Frailty and Delirium in the Elderly Surgical Patient

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Frailty and Delirium in the Elderly Surgical Patient

Kwetsbaarheid en delier in de oudere chirurgische patiënt

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van rector magnificus

Prof.dr. H.A.P. Pols
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
vrijdag 20 januari 2017 om 11:30 uur

door

Jelle Willem Raats
geboren te Oosterhout

Erasmus University Rotterdam

PROMOTIECOMMISSIE

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Chapter 1

Introduction and outline of the thesis

INTRODUCTION AND OUTLINE OF THE THESIS

Conservative treatment

Population aging is accelerating at a tremendous rate. This development is of major importance as population projections indicate that the number of persons aged over 80 years will double during the next 30 years in the Netherlands[1]. This population will be exposed more and more to high-risk surgical interventions and related risks of procedural adverse events. Thus, surgeons are being increasingly faced with elderly patients in a poorer mental and physical state

An elderly patient in need for surgery may create new diagnostic and treatment dilemmas, especially in case of frail patients with a poor prognosis and in demand of major invasive surgical interventions. With the introduction of new surgical and supportive technologies clinical decision making has become more challenging for critically ill patients, particularly when full recovery following major surgery seems unlikely.

Nowadays, decisions are often based on the clinical expertise of a surgeon who will take into consideration age, comorbidity and health characteristics of the patient. At this moment, literature has mainly been focused on the outcome of surgical interventions. Less data is available on the outcome of wait and see policies or conservative treatment schedules for comparable diseases.

In particular with frail patients, a conservative treatment may be considered as the preferred treatment option when collateral damage that may be due to major interventions can be prevented. However, evidence to guide clinical decision making for these patients is scarce in current literature.

Delirium and frailty

When considering surgery in elderly patients, delirium is a complication with major impact that should be taken into account. Delirium is defined as an acute disorder with transient fluctuating disturbance of consciousness, attention, cognition, and perception[2]. It is associated with high mortality, increased morbidity, increased need for nursing surveillance, longer hospital stays and a high rate of institutionalization following discharge[3-8]. The impact on patients, families, nursing staff as well as on the related economic cost are tremendous. In addition, delirium in the elderly may result in persistent cognitive decline after hospitalization. While delirium may occur in patients of any age, it is a particularly common after surgery in the elderly. Since the number of elderly people requiring surgery continuous to grow, the number of patients with delirium and associated problems can be expected to increase in future. Most studies on post-operative delirium focus on patients having orthopedic- or cardiothoracic surgery, less literature is available concerning postoperative delirium after general surgery.

The exact cause of delirium is unknown, but it seems the outcome of a process caused by many interacting factors, affecting the vulnerability of a patient[9]. Even with minimal invasive surgery an elderly patient with multiple diseases is more likely to develop postoperative delirium as

compared to younger patients who enjoy better overall health. The vulnerable, high aged patients with significant comorbidities can be described as frail and at risk for the development of delirium.
Most importantly, several large multi-component intervention studies reported that delirium could be prevented in one third of cases[10-12]. Therefore, identification of patients with increased risk for delirium is crucial.
Since 2008 all Dutch hospitals have implemented the National Patient Safety Program (in Dutch: VMS Veiligheidsprogramma). This nation-wide program intended to reduce potentially preventable adverse events for hospitalized patients and included the topic "vulnerable elderly". All elderly patients (>70 years) admitted to hospitals were screened for the risk on delirium, in order to implement preventing actions timely. Unpublished work revealed that screening for delirium was accomplished in 94% of the patients admitted. However, although 76% of patients screened were identified at risk for the development of delirium subsequent preventing actions were not executed on a regular base for all these patients. Determination of predictive factors for delirium are needed to better identify patients at risk, thus enabling the application of preventing actions and making care more cost-effective[13].

Aims and outline of this thesis

The aims of the research in this thesis were to explore the role of conservative therapies in frail elderly patients in need for (extensive) surgery. Also, delirium incidence and predictive factors of delirium in elderly patients having surgery were examined.

In **Chapter 2** we evaluate the clinical outcomes of conservative treatment in selected elderly patients with severe critical limb ischemia.
A ruptured Abdominal Aortic Aneurysm (AAA) is a condition in which acute surgical intervention is required to prevent death. Most relevant literature is limited to reports of survival after surgical or endovascular repair. Accurate information on the non-intervention rate (patients who die in hospital without undergoing surgery) and perioperative mortality is lacking. We investigated the results of emergency endovascular aneurysm repair (eEVAR), conventional open repair, and conservative treatment in elderly patients with ruptured Abdominal Aortic Aneurysm.
In **Chapter 3** we focus on the effect of major surgical interventions versus the effects of minimal invasive techniques, including endovascular repair, on the risk of adverse events and mortality. In addition, we report the outcome of patients with the same disease but treated in a conservative manner.
Current literature is systematically reviewed in **Chapter 4** concerning potential predictive factors for delirium in elderly patients having major elective vascular surgery. The Amphia Delirium Database was created, including all patients admitted from February 2013 until July 2014 with vascular surgical disease or colorectal surgery. The following chapters studied delirium based on the Amphia Delirium Database.

In **Chapter 5** we focus on elderly patients having elective or acute colorectal surgery. The incidence of post-operative delirium and role of operative setting (acute or emergency) are investigated. The objective of the study reported in **Chapter 6** was to evaluate predictors for delirium, in elderly patients receiving major elective surgery. In addition, the outcome measures were the clinical consequences of delirium including adverse events, length of stay, costs and mortality.

In **Chapter 7** results of an observational study on delirium and frailty are reported concerning patients admitted to the vascular surgical ward. The risk factors for delirium among patients undergoing in hospital treatment for critical limb ischemia, diabetic foot ulcers, Abdominal Aortic Aneurysm, and carotid surgery are analyzed. In **Chapter 8** we analyze the perioperative risk factors and outcomes of perioperative delirium in patients with critical limb ischemia having surgery.

The general discussion in **Chapter 9** elaborates on the methodology and results of our studies. Based on our expertise we will offer future perspectives for further research.

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Chapter 2

Conservative treatment in selected patients with critical limb ischemia

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World Journal of Surgery. 2015 Aug;39(8):2090-5

ABSTRACT

Objective: to assess the outcome of conservative treatment of severe critical limb ischemia (CLI) classified as Rutherford 5/6

Background: The preferred therapy for CLI is either endovascular revascularization or bypass surgery. With a growing aged population with more serious comorbidities, these therapies are not always a viable option. Primary amputation leads to decreased mobility and a reduced quality of life. There is a lack of literature regarding the outcome of conservative therapy.

Methods: Hospital charts were reviewed of all patients who were diagnosed with Rutherford classification 5–6 and received conservative treatment and lacked interventional options. Outcome measures were mortality, complete wound closure, and limb salvage rate.

Results: 38 patients were included with a median age of 80 years (range 57-97). The amputation rate during follow-up was 16 %. In 58 % of patients complete wound closure was achieved. All-cause mortality was 58 % with a 2-year survivability rate of 55 %.

Conclusions: Conservative management in our selected patients with CLI results in a moderate rate of wound closure and acceptable amputation rates albeit with a high mortality rate. For patients not eligible for endovascular revascularization or bypass surgery, conservative treatment could be a viable option besides primary limb amputation.

INTRODUCTION

Critical limb ischemia (CLI) is the most advanced form of peripheral artery disease (PAD), presenting as ischemic rest pain, ulcers, or gangrene. The incidence of CLI is estimated to be 50-100 per 100,000 every year in the Western World [1]. These numbers will probably increase in the coming years, due to an aging population, increased life expectancy and prevalence of diabetes [2]. Patients with CLI often suffer from serious comorbidities, with severe reduction in mobility, quality of life and life expectancy. The annual overall combined event rate for myocardial infarction, ischemic stroke, and vascular death is approximately 5 – 7% in this population [1]. Current vascular medicine offers a wide variety of endovascular and/or operative therapies for patients with CLI. Peripheral bypass surgery results in acceptable outcome even after technically demanding arterial reconstructions (i.e. distal-origin bypasses originating from arteries below the knee or pedal bypasses) with 5-year limb salvage rates of 78% in some series [3].

At this moment, the preferred therapy for CLI in fragile elderly patients is endovascular revascularisation. Treatment with balloon angioplasty is a valuable alternative to bypass surgery in CLI patients with limb salvage rates up to 50% during 5 years follow-up.

Unfortunately about one-third of CLI patients is not suitable for open or endovascular treatment due to comorbidities as described in the BASIL trail [4]. With an aging population, it is to be expected that this number will only increase in the future [4, 5].

In patients without revascularisation options, an amputation is most commonly performed. This results in a reduction of mobility, a lower quality of life and higher health care costs [6].

Another approach to this selected group of fragile patients could be conservative treatment. However, treatment options for patients with CLI are limited. No effective pharmacological therapy is available and studies on new non-conservative treatments such as neovascularisation by means of stem / progenitor cells reported disappointing results [7, 8]. Amputation therefore often remains the only option for these patients.

The current consensus is that conservative management including optimal pharmacological management of pain, antibiotics and intensive wound treatment is not a viable option in the initial treatment of the most severe CLI classified as Rutherford 5/6. However, results of conservative treatment in selected patients with Rutherford 5/6 are scarcely available in current literature. The primary objective of this study is to evaluate the clinical outcome of patients with severe CLI who received initial conservative therapy.

METHODS

Patient selection process

Between 2010 and 2011, demographic and clinical data were retrospectively collected from all patients referred to the Department of vascular surgery, Amphia Hospital Breda, The Netherlands. All patients with CLI with ulcers, or gangrene as a result of severe peripheral arterial disease who

were given conservative treatment were included. Conservative management was started in patients who were deemed unfit for revascularization, either because of poor general health or because of anatomical unsuitability. Patients were discussed in a multidisciplinary vascular meeting with certified interventional radiologists and vascular surgeons. All patients receiving endovascular revascularization, arterial bypass surgery or amputation as primary initiated therapy were excluded. Critical limb ischemia was defined as tissue loss and clinical symptoms of peripheral arterial disease, following the Rutherford classification 5-6 [1]. Patients who presented with severe gangrenous wounds resulting in sepsis at time of inclusion were excluded from this study. This research was based on a regular patient care, therefore, the need for individual informed consent was waived. The minimum follow-up was 24 months for all patients until complete wound regression, amputation, or death. No patients were lost during follow-up.

Baseline characteristics

Data were collected from patients' first outpatient clinic visit until January 2014. To assess the general physical state of the patient the American Society of anaesthesiologist physical status classification system (ASA) was used [9]. The location of the ischemic ulcer was noted (distal foot, heel, or lower leg). Cardiovascular risk factors and comorbidities were registered for all patients. Most patients received best medical treatment, i.e. statins, ACE inhibitors (ACEI), life style advices and thrombocyte aggregation inhibitors.

Diagnostics

In all patients basic vascular diagnostics were performed. Ankle brachial indices (ABI) were obtained. If the ankle pressure was unobtainable due to non-compressible arteries, toe pressure was measured.

In most patients, either a magnetic resonance angiography (MRA) or an arterial duplex scan was used to assess the extent of arterial stenosis or occlusion and to determine the suitability for endovascular or operative treatment. To determine the severity of the peripheral arterial disease, the Trans-Atlantic Inter-Society Consensus (TASC II) classification was determined based on duplex scanning or MRA [1]. Furthermore, the total number of open crural arteries was noted.

In some patients, no additional data besides an ankle-brachial index was obtained due to the lack of clinical consequences. In these patients, the diagnosis CLI was based on clinical symptoms such as non-palpable pulses, ulcers, and/or rest pain.

Treatment

All patients received conservative treatment consisting of optimal pharmacological treatment of pain and intensive wound care. Pain management was performed according to the WHO analgesic pain ladder. Wound care was performed with assistance of a specialized wound care practitioner, who followed patients in an out-patient setting on regular basis. The wound care practitioners had several wound dressings at their disposal, ranging from foam bandages to

antibacterial silver bandages. Small debridement of wounds was performed when considered necessary. If a bacterial infection was suspected, patients received antibiotic therapy. After wound swabs, standard antibiotic treatment of choice consisted of Amoxicilline/Clavulanic acid. Continued antibiotic treatment was adapted to the bactriogram. Every admission to hospital that occurred during follow up as result of critical limb ischemia was noted. Surgical interventions were classified as minor surgery (toe, forefoot, foot amputation, wound debridement and necrosectomy) or major surgery (below knee, through knee and above knee amputations).

Outcome

The main outcome was limb salvage during follow-up. Secondary outcome measures were the incidence of complete wound regression, duration of the treatment until complete wound regression or mortality. When applicable, the duration of the hospital admission was calculated. We confirmed the date of demise using the national death registry database (CompeT&T Eindhoven).

Statistics

Statistical analysis was performed with SPSS Version 20.0 (SPSS Inc., Chicago, Illonis, USA) software. Frequencies and descriptive statistics were used for reporting the baseline characteristics of our study population. Survival interval rates were calculated with Kaplan-Meier curves.

RESULTS

Patient selection process

From January 2010 until December 2011, a total of 38 patients were referred to our hospital diagnosed with CLI who did not receive any initial surgery (amputation or bypass) or endovascular intervention.

Baseline characteristics

Mean age was 80 years (range 57-97). Patient demographic data, ASA-classification and comorbidity are summarized in Table 1 and 2. In this study population, 34% of the included patients were active smokers. The mean follow-up of the patients was 7 months (range 1-37 months).

Table 1. Patient characteristics of all included patients treated between January 2010 and December 2011 (n=38)	
GENDER	
Female	18 (47)
Male	20 (53)
AGE	
Median age in years (range)	80 (57-97)
ASA-CLASSIFICATION	
1	2 (5)
2	4 (11)
3	31 (82)
4	1 (3)
COMORBIDITY AND RISK FACTORS	
Diabetes mellitus	18 (47)
Hypertension	26 (69)
Tobacco use	13 (34)
ESRF	2 (5)
CHF	12 (32)
MEDICATION	
Statins	24 (63)
ACEI	8 (21)
LIVING ARRANGEMENT	
Nursing home	11 (29)
Home and fully independent	5 (13)
Home with nurse care	22 (58)
LOCATION OF ISHEMIC ULCER	
Distal foot	25 (66)
Heel	7 (18)
Lower leg	13 (34)

Data are presented as n and (%), unless otherwise specified.
ASA = American Society of Anesthesiologists score. *ESRF* end stage renal failure, *CHF* congestive heart failure, *ACEI* ACE inhibitor

Table 2. Age groups specified of all included patients (*n*=38)	
Age <65	4 (11)
Age 65-70	4 (11)
Age 70-79	12 (31)
Age ≥80	18 (47)

Data are presented as n and (%)

Diagnostics

In 31 of the 38 patients, complementary diagnostic tools were used to assess the extent of their peripheral arterial disease (Table 3). In 22 (58%) patients an MRA was performed and 9 (29%) patients received additional ultra-sound duplex scanning. In 7 (18%) patients, no diagnostics were performed. Because of the lack of clinical consequences due to their general condition, 3 patients refused diagnostics and one patient died prior to performance of additional diagnostics. The median absolute arterial ankle pressure was 80 mmHg, which correlated to a median ankle brachial index of 0.52. In 9 (29%) patients an ankle brachial index could not be obtained due to non-compressible arteries. In 3 of these patients a toe pressure was obtained instead, with a median index of 0,24

Table 3. Initialized diagnostic tools for included patients	
MRA	
Yes	22 (58)
Duplex	
Yes	9 (24)
ABI	
Median pressure in mmHg (range)	80 (48-99)
Median index (range)	0.52 (0.33-0.68)
Non compressible arteries	9 (24)
Median toe pressure index (range)	0,24 (0,20-0,50)
Median surface of tissue loss in cm^2 (range)	4,00 (0.1-81)

Data are presented as n and (%), unless otherwise specified.

TASC-classification

The TASC-II classification was determined in 31 of the 38 patients (Table 4). For 16 of the 38 patients, no information concerning crural outflow was available. In the patient group in which the number of outflow vessels was known, most patients had 2 or less outflow vessels (77%).

Table 4. TASC II classification of all included patients treated between 2010 and 2011.	
TASC II -CLASSIFACTION	
Aorto-iliacal	
None	25 (81)
TASC A	3 (10)
TASC B	2 (7)
TASC C	1 (3)
TASC D	0
TASC Unknown	7 (19)
Femoro-popliteal	
None	5 (16)
TASC A	7 (23)
TASC B	4 (13)
TASC C	8 (26)
TASC D	7 (23)
Unknown	7 (18)
Number of open crural arteries	
0	2 (9)
1	9 (41)
2	6 (27)
3	5 (23)
Unknown	16 (42)

Data are presented as n and (%).
TASC II, TransAtlantic Inter-Society Consensus Document II

Treatment

Half of our patients were treated in an outpatient setting. Main reasons for admission to the hospital were the need of intensive daily wound care, problems with activities of daily living (ADL) or the need to administer intravenous antibiotics. These results are displayed in Table 5. Antibiotics, orally or intravenous administered, were used in 29 (76%) of the patients. Amoxicillin/Clavulanic acid was the most used antibiotic (80%). Six patients (16%) underwent minor surgery in order to salvage the limb.

Table 5. Specification of treatment for included patients.	
TREATMENT	
Outpatient treatment	19 (50)
Mean number of visits (SD)	6 (5)
Clinical treatment	19 (50)
Single admission	10/19 (53)
Multiple admissions	9/19 (47)
ANTIBIOTIC TREATMENT	
Yes	29 (76)
No	9 (24)
MINOR AMPUTATION	
Minor amputation	6 (16)

Data are presented as n and (%) unless otherwise specified

Outcome measures

In total 6, (16%) patients underwent a major amputation after initial conservative treatment (Table 6). Of those 6 patients, 3 died during the follow-up period, one within a year. Cause of death was unknown in 2 patients and one died due to urosepsis.

In 22 (58%) patients, complete wound regression was achieved. The time needed to achieve wound closure ranged between <1 months till 36 months (median 4 months).

During follow-up, 19 patients were admitted to the hospital in need for more intensive wound care, for intravenous administered antibiotics, or the need for surgical intervention. Median hospital stay was 12 days (range 2-73 days).

All-cause mortality rate was 58%. There were 2 CLI related deaths in which both patients died due to sepsis caused by progressive gangrene. Both deaths occurred within 30 days after diagnosis. One patient died within 30 days without a known cause of death. The remaining deaths were due to other morbidities, such as myocardial infarction, pneumonia, or malignancies (11%). The survival rate of 55% during 24-month follow-up is shown in Figure 1.

Table 6. Outcome after conservative treatment	
SURGERY	
Major amputation	6 (16)
WOUNDCARE	
Complete regression of wound	22 (58)
ABI <0.4	1/5 (20)
ABI 0.4-0.6	11/15 (73)
ABI >0.6	7/12 (58)
ABI unknown	3/6 (50)
Median duration of treatment in months (range)	4 (1-36)
Median hospital stay in days (range)	12 (2-73)
MORTALITY	
Mortality during follow up	22 (58)
30-day mortality	3 (8)
Median time to mortality in months (range)	7 (0-41)

Data are presented as n and (%), unless otherwise specified

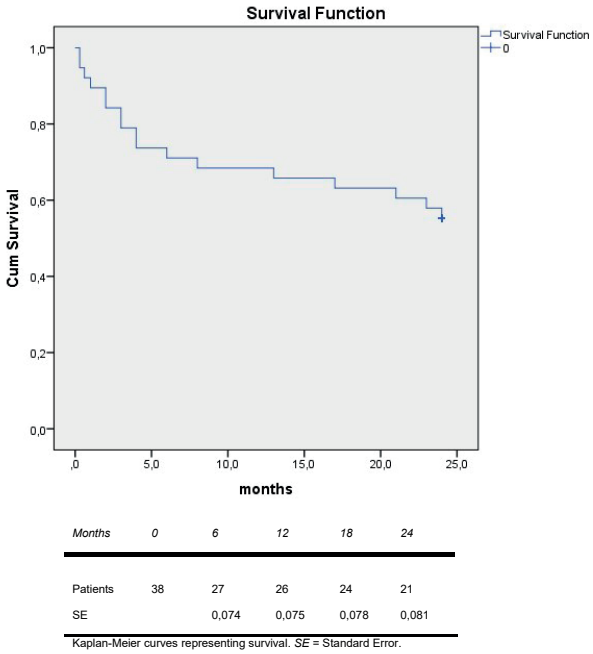

Figure 1. 2-year survival rate of all patients who were diagnosed with Rutherford classification 5–6 and received conservative treatment

DISCUSSION

Our study suggests that conservative treatment could be a viable alternative in selected patients not suitable for revascularization or bypass surgery. In this study, the limb survival rate was 84% during a minimum of 24 months follow-up, although annotated with an high mortality rate of 58%. Complete wound regression was attained in a significant number of patients (58%), comparable to previous studies [10-12].

