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Original Research

Risk factors for postoperative delirium after elective major abdominal surgery in elderly patients: A cohort study

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ABSTRACT

Background: Prehabilitation programs have recently been suggested as potentially able to lower the incidence of delirium in elderly patients undergoing major abdominal surgery. For these prehabilitation programs to become successful, it is essential to identify those patients who are most likely to develop a delirium.

Material and methods: A single-centre cohort study was conducted. Inclusion criteria were: age ≥70 years and scheduled for abdominal surgery for colorectal cancer or an abdominal aortic aneurysm between January 2013 and June 2018. Baseline patient, surgical, anaesthesiologic and haematological characteristics were collected. A risk factor analysis was conducted, with postoperative delirium as primary outcome, by performing a multivariable logistic regression analysis.

Results: In this study, 627 patients were included, of whom 64 (10%) developed a delirium. Variables that differed significantly between delirious and non-delirious patients were age, burden of comorbidity, renal impairment, hypertension, cognitive impairment, history of delirium, physical and nutritional impairment, open surgery, preoperative anaemia and erythrocyte transfusion. After multivariable logistic regression analysis, risk factors for postoperative delirium after major abdominal surgery were renal impairment (OR 2.2; 95%CI 1.2–4.3), cognitive impairment (OR 4.1; 95%CI 1.8–9.2), an ASA score ≥ 3 (OR 2.0; 95% CI 1.0–3.9), being an active smoker (OR 2.7; 95%CI 1.3–5.8), ICU admission (OR 7.1; 95%CI 3.5–14.3), erythrocyte transfusion (OR 2.4; 95%CI 1.2–4.9) and a diagnosis of colorectal cancer (CRC); (OR 4.0; 95% CI 1.7–9.6). Prehabilitation had a protective effect (OR 0.5; 95% CI 0.3–0.9).

Conclusion: Postoperative delirium is a frequent complication after major abdominal surgery in the elderly, especially in octogenarians and after open procedures. Renal impairment, cognitive impairment, being an active smoker, ICU admission, erythrocyte transfusion and a diagnosis of CRC are important risk factors for the development of delirium. Prehabilitation lowers the risk of developing a delirium.

1. Introduction

Over the last 30 years, the number of elderly patients in society has increased with 90% [1]. In the upcoming 35 years, the percentage of elderly patients is expected to double from 8.5% in 2015 to 17% in 2050 [2]. Thanks to advances in anaesthesiologic and surgical techniques, an increasing number of elderly patients are able to undergo surgery. As a consequence, a similar increase is expected in post-operative delirium, one of the most frequent and severe complications that occur in elderly surgical patients. Delirium eventually leads to increased health-care costs and increased rates of institutionalization, morbidity, and mortality, making it a substantial problem in our society [3,4].

Two conditions requiring surgery, commonly present in older patients, are colorectal cancer (CRC) and abdominal aortic aneurysm (AAA). Incidence rates of delirium in vascular surgical patients vary from 5% to 39% [5–7]. In studies on colorectal cancer patients, even higher incidence rates of up to 51% and a median of 24% are described, making this a highly relevant health-care topic [8].

A sufficient treatment for delirium still has not been identified. Non-pharmacological treatment is the preferred initial treatment since evidence for pharmacological approaches is lacking and pharmacological

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treatment options are limited. Firstly, the most likely underlying cause of delirium should be treated. After that, treatment consists of tackling important precipitators of delirium, by applying the same non-pharmacological strategies as are used to prevent delirium [9].

Strategies to prevent delirium, instead of treating it, are still considered the most effective possible method to decrease the incidence of postoperative delirium, a conclusion already drawn in 1998 by Inouye and colleagues [10]. Thirty to forty percent of delirium cases is said to be preventable [11]. Evidence from two large systematic reviews suggests that multicomponent non-pharmacological interventions, bispectral index guided anaesthesia and dexmedetomidine treatment can lower the incidence of delirium [12,13]. Multicomponent interventions that are already widely used, such as the Hospital Elder Life Program (HELP), mainly focus on non-pharmacological interventions at the nursing wards during admission [14,15]. Its effectiveness on reducing the incidence of delirium has been proven and HELP is now considered as a reference for standard care of older persons [15]. Prehabilitation programs, starting prior to admission, have recently been suggested as a possible addition to already existing programs to reduce the incidence of delirium [16].

