in patients with POD and 3.6% in patients who did not develop POD (P = .09). Furthermore, POD was associated with longer admission to the ICU and longer HLOS. Various potential risk factors for POD were identified in univariate analysis, including age, history of psychiatric disease, history of cerebrovascular disease, ASA classification, perioperative transfusion, postoperative pain management, postoperative renal impairment, CRP levels, and leukocyte blood count. The strongest independent risk factors for POD were history of psychiatric disease, age, and perioperative transfusion.

Reported incidences of POD after major gastrointestinal operation vary widely across the literature, ranging from 10% up to 60%.[8-10,12,20,21] In the specific subpopulation of patients undergoing colorectal operation for malignancy, considerably less research has been done on POD and its risk factors. In this specific group of patients, POD incidences varying from 10–35%[8-10,22] have been reported.

Compared with these studies, our results demonstrate a relatively low incidence of POD (10%). This may be partly due to the inclusion of relatively younger patients compared with other studies. The median age was 67 years in our population, while median age was 72 years in the population described by Mangnall et al[9] and 88 years in the population investigated by Brouquet et al.[8] In those studies, the reported incidence of POD was considerably greater compared with our results (35% and 24%, respectively).

Another explanation for the relatively low incidence of POD might be implementation of more preventative measures in recent years at our hospital. Well before the start of our study, DOS scores were introduced and a standardized prevention

Table II. Risk factors for POD; results of univariate analysis

Candidate predictor variable	OR (95% CI)	Overall P value
Age (y)		
<70 (ref)	1	<.001
70–80	1.2 (0.56–2.58)	
>80	5.38 (2.48–11.69)	
Charlson comorbidity index		
No comorbidity (0) (ref)	1	.28
Mild/moderate comorbidity (1–2)	1.67 (0.86–3.24)	
Severe comorbidity (≥3)	1.55 (0.55–4.36)	
ASA classification		
I/II (ref)	1	.04
III/IV	1.91 (1.02–3.56)	
Emergency operation		
No (ref)	1	.32
Yes	1.55 (0.68–3.51)	
Transfusion		
No (ref)	1	<.001
Yes	3.81 (2.00–7.27)	
Decreased postoperative hemoglobin levels		
<2 mmol/L Hb (ref)	1	.56
>2 mmol/L Hb	1.20 (0.65–2.23)	
Postoperative pain management		
Epidural analgesia (ref)	1	.08
Intravascular opioid analgesia	1.45 (1.10–1.90)	
Alcohol consumption*		
<5 units (ref)	1	.54
≥5 units	2.00 (0.21–19.00)	
History of psychiatric disease		
No (ref)	1	.002
Yes	9.44 (2.28–39.16)	
History of cerebrovascular disease		
No (ref)	1	.005
Yes	3.46 (1.45–8.28)	
Chronic preoperative use of analgesics		
No (ref)	1	.37
Yes	1.79 (0.50–6.44)	
Preoperative blood urea nitrogen		
<7.5 mmol/L (ref)	1	.93
≥7.5 mmol/L	1.04 (0.48–2.24)	
Postoperative renal impairment		
GFR ≥45 mL/min/1.73 m (ref)	1	.001
GFR <45 mL/min/1.73 m^2	3.92 (1.77–8.95)	
CRP levels		
CRP <150 (ref)	1	.06
CRP ≥150	2.00 (0.97–4.09)	
Leukocyte blood count		
<15.0 10^9/L (ref)	1	.026
≥15.0 10^9/L	2.28 (1.10–4.70)	
Complications		
CDC <3 (ref)	1	.001
CDC ≥3	2.84 (1.50–5.35)	

*Self-reported daily average.
Values in parentheses are percentages unless indicated otherwise.
CDC, Clavien-Dindo classification of operative complications.

strategy became available. This strategy consisted of promoting orientation, increasing attention toward nutritional needs, promoting mobility, and when necessary providing visual and hearing aids. Proactive geriatric consultation might have also further reduced the risk of POD.

As demonstrated by the present study and previous research, POD is associated with the development of other postoperative complications and an increased risk of admission to a nursing home, which may lead to increased morbidity and mortality in this patient group.[3,8,9,11] Not surprisingly, POD has been associated with longer hospital stay and greater costs.[11] In the long term, delirium may accelerate cognitive decline in elderly patients.[23] These potential consequences of delirium warrant the identification of predictors, as proactive geriatric consultation in combination with prophylactic, low-dose haloperidol may reduce the incidence and severity of POD.[24]

Consistent with other studies, the ASA score was found to be positively associated with POD.[8-10] Patients with an ASA score of 3 or 4 had a greater risk of POD in univariate analyses. Comorbidity reflected by the Charlson comorbidity index was also found to be positively associated with POD in univariate analysis. In a population of elderly patients, the presence of multiple comorbidities has been associated with increased risk for developing delirium, even in the absence of operation.[11] Our findings together with those from the literature suggest that multiple comorbidities and a related impaired physical condition increase vulnerability for POD in elderly patients undergoing operation for colorectal cancer.