In current practice, preferred treatment of CLI is endovascular revascularization or, whenever an endovascular treatment is not possible, bypass surgery. However, in some cases bypass surgery is not an option due to the fragility of the patient or the lack of viable bypass options. In these patients, either conservative treatment or primary amputation remains as treatment option. In our today's practice, the majority of patients are primarily treated endovascular (46-47%). Another 25% is treated with reconstructive surgery, 13% with primary amputation and only 8-15% is treated conservatively. The amputation rate was 10 % after endovascular revascularization and 11 % after reconstructive surgery [5].

Literature is scarce concerning the outcome of patients with critical limb ischemia treated conservatively. Acceptable results for limb salvage with both endovascular and surgical revascularization have been reported [4]. In 2003, Nehler et al described that in some cases, primary amputation is preferential to aggressive attempts at revascularization; however data is lacking which patients would benefit from early amputation [13]. Complementary, Lepäntalo et al, report that in patients with CLI without a vascular reconstruction, 1 year mortality is 46% and limb salvage rate is 54% [14]. In another study, where patients with PAOD and foot ulcer were treated conservatively, major amputation was performed in 23% of patients after 1 year [10].

Although the mortality rate is high, a minor part of the patients died as a result of CLI. Patients with CLI are often fragile elderly patients with significant comorbidities, therefor invasive, often physical demanding treatment modalities should be used with caution. In this population, treatment should be more patient focused and less lesion focused.

A recent systematic review attempted to assess impact of primary revascularization versus primary amputation on quality of life (QoL) of patients with CLI. Unfortunately their data were inconclusive [15]. To date no study has been performed to determine QoL in patients with CLI who were primarily treated conservatively.

Because of its retrospective nature, our study has clear limitations, which should be considered when interpreting the results. The numbers of patients in the present study does not permit further analysis.

Another possible limitation of this study may be the restriction of data collection from a single hospital, which might not be representative for other hospitals.

As these patients are specifically selected and there is no knowledge of how patients who underwent primary revascularization or amputation would have fared with conservative treatment only, the population is biased, which should be taken into account interpreting the results.

CONCLUSION

In selected patients with severe critical limb ischemia, conservative treatment could be a viable alternative to primary limb amputation.

In this study of a selected group of patients with arterial insufficiency and limb ulcers treated without revascularization, major amputation is necessary in 16% of limbs during follow-up. Wound healing is slow but eventually achieved in 58% at 12 months. We believe these are acceptable outcomes in selected patients considered unfit for surgical or endovascular intervention. Primary amputation should not be considered as standard treatment in this patient group. We state that further studies involving quality of life of those patients should be performed to properly determine the role of conservative therapy in patients with critical limb ischemia.

Acknowledgement

We would like to thank out specialized wound care practitioners for their help with delivering the necessary data.

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Chapter 3

Long-term outcome of Ruptured AAA: impact of treatment and age

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Clinical Interventions in Aging. 2014 Oct 13;9: 1721-32

ABSTRACT

Objective: To evaluate the outcomes of emergency endovascular aneurysm repair (eEVAR), conventional open repair (OPEN) and conservative treatment in elderly patients with a ruptured abdominal aortic aneurysm (rAAA).

Background: Despite advances in operative repair, rAAA remains associated with high mortality and morbidity rates, especially in elderly patients.

Methods: We conducted a retrospective study of all rAAA patients treated with an OPEN or an eEVAR between January 2005 and December 2011 at the vascular surgery department of the Amphia Hospital in the Netherlands. Outcome after patients treated for rAAA by eEVAR or OPEN repair was measured. Special attention was given to the patients who were admitted and did not receive operative repair due to serious comorbidity, extreme high age or poor physical condition. We calculated the 30-day rAAA related mortality of all rAAA patients who were admitted to our hospital.

Results: Twelve patients (*n=12)* did not receive operative emergency repair due to severe fragility (mean age: 87 years, median time to mortality was 27 hours). A total of 23 patients had eEVAR and 82 had OPEN surgery. The 30-day mortality rate of operated patients was 30% (7 of 23) in eEVAR vs. 26% (21 of 82) in patients undergoing OPEN surgery (*p*=0.64*)*. No difference in mortality was noted between eEVAR and OPEN till 5 years of follow-up. There were more cardiac adverse events in the OPEN group (*n*=25, 31%) compared to the eEVAR group (*n*=2, 9%, *p*=0.035). Re-intervention after discharge was more frequent in patients who received an eEVAR (35%) compared to patients which had an OPEN repair (5%, *p*<0.001).
Age was associated with increasing mortality (HR 1.05 [1.01-1.09]) per year for patient who received operative repair, with 67%, 76% and 100% 5-year mortality for the 34 patients with an age <70 years, the 59 patients with an age of 70-79 years, and the 12 octogenarians, respectively. The 30-day rAAA related mortality was associated by increase of age reporting 21%, 30%, 61% between respectively patients <70 years, patients of 70-79 years and the 23 octogenarians (*p* = 0.008).

Conclusions: The 30-day mortality and 5-year following survival of patients with a rAAA is equal between the treatment options of eEVAR or OPEN.
Among those octogenarians undergoing surgical repair, the 30-day mortality rate was not significant higher compared to younger aged patients. However, especially fragile and high aged patients did not receive operative repair. Selection whether to intervene in case of an rAAA should not be made by age as an isolated factor, but in relation to comorbidity and patient preference related factors.

INTRODUCTION

Rupture of an abdominal aortic aneurysm (rAAA) is a catastrophic event, occurring with increasing frequency in our increasingly elderly population.[1]

The demographic trends towards an ageing population in the Western world and an increasing incidence and prevalence of cardiovascular disease in the elderly are important considerations for current healthcare professionals. Although the established definition of "elderly patients" in current literature refers to people with an age exceeding 65 years, current demographic trends, improved health care and understanding of the discrimination between biological age and chronological age dictates that the definition of an "elderly patient" should possibly be revised. From a historical point of view the conventional method to repair a ruptured abdominal aneurysm is to perform a conventional open repair (OPEN) with replacement of the ruptured aneurysm using a synthetic tube-graft. This extensive repair carries high mortality - and morbidity rates in patients which already are on the end of their limited physical reserves.[2] Emergency endovascular aneurysm repair (eEVAR) is an alternative in patients with AAA and is becoming generally accepted in selected patients for planned AAA repair. The EVAR II trial reported no benefit for EVAR compared to no intervention in patients judged unfit for open repair concerning elective AAA repair.[3] However, several studies note eEVAR potentially could reduce morbidity and mortality rate.[4] The minimally invasive nature of this technique allows aneurysm repair in patients with a rAAA which would be at significantly risk in open surgery. The application of eEVAR could therefore be a viable alternative in patients suffering a rAAA, especially for elderly. In current literature, data are rare concerning patients with a rAAA who arrive hospital alive and do not receive emergency surgical repair. In our opinion these data are of great importance to point out the outcome of these elderly with rAAA which receive emergency surgical repair or do not. First we analyzed our recent results of operative treatment (OPEN and eEVAR) in rAAA patients, and we describe patients which did not receive operative repair. Second we analyzed our results of rAAA repair in this elderly population per age group.

PATIENT AND METHODS

Patients characteristics

This study was evaluated and approved by the institutional review board. A retrospective observational clinical review was conducted from data of 157 consecutive rAAA patients treated with an OPEN or an eEVAR between January 2005 and December 2011 at the vascular surgery department of the Amphia Hospital in the Netherlands. Exclusion criteria were patients with symptomatic abdominal aortic aneurysm and three patients were excluded for mortality prior to arrival in operating theatre. Patients with an acute onset of aortic-duodenal fistula and ruptured iliacal aneurysms were also excluded. Twelve patients (*n*=12*)* did not receive operative emergency repair and were treated conservatively.

Data analyzed per age group

All collected data of included patients were analyzed per age group. Age < 70 years (group A; *n*=34; 32%), Age 70-79 years (group B; *n*=59; 56%), age >80 year (group C; *n* =12; 11%). Operation related 30-day mortality was defined as mortality in the first 30-days after surgical repair (eEVAR or OPEN). RAAA related mortality was defined as mortality for all rAAA patients in the first 30-days after admission to our hospital receiving operative repair or not (*n*=117*)*.

Risk factors and comorbidity

Risk factors, comorbidity, vital signs and biochemistry tests were registered prospectively of all patients during their admission intake. The risk factor and comorbidity management, according to the Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC)[10] and the American Heart Association/American College of Cardiology (AHA/ACC)[11] were either conducted by a vascular specialist or cardiologist preoperatively whenever possible. Data patient characteristics, risk factors and comorbidity are listed in Table 1.

AAA characteristics

RAAA was defined as hemorrhage outside the aortic wall and diagnosed by a multislice CT scanner (Siemens Definition CT-scan). Some patients were hemodynamically unstable and no imaging could be performed. In those cases the diagnosis was confirmed intra-operatively. Data of the rAAA characteristics are listed in Table 1.

Revascularization

All vascular and endovascular procedures were performed by certified vascular surgeons and interventionist which were available around the clock.
This team consisted of intervention radiologists and vascular surgeons.

eEVAR

Two stent graft system were used for treatment of the rAAAs during the study periods: 2005-2008: the Cook® Zenith Flex® aorto-uni-iliac (AUI) device stent graft system[12], 2008-2011: the Medtronic® Endurant® II aorto-uni-iliac (AUI) - and aorto-bi-iliac stent graft system.[13] All AUI endografting were combined with a femoro femoral crossover bypassand the deployment of an occluder cuff in the contralateral common iliac artery. The requirements for these standard available stent grafts were driven by the Society of Vascular Surgery / North American Chapter of the International Society for Cardiovascular surgery (SVS/ISCVS)[14] - and the European Society for Vascular Surgery (ESVS) reporting standards.[15] The eEVAR procedure was performed according to standard vascular and endovascular techniques.
It was recommend that eEVAR was performed under local anaesthesia of the groin at the selected access site. After the AUI was inserted and the antegrade flow into the rAAA sac was blocked, general anaesthesia could be given to perform subsequent operative steps: deployment of the

Table 1. Patient characteristics of all patients treated for a rAAA with an OPEN or eEVAR procedure during the study period (2005 till 2011).

Characteristics	**Total** *n*=105	**OPEN** *n=82*	**eEVAR** *n=23*	***P*-value**
GENDER				
Male	86 (82)	69 (84)	17 (74)	0.260
Female	19 (18)	13 (16)	6 (26)	0.260
AGE				
Median age in years (range)	73 (54-89)	71 (54-87)	77 (64-89)	**<0.001**
<70 years	34 (32)	33 (40)	1 (4)	**0.001**
Between 70 to 79 years	59 (56)	40 (49)	19 (83)	**0.004**
> 80 years	12 (11)	9 (11)	3 (13)	0.783
HD STABLE	48 (46)	37 (54)	11 (48)	0.818
SBP > 80 mmHg	61 (58)	45 (55)	16 (70)	0.207
CT-SCAN OBTAINED				
Yes	80 (76)	57 (70)	23 (100)	**0.002**
No	25 (24)	25 (31)	0 (0)	**0.002**
DIAMETER AAA				
Median aneurysm in mm (range)	80.0 (4.5-13.8)	80.0 (4.5-13.8)	70.0 (5.0-10.0)	**0.044**
COMORBIDITY AND RISK FACTORS				
Cardiac disease	47 (45)	37 (45)	10 (44)	0.889
Pulmonary disease	29 (28)	22 (27)	7 (30)	0.733
Renal disease	10 (10)	8 (10)	2 (9)	0.878
Diabetes mellitus	12 (11)	7 (89)	5 (22)	0.079
Hypertension	51 (49)	38 (46)	13 (57)	0.388
Hyperlipidaemia	12 (11)	11 (13)	1 (4)	0.227
Peripheral arterial occlusive disease	8 (8)	6 (7)	2 (9)	0.826
Tobacco use	44 (42)	37 (45)	7 (30)	0.429
SECONDARY PREVENTION				
Anti-platelet agent	42 (40)	31 (38)	11 (48)	0.386
Statin	35 (33)	27 (33)	8 (35)	0.867
Coumarins	13 (12)	12 (15)	1 (4)	0.180

Data are presented as n and (%), unless otherwise specified. *AAA* = Abdominal aorta aneurysm; e*EVAR* = emergency endovascular aneurysm repair. *OPEN* = open repair. *HD-stable* = hemodynamically stable. *SBP* = systolic blood pressure in mmHg. *CT-SCAN* = Computed Tomography scan.

common iliac occluder cuff and performance of the femoro femoral crossover bypass. All these patients met the characteristics as listed in the instructions for use, according to component placement and sizing guidelines.

OPEN

The OPEN were performed according to standard vascular and endovascular techniques following the Society of Vascular Surgery / North American Chapter of the International Society for Cardiovascular surgery (SVS/ISCVS) guidelines.[14] All patients received an anterior transperitoneal approach and after aortic clamping, a minimal dissection and when necessary, intrasaccular ligation of lumbar artery branches was performed. Subsequently suture attachment of the prostatic graft to the proximal and distal aspects of the aneurysm was performed. Aorto-aortic "straight tube" grafts and bifurcated prostheses were used. Operative data of patients underwent OPEN an eEVAR are listed in Table 3.

Admission and follow-up

General

Pre-operative and operative data were collected. During follow-up mortality, hospital (surgical ward) - and Intensive Care Unit (ICU) stay were registered. Mortality rates were retrieved using the national death registry.

Adverse events (AEs)

In the Netherlands, the Association of Surgeons of the Netherlands (ASN) has agreed on one common definition of AEs.[16-20] This definition differs from that used in other studies because it has been chosen with the explicit aim of excluding subjective judgment on cause and effect, and right and wrong. The definition of an AE is: "an unintended and unwanted event or state occurring during or following medical care, that is so harmful to a patient's health that (adjustment of) treatment is required or that permanent damage results. The AE may be noted during hospitalization, until 30 days after discharge or transferee to another department. The intended result of treatment, the likelihood of the adverse outcome occurring, and the presence or absence of a medical error causing it, is irrelevant in identifying an adverse outcome".

Endoleaks

The definition of endoleaks, the decision to intervene and the type of re-intervention, endovascular – or surgical, were driven by the SVS/ISCVS[14] and ESVS reporting standards and were collected.[15]

Statistical analysis

Statistical analysis was performed with SPSS Version 20.0 (SPSS Inc., Chicago, Illonis, USA) software. Following completion of the data collection, univariate analyses was performed using Chi-

square and unpaired Students *t*-test. Survival was estimated with Logistic Regression analysis (30-day mortality) and Cox regression analysis (long term mortality, patients included till last date of follow-up of till death).

RESULTS

Patient selection process

From January 2005 until December 2011 a total of 157 patients were admitted to our hospital with diagnosis of a ruptured – or symptomatic AAA (Figure 1). Thirty seven patients (*n*=37) were excluded due to diagnosis of a symptomatic non-ruptured AAA. Twelve patients (*n*=12*)* did not receive operative emergency repair and were treated conservatively (mean age: 87 years, SD 4.6) for several different reasons and are listed in Table 2. One patient died after 15 months, in this case diagnosis of rAAA was confirmed by an uncontrasted CT due to significant renal impairment. All remaining 11 patients died within 48 hours (median mortality 27 hours).
Three patients (*n*=3) died on the emergency room and therefore were excluded.
Of all included patients (*n*=105), 82 (78%) patients underwent conventional OPEN (*n*=82), and 23 (22%) patients received eEVAR (*n*=23)

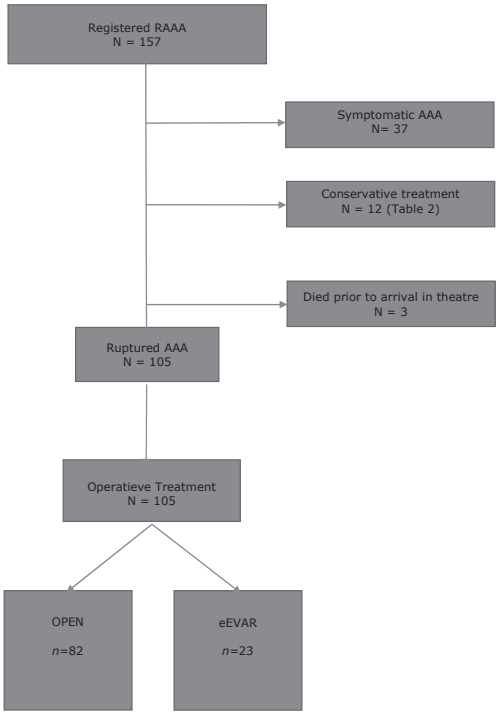


Figure 1. patient flow through identification and selection process.

Table 2. Patient overview for rAAA with conservative management (*n*=12)

Case	HD-stable	Age in years	Motivation for conservative management	Time to mortality	Time to mortality in hours
1	Yes	87	Medical history included AAA, decision for conservative treatment was made prior to rupture.	< 48 hour.	27
2	Yes	89	Diagnose was confirmed with un-contrasted CT-scan. Died 15 months later duo to re-rAAA in 5 days. Complex morphology aneurysm. Conservative due to high age and comorbidity.	483 days (15 months)	Unknown
3	Unknown	91	On demand of patient and family.	< 48 hours	33
4	No	92	Complex morphology aneurysm not eEVAR suitable.	< 24 hours	Unknown
5	No	87	Conservative management due to high age and comorbidity.	< 24 hours	4
6	No	83	Arrived undergoing CPR. Poor prognosis.	< 24 hours	2
7	Yes	85	Complex morphology aneurysm, not EVAR suitable. On demand of patient and family no open repair.	< 48 hours	32
8	No	89	Conservative due to high age and comorbidity including severe dementia.	< 48 hours	26
9	No	77	On demand of patient. History included end stage prostate carcinoma.	< 48 hours	37
10	No	90	Due to high age.	< 48 hours	31
11	Yes	82	Complex morphology aneurysm, not EVAR suitable. On demand of patient and family no open repair due to high age and comorbidity.	< 24 hours	12
12	Yes	93	Due to high age and comorbidity including severe cardiac failure.	< 24 hours	2

AAA = Abdominal aorta aneurysm, *rAAA* = ruptured abdominal aorta aneurysm. *HD-stable* = hemodynamically stable. *CT-scan*: Computed Tomography scan. *CRP* = Cardiopulmonary resuscitation.

Table 3. Summary of OPEN (*n*=82) and eEVAR procedures (*n*=23) of all patients treated for a rAAA

OPEN	
Tube graft	58 (71)
Bi-iliac tube graft	19 (23)
Died prior to placement of graft	5 (6)
eEVAR	
Cook® Zenith Flex® AAA (AUI) *Endovascular Graft system*	12 (52)
Medtronic® Endurant® AAA Stent Graft System	
AUI stent graft system	5 (22)
ABI stent graft system	6 (26)

Data are presented as n and (%). *rAAA* = ruptured abdominal aorta aneurysm; *OPEN* = open repair; e*EVAR* = emergency endovascular aneurysm repair; *AUI* = aorto-uni-iliac; *ABI* = aorto-bi-iliac

Patient characteristics and comorbidity

Patients in the eEVAR group were significant older (median 77 years) compared to the OPEN group (median 71 years, $p<0.001$). There were slightly more men ($n=69$, 84%) in the OPEN group compared to eEVAR group ($n=17$, 74%, $p=0.26$). No difference in hemodynamic status at admission was measured between both groups. Comorbidity and risk factors were similar in both groups (Table 1).

AAA characteristics

In all 23 eEVAR patients (100%) a CT-scan was made compared to 57 patients (70%) in the OPEN group ($p=0.002$). The median aneurysm diameter of the rAAA in patients treated by eEVAR (70.0 mm) was significantly larger compared to patients treated by OPEN (80.0 mm, $p=0.044$).

Revascularization (eEVAR and OPEN)

In one patient the eEVAR procedure was terminated and converted to an OPEN due to persistent hemodynamic instability and development of a distended abdomen during surgery (Table 3). The patient died direct after performance of a celiotomy, most likely due to exsanguination. In one patient eEVAR was converted to open repair with placement of a tube graft due to technical problems during placement of the main device.

eEVAR related re-interventions and endoleaks

We report 3 type-I, 4 type-IIa, 4 type-IIb and 2 type-III endoleaks in Table 4. There were no type-IV or type-V endoleaks. Overstenting of 4 renal arteries in 3 individual patients receiving eEVAR occurred. Two patients underwent a Hartmann procedure in case of bowel ischemia. Another 2 patients were re-operated because of an infected prosthesis: 1 infected EVAR and 1 infected femoro femoral crossover bypass. Other surgical adverse events and re-interventions are listed in Table 4.

Adverse events and re-interventions

At least 1 AE occurred in the eEVAR and OPEN patient, ($n=14$, 61% vs. $n=53$, 65%) respectively. There were more cardiac AEs in the OPEN group ($n=25$, 31%) compared to the eEVAR group ($n=2$, 9%) $p=0.035$. All cerebrovascular accidents occurred in the eEVAR group ($n=2$, 9%) $p=0.007$ as listed in Table 5.