Prehabilitation is the optimisation of a patients' physical, nutritional and mental health in order to withstand the stress associated with surgery. For these prehabilitation programs to become (more) successful, identification of patients who are most likely to develop a delirium, and therefore are mostly in need of these programs, is essential. Additionally, by doing so, the health care burden of these programs can be kept relatively low, which is a big advantage since these programs are costly and labour-intensive. Therefore, the aim of this study is to identify risk factors for postoperative delirium after elective major abdominal surgery. By doing so, future prehabilitation programs may focus on patients with these risk factors in particular.

2. Material and methods

2.1. Study design, setting and participants

A single-centre before-and-after study was conducted, including patients aged ≥70 years who underwent elective abdominal surgery for CRC or an AAA between January 2013 and June 2018 in a large, non-university, teaching hospital in Breda, the Netherlands. Exclusion criteria were acute hospitalization or surgery, and prior surgery within the previous six months. Extensive methods have previously been published [16]. Patients that were scheduled for surgery after November 2015 were prospectively included and followed a prehabilitation pathway in order to optimise overall physical, nutritional and mental health. The 'before' patients were retrospectively included and were not prehabilitated. Data of all included patients were prospectively stored and acquired through medical chart review. To prevent distorted results, baseline characteristics that may have been influenced by the prehabilitation program were reassessed at admission, after the prehabilitation program and prior to surgery.

All patients were clinically cared for according to the hospital's delirium prevention protocols, which are set up in accordance with the Hospital Elder Life Program [14]. Postoperative care of all CRC patients was provided according to Enhanced Recovery After Surgery (ERAS) protocols.

The work has been reported in line with the STROCSS criteria [47].

2.2. Data collection: patient characteristics

The following patient characteristics were considered as potential variables influencing the development of delirium and were extracted from patient charts: age, gender, medical history (cardiac, pulmonary and neurologic comorbidities, renal impairment, diabetes mellitus, hypertension, hypercholesterolaemia), burden of comorbidity, prior diagnosis of cognitive impairment, hearing or visual impairment, history of delirium, physical dependency, nutritional status, daily alcohol use and smoking status. Renal impairment was defined as a glomerular filtration rate of < 60 mL/min/1.73 m^2. Cognitive impairment was defined as a MMSE score of ≤24.

The burden of comorbidity was scored using the Charlson Comorbidity Index (CCI) and the American Society of Anesthesiologists (ASA) score [17,18]. The CCI ascribes points according to age and comorbidities. All included patients are aged ≥70 years, so the minimum CCI score for AAA patients was three. For colorectal cancer patients, the minimum score was five. A cut-off value of CCI ≥7 was used, based on the median CCI score.

Physical dependency was assessed using the KATZ-ADL score [19]. Patients with any score below the maximum score of 6 were considered physically impaired. Nutritional status was assessed using the SNAQ score [20]. A SNAQ score of ≥3 represents malnourishment. The KATZ-ADL score and the SNAQ score of the prehabilitated group were collected after the prehabilitation program, prior to surgery.

2.2.1. Data collection: haematological, anaesthesiologic and surgical data

Preoperative and postoperative blood levels of haemoglobin were tested. Women with haemoglobin levels below 7.4 mmol/L (< 120 g/L) and men with levels below 8.1 mmol/L (< 130 g/L)) were considered anaemic. The patients requiring blood transfusion were registered.

Data on time and method of anaesthesia were acquired by accessing anaesthesiologic patient files. The length of anaesthesia was calculated as the time from intubation to extubation.

Surgeries that were performed were open abdominal aortic aneurysm repair, endovascular abdominal aortic aneurysm repair (EVAR), open colorectal resection, laparoscopic colorectal resection and robot-assisted laparoscopic colorectal resection. The type of surgery was divided into open or minimally invasive.

2.3. Delirium assessment and risk factor analysis

The primary outcome was postoperative delirium. Ward nurses screened for delirium during regular rounds using the DOS score [21]. When delirium was suspected, a geriatrician was consulted to confirm the diagnosis using the DSM-V criteria or the Confusion Assessment Method (CAM) [22,23]. The geriatrician was not made aware of study participation and used the same standardized method for diagnosing delirium as used in non-study patients; however, the electronic patient file does show a patients' enrollment in medical research.