The strongest, independent risk factor identified in our study was a history of psychiatric disease. When looking in more detail at this

Table III. Risk factors for POD; results of multivariate analysis

Candidate predictor variable	*OR (95% CI)*	*Overall* P *value*
Age (y)		
<70 (ref)	1	.004
70–80	0.86 (0.37–1.98)	
>80	4.01 (1.55–10.37)	
ASA classification		
I/II (ref)	1	.75
III/IV	0.88 (0.41–1.90)	
History of psychiatric disease		
No (ref)	1	.02
Yes	8.38 (1.50–46.82)	
History of cerebrovascular disease		
No (ref)	1	.10
Yes	2.45 (0.85–7.06)	
Transfusion		
No (ref)	1	.03
Yes	2.37 (1.11–5.06)	
Postoperative pain management		
Epidural anesthesia (ref)	1	.21
Opioid medication	1.66 (0.76–3.63)	
Postoperative renal impairment		
GFR ≥45 mL/min/1.73 m (ref)	1	.39
GFR <45 mL/min/1.73 m^2	1.58 (0.56–4.40)	
CRP levels		
CRP <150 (ref)	1	.49
CRP ≥150	1.38 (0.54–3.56)	
Leukocyte blood count		
<15.0 10^9/L (ref)	1	.63
≥15.0 10^9/L	1.23 (0.53–2.89)	
Complications		
CDC <3 (ref)	1	.06
CDC ≥3	2.05 (0.97–4.36)	

Values in parentheses are percentages unless indicated otherwise.
CDC, Clavien-Dindo classification of operative complications.

patient group, we noticed that most patients had ≥1 episode of depression (7 out of 8). Although the pathophysiology linking POD and depression is unclear, many studies have identified depression as an independent risk factor for POD.[25] Furthermore, POD in patients with a history of depressive disorder is associated with a longer duration of POD and incomplete recovery compared with preoperative functioning.[26,27]

Because of the known relationship between intraoperative blood loss and POD,[12,13] we investigated the role of a decrease in postoperative hemoglobin levels. We chose this parameter as a proxy for perioperative blood loss. In contrast to previous studies, a decrease in hemoglobin levels was not found to be significant. However, we did establish a strong connection between POD and perioperative transfusion. In the study published by Brouquet et al,[8] a similar association was found between POD and perioperative transfusion. Although blood transfusions are usually triggered by decreased hemoglobin levels, we did not find a connection between POD and decreased hemoglobin itself. This might indicate that the transfusion of red blood cells increases the risk of POD by itself through mechanisms currently unknown.

Adequate postoperative pain control reduces stress and has a beneficial effect on the postoperative trajectory. Not all analgesics appear to be equally suitable for postoperative use in the elderly. Several studies have identified an association between POD and the administration of meperidine or tramadol in the postoperative period.[8,28] Considerably less research has been done on the relation between POD and mode of administration. To our knowledge, 2 randomized, controlled trials tested the effect of administration mode on POD occurrence and recovery after major abdominal operation in the elderly.[29,30] Both studies failed to demonstrate an effect on the occurrence of POD. By contrast, our results demonstrate a small but beneficial effect of epidural analgesia. As our results differ from previous studies, further research seems warranted to establish whether subgroups might benefit from epidural analgesia with respect to POD.

Preoperative alcohol abuse and POD are known risk factors for POD.[22] Postoperative delirium due to withdrawal from alcohol (delirium tremens) is associated with considerable morbidity and mortality.[31] It also requires supportive measures and specific pharmacologic treatment. For these reasons, it is important to recognize patients at risk at an early stage and implement preventative measures. Our study also detected an increased risk for POD in patients with a history of or current alcohol abuse. This connection was not significant in univariate analyses though. A possible explanation for the absence of statistical significance might be the instigation of preventative measures during preoperative workup. Furthermore, alcohol consumption was documented using a questionnaire during preoperative consultation by the anesthesiologist, which probably led to an underestimation of actual alcohol consumption.

Despite the many studies on the pathogenesis of POD, the underlying biochemical mechanisms are not yet fully understood.[32] One of the hypotheses is that systemic inflammation, as a response to operative trauma, causes diffuse microcirculatory impairment resulting in neuroinflammation, which in turn may lead to POD.[14,15] In our study, we found the elevated inflammatory marker CRP in the postoperative period to be positively related to POD in univariate analysis. The exact nature of the complex relation between aging, inflammatory response to operation, development of other complications, and POD remains to be determined.

The present study has a few limitations. First, since POD is characterized by fluctuating symptoms, this might have resulted in missed cases. Second, even though this was a prospective study, several known risk factors (ie, preoperative mini-mental state examination, history of encephalopathy, data on individual support systems, living arrangements, and private versus semiprivate ward hospital rooms) were not documented in the study and could not be retrieved retrospectively from the hospital records. Information on preoperative alcohol consumption and the use of chronic pain medication were recorded during preoperative consultation by the anesthesiologist. For patients requiring emergency operation, these parameters may be under reported. In general, completeness of the data was reasonable; only 6 parameters revealed having missing data. We could not establish a relation between the outcome variable POD and the occurrence of missing data. For this reason, we found it valid to use a data imputation method, thereby increasing our statistical power.

In conclusion, this prospective study shows that POD is a frequently encountered complication in patients undergoing colorectal operation for malignant disease of the colon and rectum. The present study is based on a homogeneous population of patients who underwent major colorectal operation for malignant disease and explores the relation between POD and a number of potential risk factors. By identifying high-risk patients, preventive measures might be undertaken. The high mortality and morbidity rates associated with POD warrant implementation of preventive and treatment strategies, especially in high-risk patients.

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