We report more re-interventions during follow-up in rAAA patients who underwent eEVAR ($n=8$, 35%) compared to patients who underwent OPEN ($n=5$, 6%) $p<0.001$ as shown in Table 6.

Length of stay

Hospital stay was not significant longer in the OPEN group (mean 17 days) compared to eEVAR (mean 12 days). Both patient groups were admitted to the ICU with a mean of 7 days during post-operative period. Data are summarized in Table 7.

Table 4. Summary of endoleaks and adverse events after all eEVAR procedures (*n*=23) in patients treated for a rAAA

Endoleak or surgical complication	Intra-operative	< 24 hours	<30 days	< 3 months	< 12 months	> 12 months	Further explenation
Endoleak type I	III[a]						[a]: one died, one successful treated by PTA, one treated by main device in main device placement.
Endoleak type IIa	II		I			I[b]	[b:] ligation of IIA.
Endoleak type IIb			II		I[c]	I	[c]: ligation of IMA.
Endoleak type III	I[d]					I[e]	[d:] occluder plug insufficient, coiling of IIA unsuccessful, ligation of EIA and femofemoro-crossover. [e]: surgical repair with interponate graft.
Ischemic colitis			III[f]				[f]: 2 Hartmann procedures, in one patients complicated by parastomal herniation 2 years after surgery.
Overstenting of renal artery	III[g]		I				[g]: in one patient concerning a juxtarenal aneurysm with no open surgical possibilities due to severe intra-abdominal adhesions, overstenting of both renal arteries.
Infected prosthesis		I[h]		I[i]			[h]: re-operation with replacement with an antibiotic drained prosthesis. [i]: infected femfemoro-crossover with replacement with an autologous crossover bypass.
Aorta-duodenal fistula						I[j]	[J]: conservative treatment, patient died.
Died on table after correct placement	I						
Anastomotic aneurysm of femoro femoral crossover bypass						I	Re-do.

All endoleaks and surgical complications were managed conservatively unless otherwise mentioned. e*EVAR* = emergency endovascular aneurysm repair; *rAAA* = ruptured abdominal aorta aneurysm; *PTA*: percutaneous transluminal angioplasty; *IIA* = internal iliac artery (hypogastric artery). *IMA:* inferior mesenteric artery; *EIA* = external iliac artery.

Table 5. Adverse events of all patients treated for a rAAA with an eEVAR procedure or OPEN during the study period (2005 till 2011).

Description of Adverse event	**Total** *n*=105	**OPEN** *n=82*	**eEVAR** *n=23*	*P*-value
Any adverse event	67 (64)	53 (65)	14 (61)	0.740
Any cardiac AE	27 (26)	25 (31)	2 (9)	**0.035**
Myocardial infarction	4 (4)	4 (5)	0 (0)	0.280
Cardiac arrest	5 (5)	4 (5)	1 (4)	0.916
Heart failure	14 (13)	12 (15)	2 (9)	0.459
Brady/tachycardia	3 (3)	2 (2)	1 (4)	0.627
Atrial fibrillation	7 (7)	6 (7)	1 (4)	0.614
Any Pulmonary AE	36 (34)	29 (35)	7 (30)	0.660
Respiratory insufficiency	16 (15)	11 (13)	5 (22)	0.326
Pneumonia	37 (35)	31 (38)	6 (26)	0.299
Pleural fluid	5 (5)	5 (6)	0 (0)	0.225
Atelectasis	2 (2)	2 (2)	0 (0)	0.450
Any Neurologic AE	4 (4)	2 (2)	2 (9)	0.316
Cerebrovascular incident	2 (2)	0 (0)	2 (9)	**0.007**
Neuropraxia	2 (2)	2 (2)	0 (0)	0.450
Any Renal AE	30 (29)	26 (32)	4 (7)	0.179
Renal failure	25 (24)	20 (24)	5 (22)	0.792
Renal failure haemodialysis	15 (14)	12 (15)	3 (13)	0.847
Urinary tract infection	4 (4)	4 (5)	0 (0)	0.280
Urinary retention	2 (2)	2 (2)	0 (0)	0.450
(Sub)cutis AE				
Wound infection	4 (4)	3 (4)	1 (4)	0.879
Wound dehiscence	1 (1)	1 (1)	0 (0)	0.595
Compartment syndrome	2 (2)	2 (2)	0 (0)	0.450
Fascia dehiscence	2 (2)	2 (2)	0 (0)	0.450
Bowel ischemia	10 (10)	7 (9)	3 (13)	0.515
Bowel ischemia required resection	6 (6)	4 (5)	2 (9)	0.452
Infected tube graft	2 (2)	1 (1)	1 (4)	0.332

Data are presented as n and (%). *AE* = adverse events; *rAAA*=ruptured abdominal aorta aneurysm; *eEVAR*= emergency endovascular aneurysm repair; *OPEN* = open repair.

Table 6. Re-intervention rates with details of rAAA patients receiving OPEN or eEVAR during the study period (2005 till 2011).

Intervention	**OPEN** *n*=82	**eEVAR** *n*=23	***P-value***
Patients with any re-intervention	26 (32)	11 (48)	0.153
Re-intervention during 30-day postoperative period	22 (27)	4 (17)	0.354
Re-intervention during follow-up	5 (6)	8 (35)	<0.001

Data are presented as n and (%). *rAAA*=ruptured abdominal aorta aneurysm; *OPEN* = open repair; *eEVAR*= emergency endovascular aneurysm repair.

Mortality

The 30-day mortality rate was 30% (7 of 23) in eEVAR patients vs. 26% (21 of 82) in OPEN patients (p=0.64). Intra-operative mortality was comparable in both groups, 2 patients (9%) died during eEVAR compared to 9 patients during OPEN (11%, p=0.752). We report no difference in mortality in 1-, 3- and 5 year follow up between eEVAR and OPEN. Data are outlined in Table 7.

Table 7. Mortality and hospital stay of all patients treated for a rAAA with an eEVAR procedure or OPEN during the study period (2005 till 2011).

	Total *n*=105	**OPEN** *n*=82	**eEVAR** *n*=23	*P*-value
Mortality				
Mortality intra-operative	11/105 (10)	9/82 (11)	2/23 (9)	0.752
30 day mortality-rate	28/105 (27)	21/82 (26)	7/23 (30)	0.644[a]
1 year mortality-rate	38/105 (36)	30/82 (37)	8/23 (35)	0.913[b]
3 year mortality-rate	47/89 (53)	37/70 (53)	10/19 (53)	0.913[b]
5-year mortality-rate	57/75 (76)	44/58 (76)	13/17 (76)	0.913[b]
Duration of in hospital stay				
Mean length of hospital stay in days (SD)	16 (15)	17 (16)	12 (9)	0.212
Mean length of ICU stay in days (SD)	7 (11)	7 (11)	7 (12)	0.922

Data are presented as n and (%), unless otherwise specified. *rAAA*=ruptured abdominal aorta aneurysm; *OPEN* = open repair; *eEVAR*= emergency endovascular aneurysm repair. [a] Logistic regression analysis [b] Cox regression analysis.

Impact of age

There were less male patients in group C (Age > 80 years; male 67%) compared with younger age group A (Age <70 years; male 97%) and group B (age 70-79 years; male 76%) p= 0.015. We report no significant differences in operation related 30-day mortality (21%, 29% and 33%) between respectively group A, group B and group C if patients underwent surgery (Table 8). Increase of age was also associated with mortality during 5 year follow up (p=0.012, HR 1.049 [1.01-1.09].

Table 8. Mortality rates of patients treated for a rAAA with an eEVAR procedure or OPEN for 30-days, 1-, 3- and 5-years after inclusion according to different age groups

All rAAA patients treated with an eEVAR or OPEN.	**Total** *All age groups* *n = 105*	**Group A** Age < 70 *n = 34*	**Group B** Age 70-79 *n = 59*	**Group C** Age >80 *n = 12*	***P*-value**	**HR [95% CI]**
Operation related 30-day mortality rate	28/105 (27)	7/34 (21)	17/59 (29)	4/12(33)	0.059[a]	1.9 [0.45 – 8.30]
1 year mortality-rate	38/105 (36)	11/34 (23)	22/59 (37)	5/12(42)	0.012[b]	1.049 [1.01- 1.09]
3 year mortality-rate	47/89 (53)	13/28 (46)	27/51 (53)	7/10 (70)	0.012[b]	1.049 [1.01- 1.09]
5-year mortality-rate	57/75 (76)	16/24 (67)	31/41 (76)	10/10(100)	0.012[b]	1.049 [1.01- 1.09]
All rAAA patients (treated operatively or non-operatively).	**Total** *All age groups* *n = 117*	**Group A** Age < 70 *n = 34*	**Group B** Age 70-79 *n = 60*	**Group C** Age >80 *n = 23*	***P*-value**	**HR [95% CI]**
RAAA related 30-day mortality rate[c]	39/117 (33)	7/34 (21)	18/60 (30)	14/23 (61)	0.008[a]	6.0 [1.84 – 19.53]

Data are presented as n and (%). *rAAA* = ruptured abdominal aorta aneurysm; *OPEN* = open repair; *eEVAR*= emergency endovascular aneurysm repair; *Group A*: patients under the age 70 years; *Group B*: 70-79 years; *Group C*: patients 80 years or older. HR = Hazard ratio; CI = Confidence Interval. [a]Logistic regression analysis [b]Cox regression analysis.

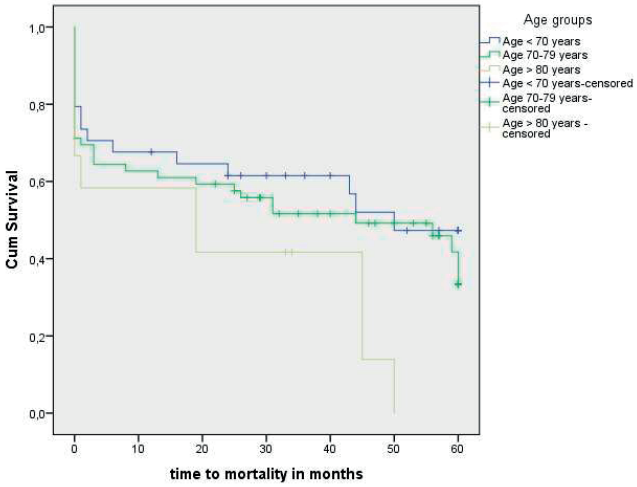
[c]Addition of non-operated patients with rAAA (*n*=117).

RAAA related mortality increased with age, 21%, 30%, 61% between group A, group B and group C (respectively, *p*=0.008). In 75% of patients in group C, at least one AE occurred, however there was no statistical difference compared to the other age groups (Table 9). A survival curve per age group are shown in Figure 2.

Table 9. Data of patients treated for a rAAA with an eEVAR procedure or OPEN after inclusion organized by age group

	Group A Age < 70 *n* = 34	**Group B** Age 70-79 *n* = 59	**Group C** Age >80 *n* = 12	*P*-value
Adverse events				
Any AE	18 (53)	40 (68)	9 (75)	ns
Any Cardiac AE	7 (21)	15 (25)	5 (42)	ns
Any Pulmonary AE	10 (2)	21 (36)	5 (42)	ns
Any Neurologic AE	0 (0)	2 (3)	2 (17)	ns
Any Renal AE	8 (24)	18 (31)	4 (33)	ns
Hospital stay				
Mean length of ICU stay in days (SD)	3.9 (4)	8.6 (13)	6.4 (9)	ns
Mean length of hospital stay in days (SD)	12.3 (7)	17.8 (17)	15.3 (20)	ns

Data are presented as n and (%), unless otherwise specified. *rAAA* = ruptured abdominal aorta aneurysm; *OPEN* = open repair; *eEVAR* = emergency endovascular aneurysm repair; *Group A*: patients under the age 70 years; *Group B*: 70-79 years; *Group C*: patients 80 years or older; *AE* = adverse events



	Months	*0*	*10*	*20*	*30*	*40*	*50*	*60*
Age								
< 70	Patients	34	23	22	16	13	10	8
	SE	0	0.08	0.082	0.083	0.083	0.097	0.097
70-79	Patients	59	36	35	27	21	17	10
	SE	0	0.063	0.064	0.065	0.066	0.068	0.075
≥ 80	Patients	12	7	5	5	3	0	0
	SE	0	0.142	0.142	0.142	0.142	0.00	0.00

Kaplan-Meier curves representing survival per age group. *SE* = Standard Error.

Figure 2. survival per age group.

DISCUSSION

Clinicians increasingly face fragile elderly in a poor mental - and physical state. These issues assume even major importance as population projects indicate that the number of persons aged >80 years will double during the next 30 years.[21] RAAA is often associated with high mortality and significant comorbidity, especially in the very elderly.[2] In current medicine, supportive care for critically ill patients has improved over the last decades. As supportive technologies become more advanced, surgeons should consider the expediency of comprehensive possible life-saving interventions and extensive surgery in the elderly population.

The non-operated patients

In recent decades interest in EVAR techniques increased and more studies were published noting potential improved outcomes for mortality and morbidity. Every clinician who deals with vascular emergencies has experienced the ethical dilemma of whether to offer a probably hopeless but potentially life-saving intervention when an highly aged, comorbid patient presents with a rAAA. A decision for OPEN or eEVAR in case of a rAAA must be made according to the wishes of the patient and family whether to proceed with emergency repair or provide comfort measures. It should be made with serious consideration and care, and could be challenging because of the time factor. Evidence is scarce in current literature to guide this clinical decision.

In 10-26% of these patients with a rAAA reaching the hospital alive were treated conservatively, because of the extensive comorbidity and high age.[23,24]
We report a high mean age of 87 years in patients who were treated conservative, compared to 75% rAAA patients > 80 years in literature[22,23].[22,23] In this study, high age in combination with fragility was mentioned most frequently as motivation for conservative treatment. As in literature, the average time to death following rAAA without repair was seven hours.[24]

Treatment: OPEN and eEVAR

Adverse events

We report high AE rates in both treatment groups. In contrast to other studies, their results were equal, the cardiac AEs were significant higher in the OPEN group.[25-29] These high rates could be partly explained by our broad definition and strict registration protocol of AE. We report strokes in the patients which received eEVAR and this may be related to the guide wire in the aortic arch during the procedure.
We report no significant difference in AEs per age group. Probably this could be explained by selection bias.

Re-interventions

The risk of a re-intervention and re-admission is higher after eEVAR compared with open repair,[30] particularly in very elderly patients. Edwards et all reported significant higher endovascular re-intervention rates in 3 year follow up for patients with a rAAA treated by eEVAR (10.9%) compared to patients treated by OPEN (1.5%).[31] We report similar results by reporting re-interventions rates in 5 year follow up for patients treated by eEVAR (35%) and OR (6%). A possible explanation is the fact that endoleaks and possible re-interventions for endoleaks occur only after eEVAR and not after OPEN. In literature, rAAA patients treated with eEVAR resulting in post-operative re-interventions were associated with a significant 30-day mortality, in contrast to this study.[30]

Hospital and ICU stay

In current literature, a significant heterogeneity in hospital stay is reported: eEVAR (range 9.4 - 14.9 days) vs. OPEN (range 10 - 25.8 days).[29,32-35] We report no difference in registered hospital an ICU stay between patients treated with eEVAR or OPEN. Other studies showed ICU rates between 0-5 days in the eEVAR group versus 3-20 days in the OPEN group.[36-45] This difference could be explained, because of the fact that the referred studies included fairly small groups. Also, in contrast to other studies we excluded all symptomatic not rAAA patients, which are likely to reduce length of ICU and hospital stay.

Mortality

No significant difference in 30-day mortality rates were registered between eEVAR and OPEN as comparable to a recent RCT by Reimerink et all including 116 cases and described a 30-day

mortality rate of respectively 25% and 21%.[28] The IMPROVE trail reported similar results and described no statistic significant difference in 30-day mortality rates for rAAA treated patient between eEVAR (35.4%) and OPEN (37.4%). Remarkably we report no statistic significant difference in 30-day operation related mortality after differentiating per age group. This could be, because of the fact that we excluded extreme fragile patients and - or in combination with high age for operative treatment. Addition of patients with a rAAA who did not received operative repair to our analysis, defined as rAAA related mortality, resulted in significant higher mortality for octogenarians compared to younger aged patients. We state that after proper selection, an octogenarian in a good condition has equal outcome as younger patients receiving emergency operative repair for rAAA. However, rAAA is more frequent in males. Life expectancy is known to be shorter in most Western societies for males compared to females and higher mortality is expected, this should be mentioned when interpreting these results.

Current studies on quality of life after EVAR in octogenarians report that recovery to baseline functioning seems to last at least > 1 year.[46] Although these numbers are remarkable high, quality of life is probably even more impaired after OPEN. Despite acceptable outcome in selected elderly, results in quality of life should be mentioned in clinical decision making whether to intervene in case of a rAAA or not.

Limitations

Because of its retrospective nature, our study has limitations, which should be considered when interpreting the results. Patient considered unstable at arrival to hospital did not receive CT-scanning and were directly transported to operating theatre for open repair and this contributes to a significant selection bias.

Anatomy suitability was certainly a source of significant bias in this study, as it is certainly the main determining factor regarding whether to perform eEVAR or not. Indeed, it significantly influenced also the decision whether to operate or not as mentioned earlier.

The number of patients in the present study does not permit further analyses, especially as numbers are small for included octogenarian patients.

Another possible limitation of this study may be the restriction of data collection for only one hospital, which might not be completely representative for all hospitals.

CONCLUSION

The 30-day mortality and 5-year following survival of patients with a rAAA is equal between the treatment options of eEVAR or OPEN, despite an increased post-operative cardiac morbidity after OPEN.

Among those octogenarians undergoing surgical repair, no major increase in mortality with age is observed. However, especially fragile and high aged patients receive no rAAA repair. Selection

whether to intervene in case of an rAAA should not be made by age as an isolated factor, but in relation to comorbidity and patient preference related factors.

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Chapter 4

Risk factors of post-operative delirium after elective vascular surgery in the elderly: A Systematic Review

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International Journal of Surgery. 2016 Sep 6;35:1-6

ABSTRACT

Background: Postoperative delirium is a common and serious adverse event in the elderly patient and is associated with significant morbidity and mortality. It is of great importance to identify patients at risk for delirium, in order to focus preventive strategies. The aim of this article is to systematically review current available literature on pre-operative risk factors for delirium after vascular surgery.

Methods: A systematic literature search was conducted using PubMed and EMBASE, using the MeSH terms and key words "delirium", "surgery" and "risk factor". Studies were retained for review after meeting strict inclusion criteria that included only prospective studies evaluating risk factors for delirium in patients who had elective vascular surgery. Diagnosis of delirium needed to be confirmed using the Diagnostic and Statistical Manual of Mental Disorders (DSM) or ICD-10.

Results: Fifteen articles were selected for inclusion, incidence of delirium across the studies ranged from 5% to 39%. Many factors have been associated with increased risk of delirium, including age, cognitive impairment, comorbidity, depression, smoking, alcohol, visual and hearing impairment, ASA-score, biochemical abnormalities, operative strategies and blood loss.

Conclusions: Delirium is a common complication after elective vascular surgery in elderly. The highest delirium incidence was observed after open aortic surgery as well as after surgery for critical limb ischemia. A picture starts to form of which predisposing factors lead to increased risk of delirium. The leading risk factors consistently identified in this systematic review were advanced age and cognitive impairment. Multi-disciplinary specialist-led interventions in the preoperative phase could decrease incidence and severity of delirium and should be focused on identified high-risk patients.

INTRODUCTION

Postoperative delirium is a common, serious, under-recognized adverse event and is associated with significant morbidity and mortality in elderly patients.

Delirium is an acute disorder with transient fluctuating disturbance of consciousness, attention, cognition, and perception [1]. While delirium may occur in every patient after surgery, the incidence is higher in the elderly patient.

The number of people over 65 years is increasing and will continue to do so over the coming decades. Similarly, elderly patients requiring surgery are expected to increase in numbers in the future. Postoperative delirium is associated with an increase of postoperative complications, a decrease in functional capacity, a prolonged hospital stay and increase of healthcare costs [2-8].

Delirium is now included on the patient safety agenda, and has been increasingly used as an indicator of healthcare quality for elderly [9].

Most importantly, several intervention studies demonstrated that delirium is preventable in estimated one third of the cases [9-12]. In addition, low-dose Haloperidol prophylactic treatment proved to be effective for delirium severity and duration for high risk patients after hip surgery [13].

Given the high incidence, increased morbidity and mortality associated with perioperative delirium, preoperative delirium risk assessment is of major importance. Especially to guide clinical decision-making and implement preventive strategies. However, this should be targeted to make it cost effective and expedient. Therefore, it is of great importance to identify patients at risk for delirium, in order to focus preventive strategies. The ability to identify patients at risk can assist physicians in clinical decision making, explaining risks to patients and families, and help families to better understand the recovery process and potential outcomes [14]. In case of planned, major elective surgery identification of high risks patients is most effective, since pre-operative geriatric input and optimization of the patient could significantly reduce postoperative delirium and the related detrimental outcome [10,11].