All collected patient, surgical, anaesthesiologic and haematological characteristics were considered as potential risk factors for developing delirium.

2.4. Statistical analysis

Dichotomous variables were presented as frequencies with percentages and continuous variables were presented as medians with interquartile range. Between-group differences were tested for statistical significance using Pearson's chi-squared test in case of categorical variables and the Mann-Whitney *U* test in case of continuous variables.

Unadjusted and adjusted regression analyses were performed to calculate odds ratios (OR) and 95% confidence intervals (CI) for the primary outcome. All baseline patient, surgical, anaesthesiologic and haematological characteristics with a univariable p-value below 0.20 were selected to simultaneously enter a multivariable logistic regression model. To correct for possible late consequences of the prehabilitation program and to correct for the combination of diagnoses, 'prehabilitation' and 'diagnosis' were inserted as variables into the model. By performing a stepwise backward elimination based on the largest p-value above 0.20, risk factors were eliminated from the model.

Effects of the risk factors were expressed as odds ratios with 95% confidence intervals (95%CI) and p-values. An effect was considered statistically significant if its p-value dropped below 0.05.

All data were prospectively stored using the electronic patient file 'Hyperspace Version IU4 (Epic, Inc., Verona, WI)' of Amphia Hospital

Breda, the Netherlands. Statistical analysis was performed using IBM SPSS statistics software version 24.0 (SPSS Inc., Chicago, Illinois, USA). Missing data were infrequent and not imputed.

This research project has been retrospectively registered in the Netherlands Trial Register (NTR5932).

3. Results

A total of 627 patients were included in this risk factor analysis, of whom 143 (23%) underwent surgery for an abdominal aortic aneurysm (45 open correction; 32%) and 484 (77%) underwent surgery for a colorectal tumour (111 open resection; 23%). The mean age was 77 years. The incidence of delirium prior to the prehabilitation program was 11.7%, while 8.2% of the patients developed a delirium post-implementation. The overall incidence of postoperative delirium was 10.2%; 7.7% in AAA patients and 11% in CRC patients. The mean length of hospital stay was 9 days. The overall mortality during admission was 3.2% and the overall complication rate was 41%.

The percentage of octogenarians who developed a delirium was almost twice as high as the percentage of patients between 70 and 79 years old (15% vs 7.9%; P = 0.004, Table 1). Over one in six patients who were physically or nutritionally impaired developed a delirium during admission. Delirious patients were significantly older (median age 79 vs. 76 years; P = 0.002), had a significantly higher comorbidity index (median CCI 7 vs. 6; P = 0.017) and were more frequently physically and nutritionally impaired (respectively 30% vs. 16%; P = 0.005 and 33% vs. 18%; P = 0.005). Individual comorbidities that differed significantly between groups were renal impairment, hypertension, cognitive impairment and history of delirium. The variables with a p-value below 0.20 were selected for inclusion in the logistic regression model.

Surgical, anaesthesiologic and haematological variables in relation to the onset of postoperative delirium are presented in Table 2. Compared to minimally invasive surgery, nearly twice as many patients who underwent open surgery developed a delirium (8.3% vs 16%; P = 0.006). Patients with delirium were also significantly more often anaemic preoperatively (P = 0.047) or needed erythrocyte transfusion during or after surgery (P < 0.001). Almost 25% of the patients who needed erythrocyte transfusion developed a delirium. Similar to Table 1, the variables with a p-value below 0.20 were selected for inclusion in the logistic regression model.

Preoperative variables per diagnosis are added to this manuscript as supplementary material (Appendix 1 and 2). The majority of AAA patients were male. Ten percent of patients between 70 and 79 years old developed a delirium compared to only 2.3% of octogenarians. Only 2% of the AAA patients developed a delirium after endovascular repair, in contrast to 20% after open surgery. No AAA patients who developed a delirium have previously been diagnosed with cognitive impairment or with delirium. None of the preoperative variables varied significantly between delirious and non-delirious patients for AAA patients.

Over twice as many CRC patients over 80 years old developed a delirium compared to those aged between 70 and 79 years old (19% vs 7.2%; P < 0.001). More than a third of the patients with a history of delirium and 40% of the cognitively impaired patients were diagnosed with delirium. Almost one in five physically impaired CRC patients and one in six nutritionally impaired CRC patients developed a delirium. Median age, Charlson comorbidity index, physical and nutritional impairment, smoking, and visual and hearing impairment significantly differed between delirious and non-delirious CRC patients.