Post-operative delirium and the associated risk factors have been studied quite extensively in patients having orthopedic or cardiac surgery. However, recent studies report arresting incidences of delirium up to 24% in patients with critical limb ischemia and up to 51% after major abdominal surgery [15-18]. In addition, during six month follow up 26% of the patients with a delirium episode died [16].

The aim of this article is to systematically review current available literature on pre-operative risk factors for delirium for elective vascular surgery.

METHODS

Search

An electronic literature search was performed of PubMed and EMBASE (until February 2015) by two independent investigators (Raats and Steunenberg) to identify articles in the English

language investigating risk factors for delirium in elderly having elective vascular surgery. Search terms were determined using PICO, describing the patient population (elderly aged 65 years or older having elective surgery), the intervention (patients diagnosed with a delirium), the controls (patients without a delirium), outcome (risk factors for delirium or predication model for delirium), and combinations of these search terms (Table 1). Manual searches of references from study articles and individual author searches of prominent researchers in the field were also conducted to obtain additional articles.

Table 1: Terms used in the systematic search for the present review

Database	Search terms
Pubmed	(("Delirium" OR delirium[tiab]) AND ((("General Surgery"[Mesh] OR "Surgical Procedures, Operative"[23] OR surgery[tiab])) OR (("Surgical Procedures, Operative"[Mesh]) OR "Postoperative Complications"[Mesh] OR postoperative[tiab] OR complication[tiab]))) AND ("Risk Factors"[Mesh] OR risk[tiab] OR Prediction [tiab]) NOT hip[tiab] NOT cardiac[tiab] NOT orthopedic[tiab] NOT cerebrovascular[tiab] NOT coronary[tiab]
Limits	Humans, English, Aged: 65+ years
Date of search	22 Februari 2016
Embase	delirium:ab,ti AND (risk* OR predict*:ab,ti) AND (surg* OR operat*:ab,ti) NOT cardiac:ab,ti NOT ortho*:ab,ti NOT hip:ab,ti NOT cerebrovascular:ab,ti NOT corona*:ab,ti
Limits	Humans, English, Aged: 65+ years, Article, Article in press, Short Survey
Date of search	22 Februari 2016

Inclusion criteria

Prospective studies evaluating risk factors for delirium in patients who had elective vascular surgery were considered. Vascular surgery included open and endovascular aortic repair, peripheral bypass surgery, amputation surgery, endovascular interventions, carotid surgery and arteriovenous shunt surgery.

Diagnosis of delirium needed to be confirmed using the Diagnostic and Statistical Manual of Mental Disorders (DSM) or ICD-10. Studies including 30 or more patients were considered for inclusion. This range was arbitrarily chosen, because it was considered plausible that risk factors are not identifiable in smaller studies.

Exclusion criteria

Reviews, meta-analysis, case reports and letters to editors were excluded. Studies that included a mix of different surgery (orthopedic, cardiothoracic, urologic, neurosurgical, head and neck surgery and transplantation surgery) were rejected for further analysis since the population was considered too heterogeneous.

Studies concerning delirium on ICU and PACU as well as studies on alcohol withdrawal delirium were excluded. Retrospective studies were excluded because delirium is not reliable traceable in retrospect.

Selection process

In the first stage, of all search results, the titles and abstracts were read and selected based on the mentioned in- and exclusion criteria. In the second stage, full text was obtained for relevant papers, as well as any citations for which a decision could not be made from the abstract. In both stages, articles were selected that assessed the predictive value of variables to cause delirium, and were judged by the two reviewers (Raats and Steunenberg). Final decision regarding inclusion was based after reading the full article.

Analysis

For all included articles, number of patients, type of surgery, incidence of delirium, used delirium assessment method and the identified risk factors were noted (Table 3). To identify risk factors for delirium decently, correction for possible confounders is mandatory by use of a multivariable analysis. An overview of the performed analysis in the selected studies and identified risk factors is shown in Table 4.

RESULTS

A total of 428 abstracts and titles were reviewed for potential eligibility. Three hundred and sixty-nine abstracts were excluded based on title or abstract based on the criteria for exclusion. A total of 59 original articles were selected for further reading. Forty-nine studies were excluded after full reading by several reasons (listed in Figure 1). Ten articles were selected for inclusion in this systematic review [15,19-27]. Two studies were based on one study cohort (preliminary [28] and follow up [24]), the latest study was used in this systematic review [24].

The incidence of delirium across the studies ranged from 5% to 39%. The most high incidence of delirium was described after open aortic surgery (18% to 65%) [15,19,21-23,27] as well as after surgery for critical limb ischemia (24-43%) [15,24,26]. Lower incidence rates of delirium are reported after carotid- and endovascular aortic repair. An overview of delirium incidence rates classified per vascular procedure are shown in Table 2.

Most studies seeking to determine predicting factors for delirium and performed prospective observational studies. Risk factors were selected and were measured prior to surgery and subsequently were analysed if prevalence was increased in patient with delirium compared to non-delirious patients. Mostly, an additional multivariable analysis was performed because risk factors relate and influence each other. After correction for confounders, independent risk factors were identified.

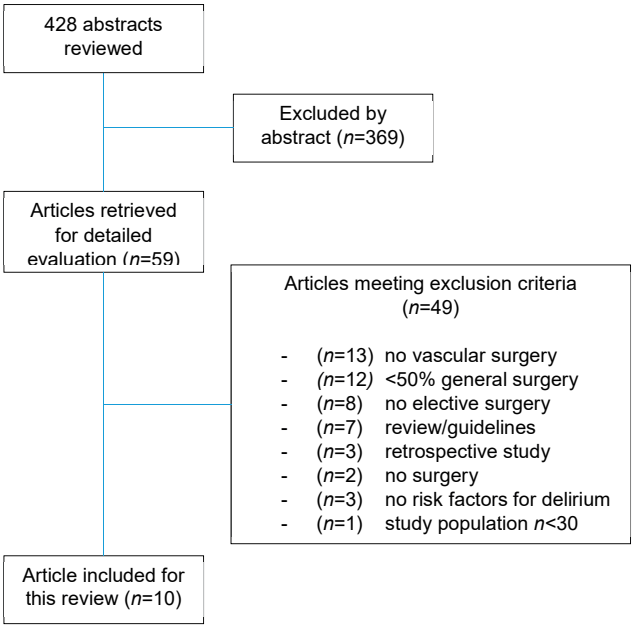

Figure 1. PRISMA diagram showing selection of articles for review

Table 2: incidence of delirium reported per vascular procudure

Type of surgery	Incidence of delirium	Reference
Carotid surgery	8-17%	[15,20,25]
Endovascular AAA Repair	0-5%	[15,19,22]
Open AAA Repair#	13-65%	[15,19,21,23,27,39]
Critical limb ischemia	24-43%	[15,24,26]

includes open aortic aneurysm repair and aortic occlusive surgery

Pre-operative risk factors

Age

Older age was assessed as a risk factor for delirium in 9 (90%) of the studies reviewed. In one study, no statistical test was performed to explore the relation between age and the occurrence of delirium [25]. The mean age of the included patients in the studies varied between 66 [20] and 76 years [26]. In five studies age was included in a multivariable analysis to predict delirium. Older age was identified as independent risk factor for delirium after vascular surgery in three studies [20,24,27]. Data are summarized in Table 3.

Cognitive function

In most studies (70%) cognitive function was analysed as potential risk factor for delirium [19-21,23-25,27]. A certain heterogeneity was observed in these articles. Eight different tools were

Table 3: Characteristics and outcome measures of the included studies describing identified risk factors for delirium

Study Author	Year published	Sample Size	Type of elective Surgery	Delirium assessment method	Incidence of delirium	Identified Risk Factors
Schneider **[25]**	2002	47	Carotid, aortal, peripheral artery surgery	DRS, DSM IV	36%	Depression (OR 3.3), cognitive impairment (OR 3.8), higher infusion and transfusion requirements (OR 2.9)
Böhner **[20]**	2003	153	Aortal, carotid, peripheral bypass surgery	DRS, DSM IV	39%	No history of supraaortic occlusive disease (OR 6.7), history of major amputation (OR 24.4), no history of hypercholesterolemia (OR 5.5), age> 64 years (OR 3.0), body length <170 cm (OR 4.0), cognitive impairment (OR 28.0), intraoperative colloid infusion > 800 mL (OR 2.6), intraoperative minimal potassium < 3.5 mmol/L (OR 3.2)
Benoit **[19]**	2005	102	AAA repair: endovascular and open repair	DSM IV, CRDI	33%	Pack years smoked (OR 0.95), cognitive impairment (OR 2.1), no. of psychoactive meds (OR 0.147), no. of vasoactive meds (OR 3.8)
Bryson **[21]**	2010	168	Open aortic repair	CAM	36%	No association between serum Apolipoprotein genotype and delirium
Koebrugge **[22]**	2010	85	Open and endovascular aortoiliac surgery	DOS / DSM IV	14%	ASA score ≥3 (OR 8.7)
Sasajima **[24]**	2012	299	Chronic limb ischaemia having arterial bypass surgery	CAM / DRS	29%	Age (OR 5.5) end stage renal failure (OR 5.0) multiple segments vascular occlusion (OR 2.9) dementia (OR 2.8) CLI (OR 2.0)
Pol **[23]**	2014	277	Open and endovascular aortic repair, endovascular procedures, peripheral bypass surgery, Percutaneous interventions, amputation surgery	DOS / DSM IV	6%	Post-operative CRP > 5mg/L (OR 1.01), open aortic sugery or amputation surgery (OR 5.39)
Visser **[27]**	2015	463	Open and endovascular aortic repair, peripheral bypass, arteriovenous shunt surgery, percutaneous interventions, different types of amputation	DOS / DSM IV	5%	Cognitive impairment (OR 16.4) open aortic sugery or amputation surgery (OR 14.0) Current smoking (OR 10.5) Hypertension (OR 7.6) Age ≥80 years (OR 7.3)
Raats **[15]**	2015	206	Critical limb ischemia, diabetic foot ulcers, AAA, carotid surgery	DOS / DSM IV	17%	Amphia Risk Score for delirium (OR 1.77) Nurse help at home before admission (OR 3.61)
van Eijsden **[26]**	2015	92	Critical limb ischemia	DOS / DSM IV	32%	Diabetes mellitus (OR 6.2) SNAQ-RC≥3 (OR 5.6)

OR: Odds Ratio, CAM: Confusion Assessment Measure, DSM: Diagnostic and Statistical Manual of Mental Disorders, DRS: Delirium Rating Scale, CRDI: Clinician-Rated Delirium Index, DOS: Delirium Observation Scale, CLI: Critical Limb Ischemia, AAA: Abdominal Aortic Aneurysm, SNAQ-RC: Short Nutritional Assessment Questionnaire for Residential Care

Table 4: overview of analysed and identified risk factors for delirium by univariable and multivariable statistics

Study Author	Age	Cognitive function	Comorbidity	Depression	Smoking	Alcohol	ASA-score	Visual and hearing impairment	Biochemical abnormalities	Pre-operative Hb	Blood loss	Duration of surgery
Schneider **[25]**	-	M*	M	M*	-		M	-	U	U	M*	-
Böhner **[20]**	M*	M*	M*	M	U	U	U	U	M*	U	M	U
Benoit **[19]**	U	M*	U	U	M*	M	-	-	-	-	-	-
Bryson **[21]**	U	U	-	U	-	-	U	-	U		-	-
Koebrugge **[22]**	U	-	U	-	-	-	M*	-	U	U	M	M
Sasajima **[24]**	M*	M*	M*	-	-	-	-	-	M	U	M	M
Pol **[23]**	M	M	M	M	-	-	U	-	M*	U	U	-
Visser **[27]**	M*	M*	U		M*	-	U	-	U	U	U	U
Raats **[15]**	M	-	M	-	U	U	M	-	-	-	-	-
van Eijsden **[26]**	U	-	M*	-	-	M	U	M	-	U	M	U

U: univariate analysis of risk factor for post-operative delirium
M: multivariable analysis of risk factor for post-operative delirium
M*: confirmed this factors as an independent risk factor for delirium (after correction for confounders)

used in these studies to measure cognitive function (MMSE, cognitive assessment battery, GFI (Groningen Frailty Indicator) and HDS-R (Hasagawa's dementia scale-revised version). The MMSE was the tool which was used most often [19-21,25]. In five of the seven studies cognitive impairment was confirmed as independent risk factor for delirium [19,20,24,25,27].

Comorbidity

Comorbidity was measured using the Carlson Comorbidity Index in three studies [22,23,27]. The Charlson Comorbidity index was not confirmed as independent predictor for delirium. Six other studies examined counts of medical conditions (i.e. diabetes mellitus, cardiopulmonary disease) [15,19,20,24-26]. The following factors were identified as independent risk factors for delirium: no history of supraaortic occlusive disease [20], history of major amputation [20], hypercholesterolemia[20], end stage renal failure [24], diabetes mellitus [26] and hypertension [27].

Depression

Because depression may be undetected unless specifically screened for, analysis was restricted to studies that used a validated depression scale to screen for depression. In five studies depression was assessed, using different screening instruments (HAMD, GDS, and GFI). Depression was identified as independent risk factor in one study including patients having oartic, carotid and peripheral artery vascular surgery [25]. However, in other studies this was not confirmed [19-21,23].

Schneider et al. reported that pre-operative depression was associated with more severe delirium and prolonged duration of the delirium episode [25].

Smoking

Smoking behaviour is included in several studies describing current smoking, amount of packed years and reports on history of smoking [15,19,20,27]. In one study the amount of packed years was identified as independent risk factor for delirium in patients having AAA surgery [19].

Alcohol abuse

Four studies included alcohol consumption as potential risk factor for delirium. Most importantly, studies varied in reports of the usage of alcohol and described numbers of alcohol units per year, per week, per day, or reported alcohol abuse without a clear definition. In none of the studies a relation between alcohol use and occurrence of delirium was confirmed [15,19,20,26].

ASA-score

In 80% of the included studies, ASA-score was analysed as potential risk factor for delirium. In one study, ASA-score ≥3 was confirmed as risk factor after correction for possible confounders [22]. In more studies ASA-score was not confirmed as risk factor [15,20,21,23,25-27].

Visual and hearing impairment

Two studies analysed visual and hearing impairment as potential risk factor for delirium and reported different associations.

Böhner et al reported only hearing impairment was more prevalent in patient with a delirium (35%) compared to patients without a delirium (16%) [20]. In another study, hearing impairment was not associated with delirium. In this study, visual impairment was related to postoperative delirium [26].

Laboratory abnormalities

In seven studies, pre-operative laboratory abnormalities were analysed as potential risk factor for delirium. Two studies analysed pre-operative CRP (C-reactive Protein) levels as possible risk factor for delirium [23,27]. In one study, multivariate logistic regression analysis confirmed the relation between an elevated CRP value (> 5 mg/L) and postoperative delirium [23].

Böhner et al reported that several laboratory abnormalities were associated with delirium for patients having vascular surgery. However, after correction for confounders intra-operative potassium <3.5 mmol/L was the only laboratory abnormality that was confirmed as independent risk factor for delirium [20].

Bryson et al explored the relation between the serum apolipoprotein E (associated with Alzheimer disease [29,30]) and delirium and reported no convincing evidence that carriers of the APOE ε4-allele have a higher risk of delirium [21].

Operation related risk factors

Blood loss and haemoglobin

Seven of the included studies in this review analyzed hemoglobin level or bleeding related factors (tachycardia during surgery, blood or crystalloid transfusion requirements, intra-operative blood loss) as risk factor. Five of these studies found an association between delirium and bleeding related factors [20,22,24,25,27]. However, after correction for confounders, two studies confirmed bleeding related factors as independent risk factors for delirium [20,25].

Low pre-operative hemoglobin is associated with occurrence of delirium [26], as well as predictor for delirium severity [25]. Furthermore, low pre-operative hemoglobin was related to prolonged duration of delirium.

Operative planning

Koebrugge et al reported that delirium was not prevalent after endovascular treatment (EVAR), compared to 14% after open repair for AAA [22]. *Benoit et al* described comparable results reporting no delirium after EVAR compared to 41% delirium after open repair [19]. In a small study sample, delirium incidence after EVAR (5%) was lower compared to open repair (18%) [15]. Two studies included a small sample of patients undergoing percutaneous endovascular interventions (angioplasty and stenting procedures) and reported no delirium occurrence [23,27].

DISCUSSION

The incidence of delirium in the studies reviewed in this study varied from 5% to 39%, with open AAA and critical limb ischemia having the highest associated delirium risk [15,19-27]. These wide ranges could be explained by variation in the populations studied, delirium diagnostic criteria, levels of assessment, frequency of screening, and proximity to death.

In this review, different studies were systematically analyzed on potential risk factors for delirium in elderly having elective major surgery. The leading risk factors consistently identified in this systematic review were advanced age and cognitive impairment [19,20,24,25,27].

Age represents a strong risk factor for delirium, likely due to the accumulation of medical and other comorbidities together with decreasing reserve throughout later life [31]. The multifactorial model for the etiology of delirium has been widely accepted [32]. Following this model, patients who are highly vulnerable to delirium, such as high aged patients with underlying dementia and multimorbidity, a relatively benign insult may be enough to induce delirium. In contrast, in a younger patient in better health, delirium will only occur after more stressors.

Vulnerable, high aged patients with significant comorbidities, at risk for delirium may be better described as frail. Therefore measuring frailty may be a more sensitive marker of determining delirium risk than identify single risk factors [33].

Despite strong evidence is lacking, atherosclerosis might be the factor connecting advancing age, cognitive impairment and the related increased risk for delirium after vascular surgery. Patients having vascular surgery differ from the other populations because they suffer from both loco-regional and systemic atherosclerosis [34]. Micro-vascular changes in the brain caused by atherosclerosis can lead to impaired cognitive functioning and reserve and subsequently increase the risk for delirium [35].

The value of the other evaluated potential risk factors for delirium remains uncertain for multiple reasons.

Fist, the available studies are of varying quality and each with a heterogeneous population. Every population studied was unique, and therefore introduced significant heterogeneity. The composition of the populations studied, and the incidence of the risk factors analyzed in the studies is decisive for the identified risk factors. In example, when only octogenarians are included in a study, age may not be confirmed as an independent risk factor for delirium since all included patients are high aged.

Second, several studies pooled different surgical interventions along with varying levels of invasiveness. In several studies, patients having less invasive surgery were pooled with patients having major surgical procedures. Subsequently, potential risk factors for delirium were analyzed and therefore may result in less reliable outcomes.

Third, all studies measured different parameters and possible risk factors. Whilst some factors are identified as risk factor, the measurement of other parameters though to be significant were not used in comparison. Therefore, remains unclear which are the true and strongest predictors in these studies.

Fourth, different rating scales, cut-off points and definitions were used in the selected articles for this review, this hampers fair comparison of the performed studies.

Attempts to limit some of possible sources of heterogeneity were addressed in this review. Only prospective observational studies, using validated delirium instruments, including patients having elective surgery were considered for inclusion in this review.

Future perspectives

Delirium prevention studies demonstrated that delirium is preventable by performance of multicomponent interventions during admission. However, by identifying the patients during the preoperative outpatient phase, appropriate preventive arrangements can be implemented earlier and most likely result in lower delirium rates. Furthermore, delirium related outcomes as hospital stay, morbidity and mortality may improve as well. Several identified risk factors for delirium could potentially be affected by preventive measures. Outpatient consultation of a multidisciplinary coordinated team of healthcare professionals composed of a surgeon, anesthesiologist, geriatrician, dietician and physiotherapists can screen patients at risk for delirium and subsequently, optimize the modifiable risk factors.

Proactive geriatric consultation has been proven to reduce both delirium incidence and severity after surgery, giving pre- and postoperative recommendations and in particular, reduce polypharmacy [11,36,37]. Early screening and treatment of undernutrition and physical impairment could be performed by dieticians and physiotherapists. Actions to elevate hemoglobin levels pre-operatively could potentially decrease delirium incidence. Since the rate of pre-operative anemia is high in elderly, more research should be performed in patients with increased risk for delirium [38].

CONCLUSION

This review highlights the fact that delirium is a common complication after elective vascular surgery in elderly. However, there remain considerable clinical uncertainties about delirium, as the observed heterogeneity in the included studies demonstrates.

Delirium is a heterogeneous and multifactorial disorder with multiple potential risk factors. Nevertheless, a picture starts to form of which predisposing factors lead to increased risk of delirium. The leading risk factors consistently identified in this systematic review were advanced age and cognitive impairment. Multi-disciplinary specialist-led interventions in the preoperative phase could decrease incidence and severity of delirium and should be focused on identified high-risk patients.

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Chapter 5

Postoperative delirium in elderly after elective and acute colorectal surgery: A Prospective Cohort Study

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International Journal of Surgery. 2015 Jun;18:216-9

ABSTRACT

Objective: to assess the frailty and the incidence of delirium in elderly patients undergoing elective and acute colorectal surgery in correlation with morbidity and mortality.

Methods: patients aged 65 years and older having elective and acute colorectal surgery, between April 2013 and December 2013 were included in a prospective database. Patients diagnosed with a colorectal carcinoma or diverticulitis who were operated on were included. Factors that characterize frailty of patients were noted. The incidence rates of delirium after elective and acute surgery were recorded. Delirium was diagnosed using the Delirium Observation Screening Scale (DOSS). Preoperative evaluation, surgical outcome including morbidity, hospital stay and mortality were analysed.

Results: patients ≥65 years were included, 83 (75%) received elective and 28 (25%) acute surgery. The overall incidence of delirium was 21%, 18% for elective and 29% for patients having urgent surgery (p=0.24). Patients with delirium were older than the non-delirious patients (median 82 years vs. 74 years; p<0.001). Delirious patients showed higher incidence of adverse events. Hospital stay, mortality and discharge to a nursing home were significant higher in the delirious compared to the non-delirious group (p=0.01; 0.01; 0.02 respectively).

Conclusion: high incidence of delirium was found in both acute and elective colorectal surgery. Delirium was associated with adverse outcomes.

INTRODUCTION

Colorectal surgery in elderly is being performed in increasing numbers[1]. Improvements in surgical techniques and postoperative care allows surgery in patients who previously would have been considered unsuitable. As high age is a leading risk factor for postoperative delirium, the incidence of delirium is expected to increase.

Postoperative delirium is associated with worse postoperative outcome and prolonged hospital stay[2, 3]. Furthermore, delirium is associated with a higher number of complications, poor recovery and higher costs[3, 4]. Rates of postoperative delirium in patients who have abdominal surgery range from 17% to 51%[5-7]. This wide variation relates to the issues of definition, differences in diagnostic tools and variation in the populations that have been studied. Available literature that report incidence rates are limited, and based on patient undergoing a variety of surgical procedures including hernia repair, cholecystectomy and appendectomy. Patients with dementia or cognitive impairment are often excluded, though these patients are at increased risk for postoperative delirium.

The exact cause of delirium is unknown, but seems multifactorial and can be caused by many interacting factors, depending on the vulnerability of the patient[8]. A frail, elderly patient is more likely to develop postoperative delirium with lesser surgery when compared to younger patients who enjoy better overall health.

Data concerning factors on frailty, social status and living arrangement for patients receiving colorectal surgery are not well described. In our opinion this is of great importance, because the reported studied populations are varying and heterogeneous.

Compared with elective surgery, emergency abdominal surgery is associated with increased morbidity and mortality, especially in elderly patients[9-11]. Older patients undergoing acute abdominal surgery are also at risk for postoperative delirium[12]. However, to our knowledge the incidence of postoperative delirium and the associated morbidity and mortality after emergency colon surgery in the elderly has not been reported yet. In this study we focus on outcomes after elective and urgent colorectal surgery in elderly.

The aims of this study are to review elderly patients having elective or acute colorectal surgery and to assess the pre-operative parameters that characterize frailty. We also report the incidence of post-operative delirium and the associated outcomes.

MATERIAL AND METHODS

1.1 Patient selection

All elderly patients having colorectal surgery admitted to the gastrointestinal surgical department of the Amphia Hospital in the Netherlands between April 2013 and December 2013 were included in a prospective database. Patients diagnosed with a colon or rectal cancer or diverticulitis who were operated on were included. The surgical procedures consisted of elective

and acute (urgent) operations. Patients younger than 65 years old were excluded as well as all patients who could be discharged within 2 days. This research was based on regular patient care, therefore the need for individual informed consent was waived.
In all patients undergoing elective colon surgery fast-track protocols were followed[13]. Patients with colon or rectal cancer were staged following the 5th edition of the TNM staging system[14]. Patients with diverticulitis received elective surgery with partial colon resection in case of frequent episodes of diverticulitis or presence of fistulae. In case of diverticulitis with perforation and sepsis or signs of peritonitis, acute surgery was performed. We were able to prospectively collect available parameters during the study period using a full electronic patient file: Hyperspace© Version IU4 (Epic Inc., Verona, Wisconsin, USA)[15].
Patient characteristics included patient demographic data, co-morbidities (cardiac, pulmonary, neurological, diabetes) and ASA-score following The American Society of Anaesthesiologists (ASA) classification[16].

1.2 Factors on frailty

Factors that characterize the frailty of patients were noted. Physical impairment was objectified by use of the Katz-ADL Score. The Katz-ADL score ranks adequacy of performance in the six functions of bathing, dressing, toileting, transferring, continence, and feeding. We used a cutoff point of 2 or less indicating severe functional impairment[17].
The nutritional status was determined by the SNAQ-RC score[18]. This is a validated screening instrument developed for early detection of undernourished elderly patients. The SNAQ-RC combines BMI with four questions related to involuntary weight loss, loss of appetite, and eating with help. The sensitivity and specificity to detect severely under-nutrition is over 80%[19]. We used a cutoff point of 3 or more indicating severe undernourishment.
Information on the social status (living alone or with a partner) and living arrangement (home or nursing home) prior to admission to hospital was collected.

1.3 Operative data

Surgical and anaesthetic data were retrieved from the electronic patient file system.
Intraoperative data consisted of the applied surgical technique (laparoscopic or open), and duration of anesthesia. The surgical procedure was alsorecorded.

1.4 Postoperative data and delirium

Prospectively, delirium was scored using the Delirium Observation Screening Scale (DOSS) [20, 21]. The scale used was a shortened version with 13 items and was performed three times a day by a nurse while providing regular care. Delirium was defined as a DOSS score of 3 and above. Duration of delirium was defined as the total number of days with at least one DOSS score of three or more per 24 hours. The severity of postoperative delirium and the occurrence since surgical intervention were assessed using the DOSS score rates. Postoperatively data were collected in-

cluding length of delirium, all adverse events and hospital stay length. The 30-day and 6-month mortality rates were calculated regardless of mortality in hospital or after discharge. Adverse events were scored following the definition of the Association of Surgeons of the Netherlands (ASN). Adverse events consisted of surgically related (wound infections, hemorrhage, anastomotic leakage) and non-surgically related (urinary, pulmonary, cardiac, renal, and neurological) complications. Our report follows STROBE guidelines.

1.5 Statistics

Statistical analysis was performed with SPSS Version 20.0 (SPSS Inc., Chicago, Illonis, USA) software. Differences of collected factors for elective and acute surgery were analyzed by Student *t*-test and Mann-Whitney U test for continues data and chi-square or Fisher exact test or dichotomous data. Continuous variables with Gaussian distribution are presented as mean and standard deviation; otherwise as median and range. Results were compared with a *P* value < .05 to show significant differences.

RESULTS

A total of 111 patients was included in this study from April 2013 till December 2013. Patients had surgery for colon carcinoma (n=62), rectum carcinoma (*n*= 35) and diverticulitis (n=14). Of all included patients, 83 (75%) received elective surgery and 28 (25%) urgent surgery. Table 1 represents the characteristics and pre-operative data of patients receiving elective and acute colorectal surgery. Of the patients diagnosed with colon or rectal cancer they were classified as stage I (8%), stage II (43%) stage III (28%) and stage IV (18%) following the TNM V classification. Patients having emergency colorectal surgery had more frequently an ASA-score of 3-4 and were more physically impaired (KATZ ADL ≥2) compared to patients having elective surgery. Data on frailty of patients is shown in Table 1.

Open or laparoscopic techniques were used for urgent and elective surgery, with Table 2 summarising the surgical data.

The overall incidence of delirium was 21% (23/111), 18% for elective and 29% for patients receiving urgent surgery (p=0.24). Patients with a period of delirium were significantly older than the non-delirious patients (median 82 years vs. 74 years; p<0.01).

Delirium lasted four days on average after both elective and urgent surgery and no differences in the severity of postoperative delirium were observed. Data concerning delirium is shown in Table 3.

Patients suffering delirium showed a higher incidence of pulmonary, urinary and renal adverse events (p<0.01; 0.03; 0.04 respectively) and hospital stay. Mortality and discharge to a nursing home were also significantly higher (p<0.01; 0.01; 0.02 respectively). Data concerning outcome and delirium is shown in Table 4.

Table 1 Basic patient characteristics and pre-operative data of all elderly patients having elective or acute colon- or rectal surgery from April 2013 until December 2013

	All *n*=111	Elective *n*=83 (%)	Acute *n*=28 (%)	*P* value
Gender				
Male	58	48 (83)	10 (17)	0.04
Female	53	35 (66)	18 (34)	0.04
Age				
Median age (range)	76 (65-94)	76 (65-89)	76 (66-94)	0.48[c]
Age 65-70 years	26	21 (81)	5 (19)	0.42
Age 70-79 years	48	35 (73)	13 (27)	0.69
Age ≥ 80 years	37	27 (73)	10 (27)	0.76
Diagnosis				
Colon cancer	62	55 (89)	7 (11)	<0.01
Rectal cancer	35	22 (63)	13 (37)	0.05
Diverticulitis	14	6 (43)	8 (57)	<0.01[b]
Comorbidity				
Cardiac	31	21 (68)	10 (32)	0.29
Pulmonary	19	13 (68)	6 (32)	0.56[b]
Renal impairment	11	7 (64)	4 (36)	0.46[b]
Neurological	16	10 (62)	6 (38)	0.23[b]
Diabetes Mellitus	23	18 (78)	5 (22)	0.67
ASA-classification				
ASA 1-2	69	58 (84)	11 (16)	<0.01
ASA 3-4	42	25 (60)	17 (40)	<0.01
Functional impairment				
KATZ-ADL score				
3-6	93	73 (78)	20 (22)	0.07[b]
≤ 2[a]	9	3 (33)	6 (67)	0.01[b]
Nutritional status				
SNAQ-RC-score				
0-2	63	51 (81)	12 (19)	0.09
≥ 3[b]	38	25 (66)	13 (34)	0.12

Table 1 Basic patient characteristics and pre-operative data of all elderly patients having elective or acute colon- or rectal surgery from April 2013 until December 2013 (continued)

	All *n*=111	Elective *n*=83 (%)	Acute *n*=28 (%)	*P* value
Living situation				
Living without partner	37	25 (68)	12 (32)	0.16
Daily nurse visits home	13	9 (69)	4 (31)	0.74[b]
Nursery home	4	2 (50)	2 (50)	0.28[b]

Data are presented as n and (%), unless otherwise specified.
P-value is calculated with Chi-squared test
b= Fisher exact test,
c= Mann Whitney Ú test
[a] Katz-ADL Score 2 or less indicates severe functional impairment [17]
[b] SNAQ-RC Score 3 or more indicates severe undernourishment [19]

Table 2 Surgical data of all elderly patients having elective or acute colon- or rectal surgery from April 2013 until December 2013

	All *n*=111	Elective *n*=83 (%)	Acute *n*=28 (%)
Surgical technique			
Laparotomy	76	53 (70)	23 (30)
Laparoscopy	35	30 (86)	5 (14)
Surgery performed			
Right hemicolectomy	46	43 (93)	3 (7)
Transversectomy	4	4 (100)	0 (-)
Left hemicolectomy	10	9 (90)	1 (10)
Sigmoid resection	11	11 (100)	0 (-)
Hartmann procedure	21	5 (24)	16 (76)
Low anterior resection	8	8 (100)	0 (-)
Subtotal colectomy	2	1 (50)	1 (50)
Stoma placement only	7	2 (29)	5 (71)
Other[a]	2	0 (-)	2 (100)
Mean duration of surgery in minutes (SD)			
Laparotomy	105 (41)	106 (44)	104 (34)
Laparoscopy	141 (45)	146 (42)	118 (57)

Data are presented as n and (%), unless otherwise specified.
[a] explorative laparoscopies because of free air after diagnostic colonoscopy (no resection of bowel or placement of stoma)

Table 3 Data on postoperative delirium for all elderly patients having elective or acute colon- or rectal surgery from April 2013 until December 2013

	All *n*=23	Elective *n*=15 (%)	Acute *n*=8	*P* value
Occurrence of delirium				
All ages	23	15 (65)	8 (35)	0.24
Per age group				
Age 65-70 (*n*=26)	2	1 (50)	1 (50)	0.35
Age 70-79 (*n*=48	6	4 (67)	2 (33)	0.66
Age ≥ 80 (*n*=37)	15	10 (67)	5 (33)	0.71
Surgical procedure				
Delirium after laparotomy	16	9 (56)	7 (44)	0.19
Delirium after laparoscopy	7	6 (86)	1 (14)	1.00
Occurrence of delirium				
Postoperative day 1	11	7 (64)	4 (36)	1.00
Postoperative day 2	6	5 (83)	1 (17)	0.37
Postoperative day 3 or later	5	2 (40)	3 (60)	0.30
Severity of delirium				
Highest DOS-scores				
3-6	13	9 (69)	4 (31)	0.69
6-9	5	3 (60)	2 (40)	1.00
9-13	5	3 (60)	2 (40)	1.00
Duration of delirium				
Mean duration of delirium in days(SD)	4 (4)	4 (4)	3 (2)	0.49[a]

Data are presented as n and (%), unless otherwise specified.
P-value is calculated with Fisher exact test
[a] Student's T-test

DISCUSSION

The number of elderly patients, the main risk factor for delirium, receiving major abdominal surgery is increasing. This study evaluates several potential variables in selected patients 65 years of age and older, receiving acute or elective colorectal surgery. Delirium occurred in 21% of our patients and the incidence was similar in both acute (29%) and elective surgery (18%; *p*=0.24. Aging is associated with an increase in both operative and anaesthetic risk during emergency surgery and high morbidity and mortality rates are common[22].

Table 4: Data on comorbidity, hospital stay length, mortality and postoperative delirium of all included patients

	Delirium *n*=23 (%)	No delirium *n*=88 (%)	*P*-value
Adverse events			
Urinary	3 (13)	1 (1)	0.03
Pulmonary	5 (22)	3 (3)	0.01
Cardiac	1 (4)	5 (6)	1.00
Renal impairment	2 (9)	2 (2)	0.19
Neurological	2 (9)	0 (-)	0.04
Surgical adverse events			
Wound infection	4 (17)	4 (5)	0.06
Haemorrhages	2 (9)	1 (1)	0.11
Ileus	3 (13)	10 (11)	0.73
Anastomotic leakage	3 (13)	3 (3)	0.10
Hospital stay			
Median stay in days (range)	14 (6-90)	9 (4-67)	0.01[a]
Mortality			
30-day mortality	4 (17)	1 (1)	0.01
6-month mortality	6 (26)	8 (9)	0.07
Living situation			
Transferred to nursery home	3 (13)	1 (1)	0.02
Additional nurse visits at home	2 (9)	20 (23)	0.15

Data are presented as n and (%), unless otherwise specified. P-value is calculated with Fisher exact test
[a] Mann Whitney U test

Reports on the incidence of delirium after acute colorectal surgery are scarce in the current literature. Ansaloni et al reported a lower incidence of delirium (18%) after acute surgery whilst other reported delirium rates in 33% in elderly patients (>70 years) with secondary peritonitis[12, 23]. The wide range in these reported series may be explained by variations in included patient populations and the application of other diagnostic tools and procedure.

In our study half of the octogenarians receiving acute colorectal surgery developed postoperative delirium. This issue is of major importance, with population projections indicating that the number of persons aged over 80 years will double during the next 30 years[24].

The reported incidence of delirium is comparable to our previously reported data concerning elderly receiving elective vascular surgery (Raats et al)[25].

Furthermore, higher post-operative morbidity, prolonged hospital stay and higher mortality are observed in patients with delirium in this study. Clearly, delirium is a serious and common complication with adverse effects and remains undetected in approximately 50% of all hospitalized patients[26]. Early identification of elderly patients with delirium can potentially allow early interventions that could prevent detrimental outcomes.

Many non-pharmacological interventions, for example aiding in patients orientation, care for auditory and visual impairment and prevention of dehydration and malnutrition have proven to be effective in the elective situation[27]. These interventions probably result in a better outcome and could be even more useful in the group of high-risk patients. However, these interventions are not easy to implement in patients having acute surgery due to time constraints.

Limitations

Although this study shares limitations similar to other observational studies, some require further attention. We defined a DOSS-score of ≥3 as a delirium in this study. This may have led to flaws in the reporting of delirium because the DOSS-score is a screening instrument and not validated as diagnostic tool. In addition, results may underestimate delirium incidence rates by missing clinical subtypes such as hypoactive delirium. Finally, the prospective data collection and relatively small numbers further hinders in-depth analysis on risk factors and outcomes on delirium. Further research is needed to investigate these factors in patients at risk for delirium receiving elective and acute colorectal surgery. The next step would be to perform a multivariate analysis to reveal the true risk factors and outcome after postoperative delirium in this specific group of patients. In addition, other studies will have to answer the question whether specific interventions may improve the outcome in patients who develop postoperative delirium in the context of acute and elective colorectal surgery in elderly.

CONCLUSION

High incidence of delirium was found in both acute and elective colorectal surgery, especially in the elderly patient. Delirium was associated with adverse events and detrimental outcome. Further studies will have to investigate which risk factors and specific interventions may improve the outcome in patients with delirium after acute or elective colorectal surgery.

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Chapter 6

Risk factors and outcomes for postoperative delirium after major surgery in elderly patients

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PLOS One, 2015 Aug 20;10(8)

ABSTRACT

Background: early identification of patients at risk for delirium is important, since adequate well timed interventions could prevent occurrence of delirium and related detrimental outcomes. The aim of this study is to evaluate prognostic factors for delirium, including factors describing frailty, in elderly patients undergoing major surgery.

Methods: We included patients of 65 years and older, who underwent elective surgery from March 2013 to November 2014. Patients had surgery for Abdominal Aortic Aneurysm (AAA) or colorectal cancer. Delirium was scored prospectively using the Delirium Observation Screening Scale. Pre- and peri-operative predictors of delirium were analyzed using regression analysis. Outcomes after delirium included adverse events, length of hospital stay, discharge destination and mortality.

Results: We included 232 patients. 51 (22%) underwent surgery for AAA and 181 (78%) for colorectal cancer. Postoperative delirium occurred in 35 patients (15%).

Predictors of postoperative delirium included: delirium in medical history (Odds Ratio 12 [95% Confidence Interval 2.7-50]), advancing age (Odds Ratio 2.0 [95% Confidence Interval 1.1-3.8]) per 10 years, and ASA-score ≥3 (Odds Ratio 2.6 [95% Confidence Interval 1.1-5.9]). Occurrence of delirium was related to an increase in adverse events, length of hospital stay and mortality.

Conclusion: Postoperative delirium is a frequent complication after major surgery in elderly patients and is related to an increase in adverse events, length of hospital stay, and mortality. A delirium in the medical history, advanced age, and ASA-score may assist in defining patients at increased risk for delirium. Further attention to prevention of delirium is essential in elderly patients undergoing major surgery.

INTRODUCTION

The number of people over 65 years is increasing and will continue to do so over the coming decades. Similarly, the number of elderly patients requiring surgery is expected to increase. Delirium is a common and serious problem in hospitalized patients, especially in the elderly. Postoperative delirium is associated with an increase in postoperative complications, a decrease in functional capacity, a prolonged hospital stay and a direct increase of healthcare costs [1-6].

Early identification of patients at risk for delirium is important because adequate well timed interventions could prevent occurrence of delirium and the related detrimental outcome.

Several prediction models have been developed, including multiple risk factors for postoperative delirium [7-9]. However, these studies are of varying quality and each with a heterogeneous population.

Measuring frailty may be a more sensitive marker of determining post-operative delirium [10]. However, to this date, there is no consensus on a clear definition and quantification of frailty. Several assessment instruments have been developed for frailty during the last decades. The most evidence based process to identify frail patients at this moment is comprehensive geriatric assessment. However, this is a resource intensive, time consuming process and therefore not suitable for clinical practice [11,12].

Preventing delirium is probably most effective in elective surgery because preventive actions could be initiated timely. Aortic Abdominal Aneurysm (AAA) and colorectal surgery are among the most performed elective major interventions and are hence of interest to study in detail. The primary objective of this study was to evaluate predictors of delirium, including factors describing frailty, in elderly patients undergoing elective colorectal or AAA surgery. Secondary outcome measures were the clinical consequences of delirium including adverse events, length of stay and mortality.

METHODS

Patient selection

We prospectively registered data on patients of 65 years and older, who underwent surgery from March 2013 to November 2014. All patients underwent surgery in an elective setting at the Amphia Hospital, Breda, the Netherlands. We included patients having surgery for AAA and colorectal cancer. Exclusion criteria were: patients who were discharged within 2 days, patients receiving non-operative treatment, and patients who underwent non-elective (emergency) surgery. Emergency surgery included ruptured or symptomatic AAA surgery, or colorectal surgery with pre-operative obstructive ileus, active bleeding from colorectal cancer resulting in hemodynamic instability or perforation of bowel. The medical ethical committee of the Amphia Hospital in Breda, the Netherlands, permitted this project and waived informed consent.