Robot-assisted laparoscopic colorectal resection had the lowest percentage of delirium as a complication in CRC patients (6.3%), while 9.9% of the patients developed a delirium after laparoscopic resection and 14% after open resection. In AAA patients, type of surgery differed significantly between both groups.

In the adjusted logistic regression analysis, the following variables were successively deleted from the model: neurologic comorbidity, hearing impairment, KATZ < 6, type of surgery, daily alcohol

Table 1
Preoperative variables in relationship to onset of postoperative delirium in all patients (N = 627).

	Full sample		P-value
	Delirium N = 64 (%)	No delirium N = 563 (%)	
Age			
Age in years, median (IQR)	79 (74–84)	76 (73–80)	0.002[a]
70–79	34 (53.1)	397 (70.5)	0.004
≥80	30 (46.9)	166 (29.5)	
Gender			
Male	44 (68.8)	354 (62.9)	0.36
Comorbidities			
Cardiac	26 (40.6)	224 (39.8)	0.90
Pulmonary	13 (20.3)	138 (24.5)	0.46
Neurologic	24 (37.5)	147 (26.1)	0.053[a]
Renal impairment	25 (39.1)	105 (18.7)	< 0.001[a]
Diabetes mellitus	18 (28.1)	108 (19.2)	0.091[a]
Hypertension	45 (70.3)	315 (56.0)	0.028[a]
Hypercholesterolemia	22 (34.4)	172 (30.6)	0.53
Cognitive impairment	16 (25.0)	28 (5.0)	< 0.001[a]
History of delirium	10 (15.6)	26 (4.6)	0.002[a]
CCI, median (IQR)	7 (5–7)	6 (5–7)	0.017
CCI ≥ 7	33 (51.6)	190 (33.7)	0.005[a]
ASA score ≥ 3	44 (68.8)	253 (44.9)	< 0.001[a]
Physical impairment			
KATZ-ADL score, median (IQR)	6 (5–6)	6 (6–6)	< 0.001
KATZ-ADL score < 6	19 (29.7)	88 (15.6)	0.005[a]
Nutritional status			
SNAQ score, median (IQR)	1 (0–3)	0 (0–2)	< 0.001
SNAQ score ≥ 3	21 (32.8)	102 (18.1)	0.005[a]
Intoxications			
Daily alcohol use	19 (29.7)	225 (40.0)	0.11[a]
Active smoker	15 (24.2)	86 (15.5)	0.078[a]
Sensory impairment			
Visual impairment	27 (42.2)	176 (31.3)	0.077[a]
Hearing impairment	27 (42.2)	172 (30.6)	0.058[a]
Diagnosis			
AAA	11 (17.2)	132 (23.4)	0.26
Colorectal carcinoma	53 (82.8)	431 (76.6)	

[a] Included in the multivariable logistic regression model.

Table 2
Surgical, anaesthesiologic and haematological variables in relation to onset of postoperative delirium in all patients (N = 627).

	Delirium N = 64 (%)	No delirium N = 563 (%)	P-value
Surgery			
Open surgery	25 (39.1)	131 (23.3)	0.006[a]
Minimally invasive surgery	39 (60.9)	432 (76.7)	
Anaesthesia and ICU			
Length of anaesthesia	2:30 (1:58–3:42)	2:35 (1:54–3:41)	0.99
ICU admission	30 (46.9)	69 (12.3)	< 0.001[a]
Haematology			
Preoperative anaemia	33 (51.6)	218 (38.7)	0.047[a]
Postoperative anaemia[b]	57 (90.5)	446 (80.4)	0.051[a]
Erythrocyte transfusion	20 (31.3)	61 (10.8)	< 0.001[a]

[a] Included in the multivariable logistic regression model.
[b] 9 cases missing.

Table 3
Multivariable logistic regression analysis of risk factors for postoperative delirium.