Delirium

Delirium was scored prospectively using the Delirium Observation Screening Scale (DOSS) [13,14]. The scale used was a shortened version with 13 items and was scored three times a day by a nurse while providing regular care. All patients were seen on a daily basis by a physician. When delirium was present or suspected a geriatrician was consulted, and the diagnosis was confirmed using the DSM-IV criteria. A delirium was diagnosed if the patient had a Delirium Observational Screening Scale (DOSS) score of ≥3. All types of delirium were included (hypoactive, hyperactive and mixed form). All patients were evaluated for pre- and peri-operative characteristics.

Predictors of delirium: factors related to frailty

We collected data on main factors related to frailty and subsequently analysed them if prevalence was increased in patients with delirium compared to non-delirious patients.

A standardized history was taken to document comorbidity (cardiac, pulmonary, neurological and renal) of all included patients. Cardiac comorbidity included valve disorders, arrythmia's, heart failure and ischemic heart disease. Pulmonary comorbidity included chronic obstructive pulmonary disease. Neurological comorbidity included dementia, cerebrovascular accidents, epilepsy or Parkinson's disease. Renal comorbidity included renal impairment defined as a glomerular filtration rate (GFR) of ≤60 ml/min/1.73m^2. Known predictive factors of postoperative delirium were collected: delirium in the patient's history, visual and/or hearing impairment, daily alcohol use, smoking, hypertension, hypercholesterolemia and diabetes mellitus. All patients underwent a structured interview on admission assessing these parameters.

The American Society of Anesthesiologist (ASA) status was determined before surgery, from history and physical examination by the attending anesthesiologist.

Functional autonomy was assesed using the basic Activities of Daily Living (ADL) using the Katz-Scale. The inability to complete one or more ADLs was used as cutoff point for physical impairment [15].

Nutritional status was measured using the SNAQ-RC score [16]. A SNAQ-RC Score of 3 or more indicates severe undernourishment.

We were able to prospectively collect the relevant parameters during the study period using a full electronic patient file: Hyperspace© Version IU4 (Epic Inc., Verona, Wisconsin, USA) [17]. All collected patient records and information was anonymized and de- identified prior to analysis.

Predictors of delirium: operative data, hemoglobin and blood transfusion

Anesthesia time was calculated as the duration between tracheal in- and extubation.

Patients underwent surgery for colorectal carcinoma with epidural anaesthesia as a sole technique or as an adjunct to general anaesthesia. All patients who had AAA surgery received general anaesthesia. Patients were treated following the Dutch Society of Anaesthesiologists (NVA) guidelines. Patients had epidural anaesthesia as part of the fast-track protocol [18]. When

epidural anesthesia was not eligible (in case of allergies or coagulopathy), as an alternative, a Patient-Controlled analgesia pump (PCA-pump) with Morfine was described.
Hemoglobin (Hb) levels were obtained pre- and post-operatively. Anemia was defined as a Hb <7.6 mmol/L for women and <8.2 mmol/L for men [19]. The amount of peri-operative transfused Packed Cells was listed. Type of surgery was noted for AAA (open repair or endovascular aortic repair (EVAR)) and colorectal cancer (laparotomy or laparoscopic surgery).

Secondary outcome: consequences of delirium

During follow-up, data on mortality, hospital (surgical ward) stay, and Intensive Care Unit (ICU) stay were registered. Patients having open AAA surgery were admitted to the ICU for at least 24 hours following our hospital protocols. Mortality data were calculated using using the COMPET&T database from the company T&T Eindhoven. Patient destination after hospital discharge was noted (home or new nursing home client). Adverse events were collected during the first 30 postoperative days following the definition as defined by the Association of Surgeons of the Netherlands [20,21].

Statistics

Sample size:

Based on previously published studies concerning risk factors of delirium in our hospital, we made an estimation of required sample size [22]. We used the general rule of aiming for 10 events per variable to motivate the sample size.

Data analysis:

Statistical analysis was performed with SPSS Version 20.0 (SPSS Inc., Chicago, Illonis, USA) software. Univariate analyses (Student t-test and Mann-Whitney U test for continuous data and Chi-square or Fisher exact test or dichotomous data) were performed to evaluate factors that were associated with postoperative delirium.
Pre- and intraoperative parameters that varied significantly ($p < 0.05$) between delirious and non-delirious patients in the univariate analysis were included in a multivariable analysis. Results with a *P* value < .05 were considered statistically significant.

RESULTS

A total of 232 patients were included in this study, 51 (22%) having surgery for AAA and 181 (78%) having surgery for colorectal cancer. Postoperative delirium occurred in 35 (15%; 8 after AAA surgery (16%) and 27 after colorectal surgery (15%), p=0.89). Patients having colorectal surgery were older (median 75 years; Interquartile Range (IQR) 10) compared to patients undergoing AAA surgery (median 73 years; IQR 9), p=0.022.

For the 51 AAA patients, 25 (49%) underwent endovascular aneurysm repair (EVAR), and 26 (51%) underwent an open AAA repair using an aortoaortic "straight tube" graft or bifurcated prostheses (Table 1). Delirium was observed in 7 patients after open repair (27%) and in only one patient after EVAR (4%) *p*=0.050. Patients developed a delirium more frequently after laparotomy (20%) compared to patients having laparoscopic surgery (8%, *p*=0.024).

Table 1 Pre-operative characteristics in patients with AAA or colorectal cancer receiving elective surgery

	AAA *n*= 51 (%)	Colorectal cancer *n*= 181 (%)	*P* value
Gender			
Male	46 (90)	102 (56)	
Female	5 (10)	97 (54)	<0.001
Age			
Median age (IQR) ‡	73 (9)	75 (10)	0.022[b]
Age 65-70 years	17 (33)	39 (22)	0.082
Age 70-79 years	26 (51)	89 (49)	0.819
Age ≥ 80 years	8 (16)	53 (29)	0.051
Comorbidity			
Cardiac	23 (45)	53 (29)	0.034
Pulmonary	7 (14)	25 (14)	0.987
Renal impairment	6 (12)	13 (7)	0.383[a]
Neurological	8 (16)	22 (12)	0.507
Diabetes Mellitus	7 (14)	40 (22)	0.216
Operation			
EVAR	25 (49)	-	
Open procedure	26 (51)	-	
Laparoscopy	-	83 (46)	
Laparotomy	-	98 (54)	
Delirium			
Incidence of delirium	8 (16)	27 (15)	0.892

Values in parentheses are percentages unless indicated otherwise; values are ‡ median (IQR: Interquartile Range)
EVAR: EndoVascular Aortic Repair
P-value is calculated with Chi-square test
a= Fisher exact test
b= Mann-Whitney U test

Pre-operative factors

Pre-operative factors for delirium were analyzed comparing the delirious patients (*n*=35) to the non-delirious patients (*n*=197). The delirious patients were significantly older (median 80 years; IQR 7) compared to the non-delirious patients (median 75 years; IQR 10), *p*<0.001. Among the delirious patients, a delirium in the medical history was reported far more frequently (20%) compared to non-delirious patients (2%; *p*=<0.001).

Table 2 Pre-operative variables in relation to onset of postoperative delirium of all included patients having elective surgery for AAA or colorectal cancer

	Delirium *n*= 35 (%)	No delirium *n*= 197 (%)	*P* value
Age			
Median age (IQR) ‡	80 (7)	75 (10)	<0.001[b]
Predictors for delirium			
Delirium in medical history	7 (20)	3 (2)	<0.001[a]
Daily use of alcohol	9 (26)	60 (30)	0.548
Visual impairment	13 (37)	55 (28)	0.269
Hearing impairment	10 (29)	60 (30)	0.823
Hypertension	23 (66)	95 (48)	0.056
Hypercholesterolemia	13 (37)	68 (35)	0.780
Smoking	6 (17)	31 (16)	0.864
Physical impairment			
KATZ-ADL score < 6*	10 (29)	24 (12)	0.012
Nutritional status			
SNAQ-RC-score ≥ 3#	13 (37)	49 (25)	0.126
ASA-score ≥ 3	23 (66)	67 (34)	<0.001
Living situation			
Daily nurse visits at home	9 (26)	19 (10)	0.020[a]
Living in nursing home	1 (3)	5 (3)	1.000[a]

Values in parentheses are percentages unless indicated otherwise; values are ‡ median (Interquartile Range)
P-value is calculated with Chi-square test
a= Fisher exact test
b= Mann-Whitney U test
* Katz-ADL Score 5 or less indicates functional impairment [44]
# SNAQ-RC Score 3 or more indicates severe undernourishment [16]

Physical impairment (Katz-ADL<6) was observed in 29% of the patients who developed a delirium vs. 12% of the patients without a delirium (p=0.012). An ASA score of 3 or higher was more frequently observed in the patients who developed a delirium (66%) vs. the patients who were non-delirious (34%; p=<0.001, Table 2).

Hemoglobin and blood transfusion

Pre-operative hemoglobin levels were lower in the delirious patients (median 7.2 mmol/L; IQR 2.1) compared to the non-delirious patients (median 7.9 mmol/L; IQR 1.7), p=0.025). Data on all variables in relation to onset of postoperative delirium are summarized in Table 3.

Table 3 Data on anesthesia, hemoglobin and blood transfusion in relation to onset of postoperative delirium of all included patients having elective surgery

	Delirium *n*= 35 (%)	No delirium *n*= 197 (%)	*P* value
Median duration of anesthesia in minutes (IQR)	131 (74)	117 (75)	0.326[b]
Perioperative hemoglobin and anemia			
Median pre-operative Hb in mmol/L (IQR)	7.2	7.9 (1.7)	0.028[b]
Pre-operative anemia* *n*=232	26 (2.1) (74)	103 (52)	0.016
Median post-operative Hb in mmol/L (IQR)	6.7	6.8 (1.5)	0.344[b]
Post-operative anemia* *n*=221	31 (1.6) (91)	161 (86)	0.584[a]
Blood transfusion			
≥ 3 Packed Cells transfused during admission	6 (17)	9 (5)	0.014[a]

Data are presented as n and (%), unless otherwise specified.
IQR = Interquartile Range
P-value is calculated with Chi-square test
a= Fishers' Exact test
b= Mann-Whitney U test
* anemia is defined as a Hb <7.6 mmol/L for women and <8.2 mmol/L for men [19]

Multivariable analysis

Important risk factors for postoperative delirium were delirium in the medical history (Odds Ratio 12 [95% Confidence Interval 2.7-50]), advancing age (Odds Ratio 2.0 [95% Confidence Interval 1.1-3.8]) per 10 years, and ASA-score ≥3 (Odds Ratio 2.6 [95% Confidence Interval 1.1-5.9], Table 4). The area under the receiver operating characteristic (ROC) curve based on these 3 predictors was 0.76 [95% Confidence Interval 0.66-0.85].

Table 4 Univariate and multivariate logistic regression analysis on risk factors for delirium of all included patients having elective surgery for AAA or colorectal cancer

	OR (95% CI)	Adjusted OR (95% CI)
Age (+10 years)	2.5 (1.4-4.5)	2.0 (1.1-3.8)
Delirium in medical history	16 (4.0-66)	12 (2.7-50)
Katz-ADL score <6[#]	2.9 (1.2-6.7)	1.7 (0.6-4.4)
ASA score ≥3	3.7 (1.7-7.9)	2.6 (1.1-5.9)
Pre-operative anemia*	2.6 (1.2-5.9)	2.0 (0.8-4.8)

* Anemia is defined as a Hb <7.6 mmol/L for women and <8.2 mmol/L for men[19]
[#] Katz-ADL Score 5 or less indicates functional impairment [44]

Outcome after delirium

Several adverse events were more frequently observed in the delirious patients compared to the non-delirious patients. These included pulmonary and cardiac adverse events, renal impairment and urinary retention (Table 5). No differences in surgery related adverse events were observed. The total length of hospital stay was higher (median 12 days; IQR 12) in the delirious patients vs. the non-delirious patients (median 7 days; IQR 5), p=<0.001.

Intensive Care Unit (ICU) stay for 2 days or longer was observed more frequently in patients with a delirium (49%) compared to patients without a delirium (16%, p=<0.001). Occurrence of delirium was related to an increase in length of hospital stay (plus 7.7 days) and ICU stay (plus 2.1 days), after adjustment for age, delirium in medical history, Katz-ADL score, ASA score and pre-operative anemia.

Thirty-day mortality was significantly higher (9%) in the delirious patients compared to the non-delirious patients (1%, p=0.011, Table 5). This difference remained statistically significant in a logistic regression model that corrected for age, ASA score and previous delirium.

Patients with a delirium had a significantly higher mortality compared to the non-delirious patients (p=0.015, Figure 1).

DISCUSSION

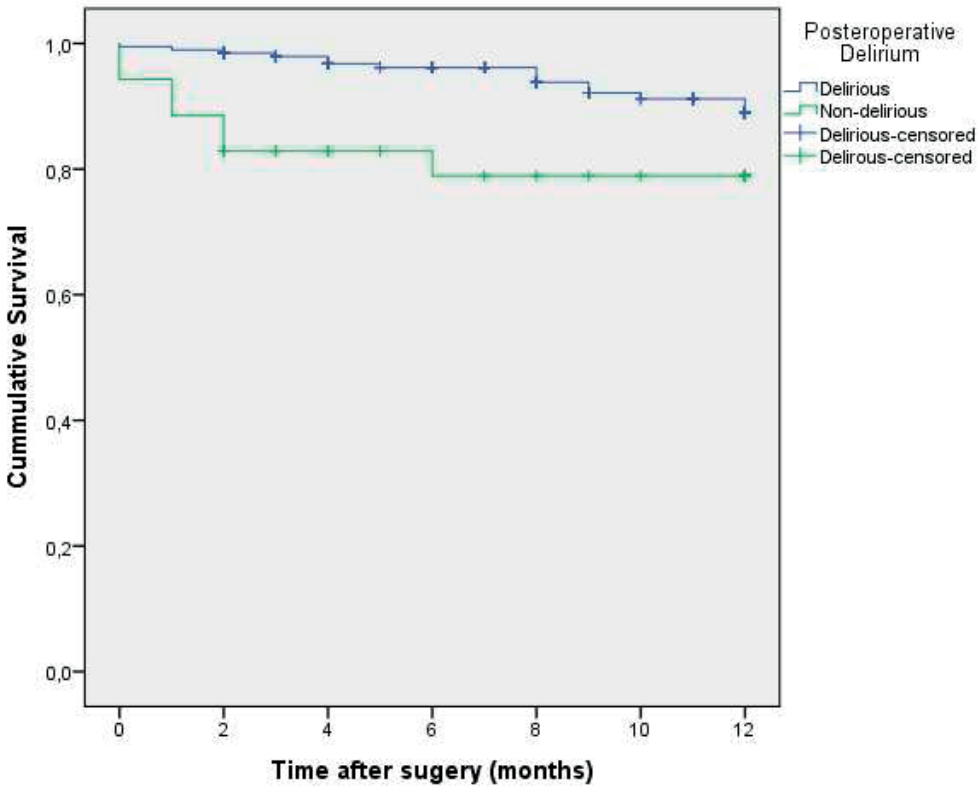
The number of elderly patients undergoing elective major abdominal surgery for AAA or colorectal cancer is expected to increase. As high age is a main risk factor for delirium, identification of patients at risk for delirium is of major importance. Delirium is related to an increase in morbidity, mortality, length of stay and care home placement [23]. Most importantly, delirium could be prevented in approximately 30-40% of the cases [24,25]. Research concerning postoperative delirium is increasing. However, large reliable studies on predictors of postoperative delirium are rare and most studies focus on cardiac- or orthopedic surgery [26].

Our reported incidence rate of post-operative delirium (15%) is comparable with other studies in recent literature (11-18%) [12,27-29]. Patients developed a delirium more often after open repair

Table 5 Adverse events, Hospital length of stay, ICU stay and mortality in relation to onset of postoperative delirium

	Delirium *n*= 35 (%)	No delirium *n*= 197 (%)	*P* value
Medical Adverse Events			
Cardiac	5 (14)	7 (4)	0.021
Pulmonary	9 (26)	12 (6)	0.001
Neurological	2 (6)	1 (1)	0.060
Renal impairment	5 (14)	6 (3)	0.014
Urinary tract infection	3 (9)	5 (3)	0.103
Urinary retention	7 (20)	2 (1)	<0.001
Central venous catheter infection	2 (6)	1 (1)	0.060
Surgical Adverse Events			
Wound infection	3 (9)	9 (5)	0.398
Seroma	1 (3)	1 (1)	0.280
Anastomotic leakage	3 (9)	6 (3)	0.139
Re-bleeding requiring intervention	2 (6)	2 (1)	0.109
Ileus	1 (3)	15 (8)	0.478
Superficial wound dehiscence	- -	1 (1)	1.000
Complete wound dehiscence	- -	2 (1)	1.000
Intra-abdominal abscess	2 (6)	3 (2)	0.165
Embolectomy	- -	1 (1)	1.000
Other complication[#]	1 (4)	8 (4)	1.000
Length of stay			
Median total hospital length of stay in days (IQR)	12 (12)	7 (5)	<0.001[b]
Admission to ICU	17 (49)	32 (16)	<0.001[a]
ICU stay in days ≥ 2	13 (37)	14 (7)	<0.001
Mortality			
30-day mortality	3 (9)	1 (1)	0.011
6-month mortality	7 (20)	6 (3)	0.001
Discharge destination			
New nursing home client after discharge	5/32 (16)	15/196 (8)	0.171
Discharge same living situation	27/32 (84)	181/196 (92)	0.337

Data are presented as n and (%), unless otherwise specified.
P-value is calculated with Fisher's exact test
a=Chi-square test
b= Mann-Whitney U test
# other complications: intoxication with morphine requiring ICU admission, bleeding gastric stress ulcer, iatrogenic injury (spleen, bladder and gallbladder), mild ischemic colitis after AAA surgery.



$p = 0.015$

Group	*Months*	*0*	*3*	*6*	*9*	*12*
Delirious	Patients	35	27	21	21	16
	SE	0.039	0.064	0.064	0.064	0.072
Non-delirious	Patients	197	178	152	110	85
	SE	0.005	0.009	0.014	0.019	0.024

Kaplan-Meier curves representing survival per age group. *SE* = Standard Error. *p*-value calculated with Mantel-Cox Log Rank test.

Figure 1. survival curve for delirious and non-delirious patients having elective AAA or colorectal surgery

(27%) compared to EVAR (4%). Despite the minimal invasive nature of the EVAR technique, previous RCT studies reported similar results of EVAR and open repair for elective AAA surgery [30,31]. Interestingly, the delirium-related costs were not included in previous cost-analysis reporting EVAR is not cost-effective compared with open repair [32]. For elderly patients at risk for delirium, EVAR could be preferable to open surgery.

Both minimal invasive surgical techniques (EVAR and laparoscopic surgery) were associated with lower rates of post-operative delirium. Probably, this could be explained by selection bias. Patients with or colorectal cancer in a more advanced stage may have been more likely to

undergo open surgery. In addition, more extensive surgery may have contributed to increased postoperative pain and use of narcotics.

As delirium was more frequently observed after open surgery, decisions regarding surgical approach (laparoscopic or open surgery) for the treatment of colon cancer should be taken into consideration, especially in elderly patients at risk for delirium.

A previous delirium, advancing age, and ASA-score were identified as independent risk factors for delirium. However, it is important to keep in mind that delirium in the patients' medical history was not highly prevalent in this study population. The identified predictive factors are also reported in earlier studies, but are largely based on non-abdominal surgery patient populations [15,33,34]. Prevalence of delirium increases with age. At multivariable analysis, we identified age as an independent predictor of delirium, consistent with literature [10]. This may explain why factors describing frailty, such as physical impairment, nutritional status, living arrangement, visual and hearing impairment, were not significant after multivariable correction.

We found that 31% (19/61) of the octogenarians developed a postoperative delirium. This is of major importance, as population projections indicate that the number of octogenarians will double during the next 30 years [35]. Reports on incidence rates of delirium after emergency major surgery are higher (18-33%), but are not uniform. This may be explained by the large heterogeneity of included populations and the use of different diagnostic tools and procedures [36-38].

Many non-pharmalogical preventive interventions, for example help in patient orientation, care for auditive and visual impairment, ensuring the day-sleep cycle, prevention of dehydration and malnutrition, have proved highly effective in an elective setting but are not easily translatable to an emergency setting [39]. In addition, timely direct treatment or optimization of identified predictive factors could potentially help in reducing delirium. However, most factors are not suitable for optimization because they are irreversible (i.e. age, ASA-score, delirium in patients' history). Still, preventive strategies should be initiated in these patients identified as at risk for delirium. In this study this included preventive nursing actions such as help in patients orientation, care for auditory and visual impairment, prevention of dehydration and malnutrition. When necessary, low dose prophylactic anti-psychotic (Haloperidol®) was prescribed based on judgement of the consulting geriatrician.

Another interesting observation in our study is the role of pre-operative hemoglobin and delirium. *Böhner et al*, did not find that pre-operative hemoglobin was linked to postoperative delirium after vascular surgery [26]. In contrast, *Joostens et al* found that in men, decreased pre-operative hemoglobin levels increased the risk of postoperative delirium in geriatric patients [40]. In our study, hemoglobin levels were not predictive of delirium after multivariable analysis with correction for confounders.

In case of elective major surgery, pre-operative treatment to increase hemoglobin levels might possibly prevent occurrence of postoperative delirium. Further research is required to explore this.

Delirium was related to multiple adverse events and increase in hospital stay. The question of whether delirium is a symptom of other postoperative complications or whether a delirium increases the risk of postoperative adverse events remains to be answered [41]. For instance, delirium could be a complication of an acquired pneumonia. On the other hand, pneumonia could be a result of aspiration provoked by delirium. In this study it remains unknown if the increased incidence of other adverse events are a cause or an effect of postoperative delirium. Probably, reducing occurrence of postoperative delirium could reduce the associated adverse outcomes and subsequently reduce costs.

Limitations

In this study we used a DOSS-score of ≥3 as highly indicative for delirium. Despite the use of a validated instrument, this may be an imperfect reflection of delirium. Our reported results could be an underestimation of delirium incidence by missing clinical subtypes such as the hypoactive delirium. Patients were not screened for psychiatric disease by admission. This is a limitation since earlier studies identified depression as an idepentent risk factor for delirium [42].

We included AAA and colorectal surgery patients and performed a pooled multivariable analysis. This may have led to a less correct identification of possible risk factors for delirium per disease group. However, incidence rates of post-operative delirium were comparable in both groups.

Medication, data regarding the anesthesia protocol and perioperative pain therapy was not included as possible predictor for delirium in this study. However, several earlier studies confirmed medication as a risk factor for postoperative delirium and therefore this should be included in further research. This is of great importance, because the increase of the elderly population, also the number of frail elderly with multimorbidity and polypharmacy will increase in future. In addition, medication could be an easy modifiable risk factor.

Another limitation of this study is the restriction of data collection to one hospital, although we consider this center representative for European large non-academic hospitals.

Finally, the number of patients in the present study does not permit strong conclusions, particularly since the numbers of patients with a delirium were relatively small. A prediction model for delirium in elderly having major elective surgery should be developed in larger series, with attention to validation and updating of existing prediction models [43].

CONCLUSION

A delirium in the medical history, advanced age, and ASA-score may assist in defining patients at increased risk for delirium. Postoperative delirium is a frequent complication among elderly patients. Since occurrence of delirium is related to an increase in adverse events, length of hospital stay and mortality, further attention for prevention of delirium is essential in elderly patients undergoing major surgery.

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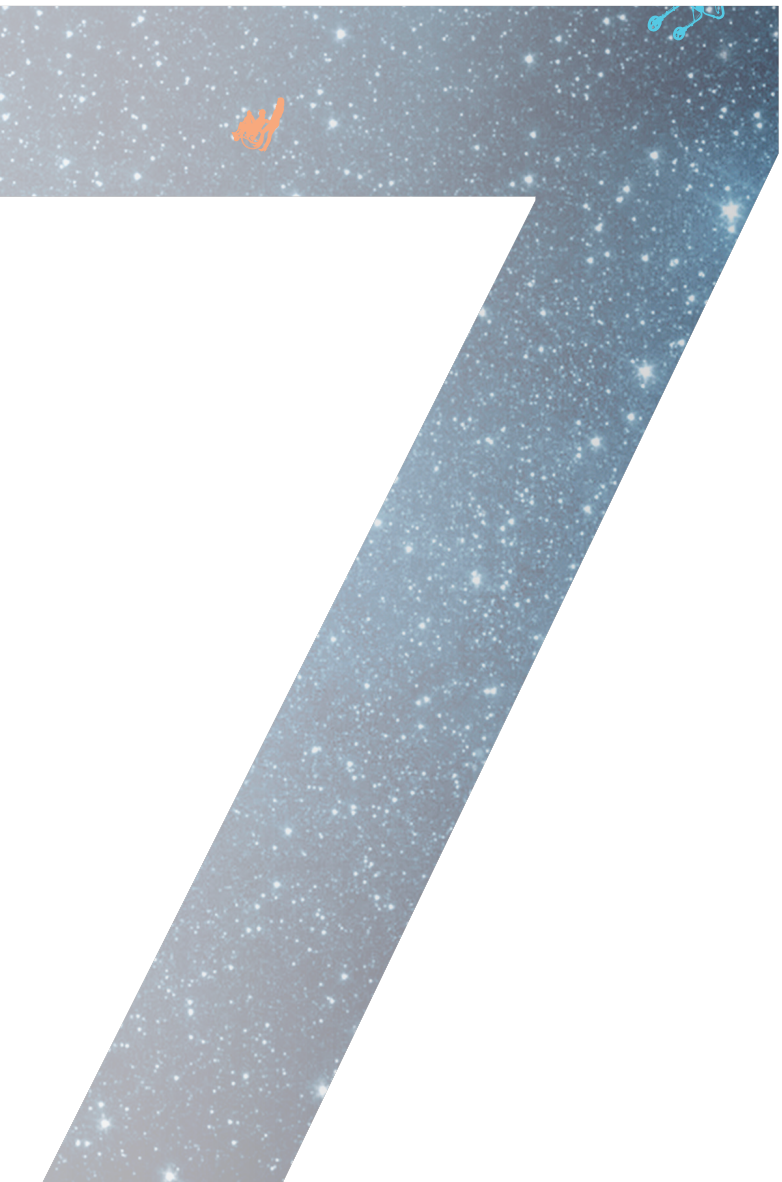

Chapter 7

Current factors of fragility and delirium in vascular surgery

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Annals of Vascular Surgery. 2015 Jul;29(5):968-76

ABSTRACT

Introduction: Vascular surgery patients are frequently deemed to be in a frail clinical condition and at risk for delirium. Therefore, we evaluated the incidence and
independent perioperative risk factors for delirium. In addition we describe factors on frailty in the various vascular disease groups in current practice.

Methods: This observational longitudinal study included 206 selected patients who were referred to a vascular surgery ward of a large-sized teaching hospital (Amphia Hospital, Breda, the Netherlands) for critical limb ischemia (n=80), diabetic foot ulcers (n=27), abdominal aortic aneurysm (AAA) (n=62) and carotid surgery (n=37) between April 2013 and December 2013. Data on factors that characterize frailty were collected. Delirium was scored using the Delirium Observation Screening Scale (DOSS). Multivariable logistic regression analysis was performed to find independent risk factors for delirium.

Results: Delirium was present in 24% of the critical limb ischemia patients, in 19% of the patients with a diabetic foot ulcer, in 7% of the patients with an AAA and in 8% of the patients undergoing carotid surgery ($p>0.05$). Of the patients with critical limb ischemia and a delirium, 53% were octogenarians. Multivariable stepwise logistic regression analysis revealed that history of delirium and nurse help at patient's home were independently associated with delirium. Patients with critical limb ischemia scored worse on factors related to frailty compared with the other disease groups in our current clinical practice in vascular surgery.

Conclusions: Delirium is a frequent complication in vascular surgery clinical practice, especially in the elderly. Nurse visits at patients' homes and the Amphia Risk Score for delirium were independent risk factors for delirium in our study population. We identified patients with critical limb ischemia in this study as the most frail and vulnerable.

INTRODUCTION

Population aging is accelerating at a tremendous rate. The number of persons aged 80 years and older is expected to double within the next 3 decades. Frailty is a state of increased vulnerability to poor maintenance of homeostasis after a stressor event, increasing the risk of adverse outcome, including falls, delirium, disability, institutionalization, and death. Recognition of frailty therefore becomes of increasing importance, especially when realizing we will face these patients in increasing numbers.

Older patients often require complex medical management and have a decreased tolerance for interventions of any kind. Most vascular procedures are major operations, such as abdominal aortic repair, carotid endartectomy, arterial bypass grafting and limb amputation. Patients undergoing such extensive vascular surgical procedures are frequently elderly and considered frail.[1] They often carry significant comorbidities such as cerebrovascular disease, cardiopulmonary disease or dementia.[2] Early identification of these patients at risk might be important because early interventions could prevent detrimental outcomes.

Over the past few decades, several programs for screening and treatment for frailty have been implemented.[3-5] A nationwide government-initiated health care project "The Dutch Hospital Patient Safety Program (DHPSP)" has been implemented in the Netherlands since 2009. The aim was to detect preventable detrimental outcomes in hospitalized frail patients.

Frail elderly are at risk for delirium when hospitalized, especially when extensive surgery is performed.[6-8] Postoperative delirium is associated with poor final outcomes such as functional decline, increased hospital length of stay, higher costs and increased mortality up to 44%. [9-12] It also impedes optimal medical treatment and requires more intensive nursing care. Therefore delirium has been increasingly used as an indicator for healthcare quality in elderly.[13] Unfortunately, delirium is no frequently recognized in approximately 50% of all hospitalized patients and is often undermanaged by clinicians.[14] It is estimated that delirium is preventable in one third of all cases. [3, 15] This is of great importance as well timed interventions probably result in a better outcome.[16]

In current literature, only a few studies focus on predictive factors for the development of delirium after vascular surgery[17, 18]. *Böhner et al* analysed risk factors after carotid, Abdominal Aortic Aneurysm (AAA) and peripheral bypass surgery and created a prediction model for postoperative delirium. However, specific factors for frailty and their relation to occurrence of delirium per vascular disease group remain scarce.

The aim of the study was to analyse the risk factors for delirium among patients undergoing in-hospital treatment for critical limb ischemia, diabetic foot ulcers, AAA and carotid surgery. In addition, we performed a detailed description of factors on frailty and their relation to the mentioned vascular disease groups.

PATIENT AND METHODS

Setting and participants

This observational longitudinal study included 206 selected patients who were referred to a vascular surgery ward of a large-sized teaching hospital (Amphia Hospital, Breda, the Netherlands) for critical limb ischemia, diabetic foot ulcers, abdominal aortic aneurysm (AAA) and carotid surgery between April 2013 and December 2013. All patients with a short hospital stay (<48 hours) and/or mortality within 48 hours after admission were excluded. This research was based on regular patient care, therefore the need for individual informed consent was waived.

Critical limb ischemia

Critical limb ischemia was defined as stage 4-6 according to the Rutherford classification.[19] Patients underwent surgical treatment (bypass graft surgery or limb amputation), endovascular treatment or conservative treatment.

Diabetic foot lesion

Diabetic foot ulcer diagnosis and treatment was based upon clinical evaluation following the Wagner classification.[20]

AAA

All patients with asymptomatic (elective) aneurysm repair of the abdominal aorta were included. Patients received open repair or endovascular aneurysm repair (EVAR). For EVAR the Medtronic® Endurant® II aorto-bi-iliac stent graft system was used.[21] Patients receiving open repair were observed for at least one day at the Intensive Care Unit (ICU).

Carotid surgery

Patients received carotid revascularization after recent occurrence of neurological symptoms due to a significant stenosis. All patients were discussed in a multidisciplinary cerebrovascular meeting with a certified neurologist, interventional radiologist and vascular surgeon. All patients were operated within 2 weeks after the cerebrovascular incident. After surgery all patients were observed for at least one day at the ICU of our hospital.

Characteristics of patients

Information on age, gender, comorbidity, vascular risk factors and ASA score was extracted from electronical medical charts. Comorbidity was rated as the presence of additional diseases including pulmonary (chronic obstructive pulmonary disease), cardiac (heart failure, myocardial infarction, dysrhythmia), neurological (transient ischemic attack, stroke, Parkinson's disease, epilepsy), and cancer. An active malign neoplasm was defined as cancer of any origin requiring treatment. Vascular risk factors consisted of hypertension, diabetes mellitus, renal impairment,

hypercholesterolemia and smoking. ASA score was defined following The American Society of Anaesthesiologists (ASA) classification.[22]

The Dutch Hospital Patient Safety Program

In our hospital we follow "The Dutch Hospital Patient Safety Program (DHPSP)" protocols, developed to screen and detect frail elderly patients. After identification of high risk patients, implementation of preventive interventions could be initiated whenever necessary. All patients were scored at hospital admission on several factors that characterize frailty. We collected data on the following frailty identifiers: physical impairment, living situation, nutritional state and risk score for delirium. We were able to prospectively collect all available parameters during the study period using a full electronic patient file: Hyperspace© Version IU4 (Epic Inc., Verona, Wisconsin, USA).

Physical impairment

The Katz Index of Independence in Activities of Daily Living (Katz- ADL) is an instrument for the assessment of functional status as a measurement of a patient's ability to perform daily activities independently. A score of 6 indicates full function, 4 indicates moderate impairment, and 2 or less indicates severe functional impairment.[23]

Nutritional state

The nutritional state was estimated by the Body mass index (BMI) and the Short Nutritional Assessment Questionnaire for Residential Care (SNAQ RC-score).[24] The SNAQ RC is an adapted validated version of the more widely used SNAQ-score and adds BMI as a contributory parameter. A SNAQ RC-score of 2 or higher is considered as high risk for undernourishment. After identification of high risk patients further treatment was started by dieticians.

Living situation

The social status (living alone or with a partner) and living arrangement (home or nursing home) prior to admission to hospital were noted. These patients require intensive nursery care during day and night due to extensive cognitive or physical impairment. Therefore, we considered patients living in a nursing home as a factor reflecting frailty.

Delirium

Risk for delirium was scored following the Amphia Risk Score for Delirium, developed as a screening instrument for the identification of patients at risk for delirium (Addendum 1). This screening tool has already been widely used in various departments in our hospital. A Risk Score of Delirium of 1 or higher was defined as high risk. When a patient was identified as high risk, two main actions were taken. Preventive nursing actions for delirium (help in patients orientation, care for auditory and visual impairment, prevention of dehydration and malnutrition) were

initiated. In addition, the Delirium Observation Screening Scale (DOSS) was scored three times a day by trained nurses during regular care for at least the first 48 hours after admission.[25] Duration of delirium was defined as the total number of days with at least one DOSS score of three or more per 24 hours.

Three or more points were considered highly indicative for delirium. All patients were visited on daily basis by a physician. When delirium was present or suspected a geriatrician was consulted and the diagnosis was confirmed based on the DSM-IV criteria.

All possible predicting factors relating to occurrence of delirium were analysed in a multivariate logistic regression analysis. Included were all collected basic patient characteristics, pre-operative factors, factors on frailty and the four disease groups.

Statistical analysis

Continuous variables with a Gaussian-shaped distribution were summarized by mean and standard deviation; otherwise by median and interquartile range.

The outcome variable of the core statistical analysis is the incidence of delirium (yes/no). In a first selection stage, all possible pre- and intra-operative variables related to delirium were selected based on a *p*-value <0.4. For categorical variables Chi-square and Fisher's exact test were used. For numeric variables the unpaired t-test or the Mann-Whitney test was used. Selected variables (*p*-value <0.40) were entered in a multiple logistic regression model. In a second selection stage variables were eliminated from the model using a stepwise backwards method with at each step the variable with the largest *p*-value >0.40 left out. The categorical variable diagnosis representing the four selected vascular disease groups was precluded for backwards elimination and retained in the logistic model as these variable represent selection of patients. The remaining variables after the described second stage were included in the final a multiple logistic regression model. Variables with a *p*-value below 0.05 were considered statistically significant. Statistical analysis was performed with SPSS Version 20.0 (SPSS Inc., Chicago, Illonis, USA) software.

RESULTS

Patient selection process

From April 2013 until December 2013 a total of 206 patients were admitted to the vascular department of our hospital. We included patients with critical limb ischemia (*n*=80), diabetic foot ulcers (*n*=27), AAA (*n*=62) and undergoing carotid surgery (*n*=37).

Basic patient characteristics, comorbidity and risk factors

We report 55%, 78%, 89% and 84% male patients in the respectively groups with critical limb ischemia, diabetic foot ulcers, AAA and carotid surgery. Basic patient characteristics, vascular risk factors and comorbidity are summarized in Table 1.

Table 1: Patient characteristics and data on factors that characterize frailty in the various vascular disease groups included from April 2013 until December 2013

	critical limb ischemia *n* = 80	diabetic foot ulcer *n* = 27	AAA *n* = 62	carotid surgery *n* = 37
Male	44 (55)	21 (78)	55 (89)	31 (84)
Median Age (IQR)	74 (16)	68 (17)	71 (11)	73 (15)
Age < 65	22 (28)	13 (48)	14 (23)	9 (24)
Age 65-70	13 (16)	4 (15)	14 (23)	7 (19)
Age 70-79	22 (27)	8 (30)	29 (47)	12 (33)
Age >80	23 (29)	2 (7)	5 (8)	9 (24)
Vascular risk-factors				
Hypertension	20 (57)	15 (56)	41 (66)	30 (81)
Diabetic	30 (38)	27 (100)	9 (15)	9 (24)
Renal impairement	2 (6)	2 (7)	10 (16)	9 (24)
Hypercholesterolemia	24 (30)	21 (78)	53 (86)	35 (95)
Active smoker	26 (33)	4 (15)	18 (29)	14 (38)
Comorbidity				
Cardiac comorbidity	41 (51)	10 (37)	23 (37)	16 (43)
Pulmonary comorbidity	14 (18)	2 (7)	9 (15)	2 (5)
Neurologic comorbidity	23 (29)	12 (44)	5 (8)	37 (100)
Active malign neoplasm	9 (11)	- -	1 (2)	1 (3)
Non-active malign neoplasm	7 (9)	2 (7)	10 (16)	4 (11)
ASA score				
1	2 (3)	- -	- -	- -
2	26 (33)	2 (7)	35 (56)	19 (51)
3	44 (55)	23 (85)	24 (39)	17 (46)
4	7 (9)	2 (7)	3 (5)	1 (3)
5	- -	- -	- -	- -
Physical impairment				
Katz-ADL Scale	39 (49)	19 (70)	55 (89)	32 (86)
5-6	37 (46)	8 (30)	3 (5)	3 (8)
0-4	4 (5)	- -	4 (6)	2 (5)
Unknown				
Nutritional status				
SNAQ RC-score	47 (59)	21 (78)	51 (82)	31 (84)
0	6 (8)	2 (7)	3 (5)	1 (3)

Table 1: Patient characteristics and data on factors that characterize frailty in the various vascular disease groups included from April 2013 until December 2013 (continued)

	critical limb ischemia *n* = 80	diabetic foot ulcer *n* = 27	AAA *n* = 62	carotid surgery *n* = 37
1	7 (9)	1 (4)	2 (3)	1 (3)
2	20 (25)	3 (11)	6 (10)	4 (11)
≥3				
Living situation prior to admission				
Living without partner	25 (31)	13 (48)	7 (11)	9 (24)
Nurse visits at home	15 (19)	11 (41)	2 (3)	3 (8)
Living in nursing home	15 (19)	3 (11)	1 (2)	1 (3)

Data are presented as n and (%), unless otherwise specified
AAA = abdominal aorta aneurysm
ASA score= American Society of Anesthesiologists score physical state score[22].

Frailty: Physical impairment

A Katz-ADL score ≥2 was more frequently observed in the patients with critical limb ischemia (46%) when compared to the patients with an AAA (5%) or receiving carotid surgery (8%) (p<0.001). For the patients with a diabetic foot ulcer 30% had a KATZ-ADL score of 2 or higher.

Frailty: Nutritional state

A SNAQ RC ≥3 is more frequently observed in 25% of the patients with critical limb ischemia compared to the 10% with an AAA (p=0.02). A SNAQ RC ≥3 is observed in 11% patients with diabetic foot ulcer, and in 11% of the patients receiving carotid surgery.

Frailty: Living situation

Nineteen percent of all patients with critical limb ischemia were living in a nursing home prior to admission to the hospital, this is more frequent than the patients with an AAA (2%) or patients receiving carotid surgery (3%) p=0.001. Of the patients with a diabetic foot ulcer, 11% were living in a nursing home. Data concerning frailty are summarized in Table 1.

Delirium

There were 75% patients identified as high risk for delirium in the critical limb ischemia group, 81% of the patients with a diabetic foot ulcer, 56% of the AAA patients and 70% of the patients with carotid surgery.