	Coefficient	SE	Odds Ratio (95% Confidence interval)	P-value
Age per 10 years	0.47	0.29	1.6 (0.9–2.8)	0.10
Renal impairment	0.80	0.33	2.2 (1.2–4.3)	0.017
Cognitive impairment	1.41	0.42	4.1 (1.8–9.2)	0.001
ASA ≥ 3	0.70	0.33	2.0 (1.0–3.9)	0.037
Active smoker	1.01	0.38	2.7 (1.3–5.8)	0.009
ICU admission	1.96	0.36	7.1 (3.5–14.3)	< 0.001
Erythrocyte transfusion	0.89	0.35	2.4 (1.2–4.9)	0.011
Diagnosis of CRC	1.39	0.45	4.0 (1.7–9.6)	0.002
Prehabilitation	−0.72	0.33	0.5 (0.3–0.9)	0.030

Significance of model: chi-square = 97.43; df = 9; $p < 0.001$.
Area under the ROC curve: 0.83 (95% CI 0.78–0.89).
Positive predictive value 62%; Negative predictive value 92%.

consumption, diabetes comorbidity, postoperative anaemia, preoperative anaemia, SNAQ ≥ 3, CCI ≥ 7, visual impairment, hypertension, and delirium in history. Table 3 presents the odds ratios and 95%CI of the remaining risk factors after successive deletion based on a p-value below 0.20. Risk factors for postoperative delirium after major abdominal surgery are renal impairment (OR 2.2; 95%CI 1.2–4.3), cognitive impairment (OR 4.1; 95%CI 1.8–9.2), ASA ≥ 3 (OR 2.0; 95% CI 1.0–3.9), being an active smoker (OR 2.7; 95%CI 1.3–5.8), ICU admission (OR 7.1; 95%CI 3.5–14.3), erythrocyte transfusion (OR 2.4; 95%CI 1.2–4.9) and diagnosis of CRC (OR 4.0; 95% CI 1.7–9.6). The prehabilitation program has a protective effect on the development of delirium (OR 0.5; 95% CI 0.3–0.9).

The current data was inserted in the Raats model, to validate the model that was previously created based on historic data. Table 4 presents outcomes after inserting the historic data [24] and the current data into the Raats model. While the risk factors for postoperative delirium remain the same, odds ratios are lower compared to what was previously calculated. Moreover, the area under the ROC curve dropped to 0.68 (95%CI 0.61–0.75) when using the same three predictors that were used in the study by Raats et al. The area under the ROC curve for the newly developed model with current data was 0.83 (95%CI 0.78–0.89).

4. Discussion

The aging of the world's population requires new methods to prevent delirium in elderly patients, since a higher age is associated with an increase in delirium, but also other postoperative adverse events [25]. Identification of specific risk factors that can be addressed in prevention programs is therefore imperative. This research aimed to identify risk factors for postoperative delirium in elderly patients who undergo elective major abdominal surgery. It elaborates on a previously designed prognostic model in a study conducted by Raats et al. [24], wherein higher age, delirium in medical history, and ASA ≥ 3 were proven to be risk factors for postoperative delirium in a similar patient group.

Table 4
Comparison between the Raats model[a] based on historic data and based on current data: Odds ratios and area under the ROC curve.

	Historic data[a](95% Confidence interval)	Current data (95% Confidence interval)
Age per 10 years	2.0 (1.1–3.8)	1.6 (1.0–2.6)
Delirium in history	12 (2.7–50)	3.0 (1.3–6.8)
Katz-ADL score < 6	1.7 (0.6–4.4)	1.5 (0.8–2.8)
ASA score ≥ 3	2.6 (1.1–5.9)	2.1 (1.2–3.7)
Preoperative anaemia	2.0 (0.8–4.8)	1.4 (0.8–2.3)
Area under the curve	0.76 (0.66–0.85)	0.68 (0.61–0.75)

[a] J.W. Raats, W.A. van Eijsden, R.M. Crolla, E.W. Steyerberg, L. van der Laan. Risk Factors and Outcomes for Postoperative Delirium after Major Surgery in Elderly Patients. PLoS One. 2015; 10(8):e0136071.

When recalculating the area under the curve of the previous model by inserting the current data, the accuracy of the model dropped from 0.76 to 0.68. The newly created model, created with a larger population, had a much bigger accuracy of 0.83. The risk factors for postoperative delirium identified by this model are renal or cognitive impairment, an ASA score ≥ 3, being an active smoker, ICU admission, erythrocyte transfusion and the diagnosis of CRC. In line with the previous study in this hospital by Raats et al. [24], but also to several meta-analyses conducted in the past [5–8,11], a high burden of comorbidity identified by an ASA score of three or more was found to be a risk factor for delirium. Delirium in medical history was no longer found to be a risk factor for delirium in surgical patients, a finding supported by the previously mentioned meta-analyses.

The number of elderly patients is likely to more than double in the next 35 years according to current projections [26], making age a specifically important factor. In contrast to previous studies in vascular and gastrointestinal surgery however, age was not identified as an independent risk factor for postoperative delirium [5–8,24]. Based on currents results in elderly patients undergoing elective major abdominal surgery, other factors are more relevant when assessing the risk for delirium and the need for prehabilitation. Prior research in CRC patients likewise concluded that age on itself was not a risk factor for postoperative adverse events, in contrast to the burden of comorbidities [27,28]. In AAA patients, increasing age was associated with a small increase in risk for in-hospital morbidity, however comorbidities are associated with a much greater risk for postoperative complications [29].

Cognitive impairment is a known risk factor for delirium in both general medicine and non-cardiac and vascular surgical patients [7,11,30]. Findings of the current study elaborate on these findings by proving that cognitive impairment is also a risk factor for delirium in elderly patients after major abdominal surgery. Although age is associated with increased risk of cognitive impairment, it is not a risk factor for postoperative delirium on itself. This again exemplifies the importance of other comorbidities such as cognitive impairment, rather than age, to take into account when assessing whether a patient is in need for prehabilitation.

No previous studies have reported active smoking as a risk factor for delirium. History of smoking was previously described to be a risk factor for delirium in vascular surgical patients, however it is unclear whether this variable also included patients that were currently smoking [5]. It is plausible that active smokers who cannot smoke because of admission in the hospital can experience physical and mental unrest, making them more prone to developing a delirium. This finding emphasizes the importance of smoking cessation as a part of future prehabilitation programs.

Delirium is a frequent complication in ICU patients, with incidence rates varying widely between studies. Demonstrated by a 2015 systematic review, incidence rates vary from 9% to 91% (with an overall delirium incidence of 32%), depending on the population included per study. Previous studies have also demonstrated the association between ICU admission and delirium in vascular surgical patients. No previous studies have reported ICU admission as a risk factor for delirium in colorectal cancer patients [5,31,32].

In line with two previous studies on risk factors for delirium after gastrointestinal surgery [8,33], erythrocyte transfusion was found to be a risk factor for postoperative delirium. This has not been reported before in vascular surgery. Precautions should be taken in future programs to prevent the need of an erythrocyte transfusion as much as possible, for instance by optimising preoperative haemoglobin levels. In CRC patients, where iron deficiency is the most frequent cause of low preoperative haemoglobin levels, intravenous iron injections can successfully increase haemoglobin levels and may therefore be a good addition to prehabilitation programs [34,35].

Impaired mobility [11,36], visual and hearing impairment [11] have previously been proven to be risk factors for delirium and are all included to be optimised by non-pharmacological approaches in the Hospital Elder Life Program [15]. Since these approaches are standard care in the study hospital, it is of no surprise that these could not be identified as risk factors for delirium in the current study.

Large prospective trials, such as the Dutch DREAM trial and a large meta-analysis based on four large prospective trials, have questioned the long-term benefits of EVAR compared to open correction for AAA since survival rates are comparable between both procedures and EVAR often needs secondary interventions [37,38]. In this study, significantly less delirium cases were present after EVAR compared to open repair. By significantly reducing the incidence of delirium, EVAR might be more beneficial than described in the past.

Compared to AAA patients, CRC patients have an increased risk of developing delirium. This finding can also be deduced by the incidence rates of delirium in these cohorts, with higher rates described in CRC patients [6,8]. Based on the supplementary material, delirium is much more frequent after open aortic repair compared to endovascular aortic repair. Since the percentage of delirium cases after EVAR is below 2%, prehabilitation of these patients might not be worthwhile.

In recent years, there has been an increasing interest in prehabilitation. Common concerns are the economic and societal costs of these programs. For now, few studies have demonstrated the advantage of prehabilitation programs in terms of conventional outcomes [39–41]. This study however, shows a protective effect of prehabilitation on the development of delirium, in line with a previous study [42]. Since the benefits of these programs are therefore hard to quantify, many of these studies may suffer from difficulties in getting funding. By identifying patients who are most at risk for developing a delirium or other postoperative complications, prehabilitation programs can be made more effective and cost-effective.

4.1. Limitations

An important limitation is the inclusion of both AAA and CRC patients for this trial. Both conditions, but also minimally invasive laparoscopic and endovascular procedures, are fairly different. Including this combination can be substantiated by the fact that both conditions are common in the elderly population, requiring major abdominal surgery. Within this population, postoperative complications are frequent. Previous studies on risk factors for delirium have likewise used a combination of diseases in their trials [24,36,43–45]. For example, Gleason et al. included 81% orthopaedic, 13% colon and 6.2% vascular patients in their study, which was published in the JAMA Surgery; Raats et al. included 22% vascular and 78% colon patients; and Schmitt et al. propose to include orthopaedic, vascular and colon patients. As a consequence of combining these conditions, a less accurate identification of risk factors per disease can be achieved and generalisability is limited. If desired, this study may be used as a basis on which future studies can build and separate risk factor analyses for CRC patients and AAA patients may be performed.

Another limitation is the issue of residual confounding, i.e. there remains a confounder for which mitigation by logistic regression is not possible. For example, may have a beneficial effect on delirium beyond that of laparoscopic or robotic colorectal surgery that cannot be fully accounted for by grouping EVAR under the heading minimally invasive surgery, since EVAR does not involve entering the peritoneal cavity.

By making use of backward elimination based on a p-value of 0.20, after adding the prehabilitation program and the diagnosis as variables, the final model includes 9 variables. Since the number of events in this study was 64, the risk of unstable regression modelling is increased.

Finally, the prehabilitation program which was implemented halfway through the study period is a major confounder. To minimise the impact of this confounder, prehabilitation was added as a variable in the multivariable logistic regression model. By implementing the program, the incidence of delirium was lowered. Therefore, it is likely that there may be some residual confounding here also.

4.2. Future studies

Previous meta-analyses have shown that multicomponent interventions can decrease the incidence of delirium [12,13,46]. Prehabilitation programs, multicomponent interventions conducted in the pre-admission phase, can possibly make an additional decrease in delirium incidence [16]. For these programs to actually become more successful, as many risk factors for postoperative delirium as possible should be tackled simultaneously. As discussed above, smoking cessation and intravenous iron injections should be considered as components of new prehabilitation programs.

Future studies on risk factors for delirium should focus on identifying risk factors that can potentially be optimised (i.e. precipitating risk factors), rather than on risk factors that cannot be influenced (i.e. predisposing risk factors). A new study should be conducted including more patients and collecting more preoperative precipitating risk factors for delirium. Additionally, these studies should include patients with the highest number of predisposing risk factors. This way, a delirium prediction model may be designed, identifying patients most likely to benefit from prehabilitation programs.

5. Conclusion

Postoperative delirium is a frequent complication after major abdominal surgery in the elderly, especially in octogenarians and after open procedures. Renal and cognitive impairment, an ASA score ≥ 3, being an active smoker, ICU admission, erythrocyte transfusion and the diagnosis of CRC are important risk factors for postoperative delirium after elective major abdominal surgery. Prehabilitation has a protective effect on the development of delirium. When designing new multicomponent prehabilitation programs to decrease the incidence of delirium, studies should focus on patients with these risk factors specifically.

Ethical approval

The Medical Ethical Research Committee of Rotterdam, Maasstad Hospital (TWOR) approved the research protocol, ID number NL55694.101.15, in June 2016. Additionally, the Local Research and Development Committee at the Amphia Hospital approved the protocol (Local ID number 1473.16).

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Author contribution

All authors made a substantial contribution to the design and set-up of this study, to collection of data and to the writing and revising of this manuscript. All authors read and approved the final manuscript.

Conflicts of interest

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Trial registry number

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Guarantor

T.L. Janssen, L. van der Laan.

Data statement

The data file contains confidential information and will also be used for future publications. Data will not be made publicly available.

Provenance and peer review

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CRediT authorship contribution statement

T.L. Janssen: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **E.W. Steyerberg:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **M.C. Faes:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **J.H. Wijsman:** Conceptualization, Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **P.D. Gobardhan:** Conceptualization, Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **G.H. Ho:** Conceptualization, Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **L. van der Laan:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.

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Appendix A. Supplementary data

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