Delirium was present in 24% of the critical limb ischemia patients, in 19% of the patients with a diabetic foot ulcer, in 11% of the patients with an AAA and in 8% receiving carotid artery surgery

Table 2: Univariate analysis for all candidate risk factors for the prediction of delirium, out of which a first stage selection was based on a univariable *p*-value of 0.40 and a subsequent second stage selection was based on a multivariable *p*-value of 0.40

	Delirious *n* = 34 (%)		Non-delirious *n* = 172 (%)		*P*-value	1st stage selection	2nd stage selection
Basic characteristics							
Mean age (SD)	76	(8.0)	69	(10.5)	<0.001#	x	x
Gender (male)	22	(65)	129	(75)	0.215	x	
Vascular risk-factors	19	(56)	109	(63)	0.442		
Hypertension	19	(56)	56	(33)	0.012	x	x
Diabetes	7	(21)	27	(16)	0.613		
Renal impairment	15	(44)	118	(69)	0.010	x	
Hypercholesterolaemia	10	(29)	52	(30)	0.861		
Active smoker							
Comorbidity							
Cardiac	23	(68)	67	(39)	0.002	x	
Pulmonary	6	(18)	21	(12)	0.406*		
Neurologic	17	(50)	60	(35)	0.002	x	x
Active malign neoplasm	2	(6)	9	(5)	0.121	x	
Non-active malign neoplasm	4	(12)	19	(11)	1.000		
Factors on frailty							
KATZ ≤5	19	(63)	42	(25)	<0.001	x	
SNAQ ≥3	8	(24)	25	(15)	0.204	x	
ASA score ≥3	30	(88)	92	(54)	<0.001	x	x
Delirium in medical history	10	(30)	9	(6)	<0.001*	x	x
Living alone	8	(24)	46	(28)	0.831		
Help of a nurse at home	10	(30)	21	(13)	0.011	x	x
Living nursing home	9	(27)	11	(7)	0.001*	x	
Dementia	4	(12)	2	(1)	0.007*	x	
Daily use of alcohol	6	(19)	39	(24)	0.649		
Mean Amphia Risk Score for delirium (SD)*	1.87	(1.3)	1.2	(0.9)	0.003$	x	x

Data are presented as n and (%)
p-value calculated with Chi-squared test
calculated with Student T-test
* calculated with Fisher exact Test
$ calculated with Mann-Whitney U Test
* Addendum 1: Amphia Risk Score for delirium
AAA = Abdominal Aorta Aneurysm
ASA score= American Society of Anesthesiologists score physical state score[22]

Table 3: Data on delirium and results of screening on delirium of all included patients.

	critical limb ischemia *n* = 80	diabetic foot ulcer *n* = 27	AAA *n* = 62	carotid surgery *n* = 37	*P*-value
Amphia Risk Score for delirium*					
0	14 (18)	3 (11)	**21 (34)**	7 (19)	0.04
1	32 (40)	12 (44)	15 (24)	13 (35)	ns
2	15 (19)	7 (26)	19 (31)	10 (27)	ns
3	**12 (15)**	2 (7)	1 (2)	2 (5)	0.03
4	-	-	-	1 (3)	ns
5	1 (1)	1 (4)	-	-	ns
Occurrence of delirium during admission	**19/80 (24)**	**5/27 (19)**	**7/62 (11)**	**3 (8)**	**ns**
Age < 65 years	2/19 (11)	-	-	-	ns
Age 65-70 years	3/19 (16)	1/5 (20)	2/7 (29)	-	ns
Age 70-79 years	4/19 (21)	4/5 (80)	5/7 (71)	1/3 (33)	ns
Age ≥ 80 years	10/19 (53)	-	-	2/3 (67)	ns
Median duration of delirium in days# (IQR)	3 (7)	1 (9)	2 (11)	1 (-)	ns

Data are presented as n and (%), unless otherwise specified
AAA = abdominal aorta aneurysm
*Addendum 1: Amphia Risk Score for delirium
ns= not significant
p-value calculated with Fisher's Exact Test# Kruskal-Wallis Test

Table 4: Multiple logistic regression analysis of all possible factors in relation to the occurrence of delirium.

Risk factor	Coefficient (SE)	*Odds Ratio (95% CI)*	*P*-value
Diagnosis			0.26
Carotid Surgery	0	1	
Diabetic Foot Ulcer	0.803 (1.064)	2.23 (0.28-17-96)	
Critical Limb Ischemia	1.358 (0.943)	3.89 (0.61-24.66)	
AAA	2.006 (0.272)	7.43 (0.98-56.35)	
Amphia Risk Score (+1 point)*	0.572 (0.272)	1.77 (1.04-3.02)	0.04
Age (+1 year)	0.043 (0.027)	1.044 (0.990-1.100)	0.11
ASA-score (+ 1 score)	0.864 (0.473)	2.372 (0.939-5.988)	0.07
Delirium history (yes)	1.136 (0.761)	3.12 (0.70-13.85)	0.14
Nurse help at home prior to admission (yes)	1.285 (0.592)	3.61 (1.13-11.49)	0.03
Diabetic (yes)	1.097 (0.572)	3.00 (0.98-9.19)	0.06
Neurologic history (yes)	0.559 (0.569)	1.75 (0.57-5.33)	0.33
Constant	-9.180 (2.470)		

Significance of this model :Chi-squre = 46.850 (10 df); $p<0.0005$
AAA = abdominal aorta aneurysm
ASA score= American Society of Anesthesiologists score physical state score[22]
* Addendum 1: Amphia Risk Score for delirium

(p>0.05). We report delirium in 6 (18%) of the 34 patients treated with open repair and in one (5%) of the 21 patients treated with EVAR for AAA (p=0.21).
Of all 34 patients with delirium, 26 (76%) were aged >70 years. For the patients with critical limb ischemia, 53% of with a delirium were octogenarians. Data concerning delirium are shown in Table 3.

The results of the univariate analysis of all collected variables are shown in Table 2.. The regression model contained two preoperative factors (P<0.05; Table 4) including the Amphia Risk Score for delirium and help of a nurse at the patient's home.

DISCUSSION

Vascular surgery is confronted in a majority of cases with patients at an advanced age, frequently burdened by significant comorbidities.[26] The number of vascular procedures in older patients is likely to increase during the next decades. Therefore, the need for identification of frail elderly patients with subsequent detrimental outcomes is critical for vascular surgeons in clinical decision making.
Critical limb ischemia patients could be identified as the frailest of the vascular surgery treatment groups included in this study. Patients with critical limb ischemia had a worse nutritional state, more severe physical impairments and were more frequently living in a nursing home. This reflects the poor general condition of this group of vascular patients in our current clinical setting. Critical limb ischemia is a manifestation of advanced disease. Therefore, it might be expected that these patients score worse on the mentioned frailty factors in relation to age.
To date there is no consensus on a method of choice for the identification and quantification of frailty. The absence of a universally accepted definition impedes precise identification of frail patients in clinical practice. However, several assessment instruments have been developed for frailty during these last decades. These tools have not been extensively investigated for diagnostic accuracy in current practice.[1, 27] Other instruments are more sensitive but are limited to use in daily clinical setting because these assessments are time consuming or require expertise.[28, 29] The most evidence-based process to identify frail patients at this moment is comprehensive geriatric assessment. However, this is a resource-intensive process and thereby is not useful in clinical practice.[30]

Delirium

In our hospital, several studies prior to implementation of the DHPSP have been performed. A study by *van der Slegt et al* reported a delirium incidence of 3% in patients receiving peripheral vascular surgery.[31] This study, performed in 2012, reported a lower incidence rate on delirium compared to this study. In this study the incidence of delirium was retrospectively scored fol-

lowing the adverse events guidelines defined by the Dutch Association of Surgeons.[32-36] Most likely the previously reported incidence rate is an underestimation due to a lack of screening tool implementation. We conclude with caution that after implementation of our protocol following the DHPSP, an increase in awareness for the detection of fragile elderly persons and delirium has been accomplished.

In current literature data concerning the incidence of delirium in vascular patients are scarce. Studies have reported incidence rates of delirium after vascular surgery ranging from 23% up to 59%.[18, 37, 38] This wide variation relates to the issues of definition, measurement and varying populations studied.

Studies concerning delirium after vascular surgery mainly focus on AAA repair, considering these patients as high risk for development of delirium.[39] In contrast to other studies, we reported only 11% of the patients with an AAA had a delirium. This could be explained because we only included patients with non-ruptured AAA's receiving elective surgical repair, whilst emergency repair for AAA is associated with higher delirium incidence rates up to 59%.[38]

We reported a 24% incidence rate of delirium in patients with critical limb ischemia, which is comparable to the reported 29% (88/299 patients) by *Sasajima et al*.[18] The small difference in reported incidence of delirium is probably caused by the more extensive screening protocol which was implemented in their study. Furthermore, the sample sizes are small in both studies and consideration should be given when interpreting these results.

Limitations

In this study we used a DOSS-score of ≥3 as highly indicative for delirium. This theoretically might have led to a less accurate reflection of delirium in the current practice. Our reported results could be an underestimation of delirium incidence by missing clinical subtypes such as the hypoactive delirium which accounts for an estimated 29% of all delirium subtypes.[8]

CONCLUSION

Nurse visits at patients' homes and the Amphia Risk Score for delirium were independent risk factors for delirium in our study population. We identified patients with critical limb ischemia in this study as the most frail and vulnerable in our current clinical practice in vascular surgery. These patients frequently develop a delirium during hospitalization. Most patient with delirium were of old age. More research is necessary in order to take further steps in treatment and prevention for frail patients who are vulnerable for development of delirium.

Acknowledgement

We would like to thank Prof. Dr. Dr. A.B. Maier for her valuable comments and suggestions, which helped us to considerably improve the manuscript.

Addendum 1: Amphia Risk Score for delirium	
1	Visual impairment despite of glasses
2	Severe illness (specialized medical treatment)
3	Cognitive impairment prior to admission to the hospital
4	Delirium in medical history
5	Sleeping disorders or restless at night
6	Daily drinking of alcohol (male: > 3 drinks ; female >2 drinks)

If present 1 point, score of ≥1 defined as high risk

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Chapter 8

New Aspects of Delirium in elderly patients with Critical Limb Ischemia

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Clinical Interventions in Aging. 2015 Sep 28;10: 1537-46

ABSTRACT

Objective: The primary objective was to identify possible risk factors for delirium in patients with critical limb ischemia having surgery. The secondary objective concerned the effect of delirium on complications, the length of hospital stay, healthcare costs and mortality.

Methods: All patients 65 years or older, with critical limb ischemia having surgery from February 2013 to July 2014 were included and followed-up until December 31, 2014. Delirium was scored using the Delirium Observation Screening Scale (DOSS). Peri-operative risk factors (age, comorbidity, factors of frailty, operation type, hemoglobulin and transfusion) were collected and analysed using logistic regression. Secondary outcomes were the number of complications, total hospital stay, extra healthcare costs per delirium and mortality within 3 and 6 months of surgery.

Results: We included 92 patients with critical limb ischemia having surgery. Twenty-nine (32%) patients developed a delirium during admission of which 17 (59%) developed a delirium pre-operatively. After multivariable analysis only diabetes mellitus (OR = 6.23; 95% CI: 1.11-52.2; p = 0.035) and SNAQ_RC ≥ 3 (OR = 5.55; 95 % CI: 1.07-42.0; p = 0.039) were significantly associated with the onset of delirium. Delirium was related with longer hospital stay (p=0.001), increased healthcare costs and higher mortality after 6 months (p<0.001).

Conclusion: Delirium is a common adverse event in patients with critical limb ischemia having surgery with a devastating outcome on the long term. Most patients developed a delirium pre-operatively which indicates the need for early recognition and preventive strategies in the pre-operative period. This study identified undernourishment and diabetes mellitus as independent risk factors for delirium.

INTRODUCTION

At the moment delirium is a serious problem in vascular surgery.[1] Due to population aging the incidence of delirium will continue to increase among vascular patients.

Reports on incidence rates of postoperative delirium vary between 2 and 72% depending on the type of surgery performed.[2] This wide variation relates to the issues of definition, differences in used diagnostic tools and varying of populations studied.

Most of the studies concerning delirium focus on orthopaedic or cardiothoracic surgery.[3,4] Post-operative delirium is of major importance due to the many related adverse effects as prolonged hospital stay, decrease in functional status, increase in healthcare cost, morbidity and mortality.[5-9]

Delirium is a serious adverse event that is often unrecognized by most medical practioners. Most importantly, delirium is preventable in estimated one third of the cases with simple non-pharmological interventions performed by a dedicated nursing staff. [10,11]

It is of major importance to identify patients at risk for delirium, in order to initiate these preventive strategies timely. Identified risk factors after vascular surgery are age, previous major amputation, end-stage renal failure and cognitive impairment. [9,12-15]

Interestingly, Sasajima et al reported that patients with critical limb ischemia develop a delirium more frequently compared to patients with intermittent claudication.[9] However in this study, only patients with bypass surgery were included and sample size was small.

Critical limb ischemia is the most advanced stage of peripheral arterial disease in which revascularisation is needed for limb salvage.[16] Limb amputation is the last treatment option when revascularisation is no longer possible. This leaves the patient in a reduced functional status.[17] Moreover the serious systemic atherosclerosis increases the likelihood of adverse cardiovascular events leading to a higher perioperative morbidity and mortality.[18] These factors contribute to the frail condition of patients with critical limb ischemia and makes them at risk for developing a delirium in a hospitalized setting. [12,14,19] At the moment information about the predisposing factors for delirium in patients with critical limb ischemia is lacking. Therefore, in this study we analyse the incidence, perioperative risk factors and the outcome of perioperative delirium in patients with critical limb ischemia having surgery.

PATIENTS AND METHODS

1. Patient selection

A retrospective study on prospectively collected data was performed lasting from February 2013 to December 2014. This research was based on a regular patient care, therefore, the need for individual informed consent was waived. All patients 65 years or older, with critical limb ischemia having surgery from February 2013 to July 2014 were included and followed-up until December 31, 2014. Critical limb ischemia was defined as stage 4-6 according to the Rutherford classification for peripheral arterial occlusive disease.[20] All patients were admitted to our vascular surgical

ward in the Amphia Hospital in Breda, the Netherlands. Treatment options were discussed in a multidisciplinary consultation between radiologists and vascular surgeons. Patients eligible for surgical treatment were selected based on comorbidity, age and overall condition. If the patient was too fragile to undergo the planned revascularization procedure, or when revascularization was unlikely leading to a functional limb, a primary amputation was discussed with the patient and, when desirable, performed.

We excluded patients with a hospital stay shorter than 2 days, because it takes at least a full day to identify a delirium. For this reason also patients receiving endovascular treatment were excluded, since almost all these patients had a hospital stay shorter than 2 days.

Multiple possible risk factors for delirium were collected during admission including, pre-operative, operative and postoperative data.

2. Pre-operative factors

Basic patient characteristics of all included patients were collected including age, gender, and comorbidities. Severity of vascular disease was classified according to the Fontaine classification. Comorbidities were divided in the following categories: cardiac disease (myocardial infarction, rhythm disorder, valve disorder, cardiomyopathy and cardiac failure), pulmonary disease (chronic obstructive pulmonary disease and asthma), renal impairment (defined as glomerular filtration rate (GFR) < 60 ml/min/1.73m^2), neurological disorder (cerebrovascular Accident (CVA), transient ischemic attack (TIA), dementia or Parkinson's disease) and vascular risk factors (hypertension, diabetes mellitus type 1 or 2 and hypercholesteremia).

Other factors related to delirium as delirium in history, hearing and/or visual impairment and daily use of alcohol were extracted from the electronic medical records. A patients was counted as visually impaired if he/she required to use glasses/contact lenses for daily activities. If a visual aid was felt not needed by the patient or was needed for reading only no visual impairment was noted. Similar format and rules were applied to hearing impairment. A person was counted as having hearing impairment if he/she needed hearing aids for basic communications. We were able to prospectively collect all available parameters during the study period using a full electronic patient file: Hyperspace© Version IU4 (Epic Inc., Verona, Wisconsin, USA).

2.2. Frailty

Frailty depends on multiple patient-related factors such as functional status, nutritional status and cognitive status. Physical impairment was scored using the Katz Index of Independence in Activities of Daily Living (Katz- ADL).[21] This instrument assesses functional status by measuring the patient's ability to perform daily activities independently. A score of 6 indicates full function and a score of 5 or lower indicates any physical impairment.

The nutritional state was scored with the Short Nutritional Assessment Questionnaire for Residential Care (SNAQ RC-score).[22] The SNAQ RC is an adapted validated version of the more widely

used SNAQ-score and adds BMI as a contributory parameter. A SNAQ RC-score of 3 or higher is considered as high risk for undernourishment.
The care dependency (receiving daily care in a nursing home or by home care at home) and living situation (at home or in a nursing home) prior to admission in the hospital were noted. All patients living in a nursing home were care dependent due to some degree of either cognitive- or physical impairment.

3. Operative data

Pre- and postoperative biochemistry data were collected, including hemoglobulin (Hb) levels. Anaemia was defined as a Hb <7.6 mmol/L for women and <8.2 mmol/L for men.[23]
Operative data were extracted from the electronic medical records of the anaesthesiologists. Duration and type of anaesthesia and the American Society of Anesthesiologists (ASA) score were collected. The total number of packed red blood cells transfused during admission were retrieved from the blood transfusion central of our hospital. The type of procedure performed was noted and divided in four categories: minor amputation (amputation below the ankle joint or nectrosectomy), major amputation (lower and upper leg amputation), bypass surgery (femoropopliteal-, femorocrural-, ileofemoral- and aortofemoral bypass) or femoral endarterectomy.

4. Delirium

The Amphia risk score for delirium was scored at admission. This is a screening tool developed for recognizing patients at risk for development of a delirium during admission. [1] The screening tool consists of 5 items that can be rated as absent or present with a maximum of 5 points. A score of 1 or higher was defined as high risk. After identifying frail patients at risk for delirium, primary nurses could consult specialized nurses for help in preventive actions for delirium. These nurses were intensively trained by geriatric medicine specialists. They further assisted the patient's primary nurse on the ward with appropriate non-medical interventions such as the improvement of patient orientation, mobilization and fall prevention.
In addition, the Delirium Observation Screening Scale (DOSS) was scored three times a day by trained nurses during regular care for at least the first 48 hours after admission (Addendum 1). [24]
Three or more points were considered highly indicative for delirium. All patients were visited on daily basis by a physician. When delirium was present or suspected a geriatrician was consulted and the diagnosis was confirmed based on the DSM-IV criteria.[25]
When required, the specialized nurse was able to consult the supervising geriatric medicine specialist. Then, low dose anti-psychotic (Haloperidol®) was prescribed on judgment of the consulting geriatrician. Duration of delirium was defined as the total number of days with at least one DOSS score of three or more per 24 hours.

5. Objectives

The primary objective was to identify possible risk factors for delirium in patients with critical limb ischemia having surgery. The secondary objective concerned the effect of delirium on the following outcomes: the number of complications (medical- and surgical adverse events), the length of stay in hospital and Intensive Care Unit (ICU), mortality (30 days and 6 months) and the number of patients newly discharged to a nursing home.

Medical adverse events were defined as all complications in the post-operative period not directly related to the procedure performed. We divided medical adverse events in 4 categories: cardiac (myocardial infarction, cardiac failure, new onset of dysrhythmia), pulmonary (pneumonia, pulmonary embolism, acute respiratory insufficiency), neurological (CVA,TIA, neurological deficit), renal/urinary (urinary tract infection, urinary retention and renal impairment)

The surgical adverse events were defined as a complication directly related to the procedure performed such as wound infection, wound dehiscence and significant bleeding.

Delirium related additional costs based on prolonged hospital were based on regular costs of admission to the surgical ward (€343 per day).

6. Statistical analysis

Differences in categorical variables between patients with and without delirium were presented as relative frequencies (percentages) and tested using the chi-square test or Fisher's exact test. Differences of numerical variables (all skewed continuous variables) were presented as medians (interquartile ranges (IQR)) and were tested using the Mann-Whitney U test. The outcome variable (onset of delirium) was analyzed using conditional logistic regression analysis. The conditioning was on operation type (4 strata). Variables entering the model were selected from the set of candidate variables based on a p-value below 0.40 of their univariable relationship with delirium. After having entered all selected variables simultaneously in the conditional logistic regression model a stepwise procedure was used where at each step the variable with the highest asymptotic p-value above 0.40 was eliminated. Thereafter, elimination continued based on the highest exact p-value above 0.40 Using exact conditional logistic regression in order to avoid to over-fitting. A cut-off of 0.40 for the p-value was chosen to avoid estimated regression coefficients being biased high (in absolute sense) and their standard errors being biased low. [26] These finally selected explanatory variables were related to the delirium occurring pre- or post-operatively in the group of delirium patients using a similar exact conditional logistic regression analysis. Effects were presented by means of odds ratios (OR) with 95% confidence intervals (CI). The relation between delirium and survival was analyzed using the Kaplan Meier method and the log rank test. A p-value of <0.05 was considered statistically significant. Delirium related additional costs based on prolonged hospital were based on costs of admission to the surgical ward (€343 per day). The impact of delirium on costs was estimated with linear regression analysis with correction for confounders found within this study after multivariable analysis. The univariable analysis and survival analyses were performed using the Statistical Package for the

Social Sciences (IBM SPSS Statistics for Windows, Version 21.0. released 2012, Armonk, NY, USA). The multivariable analysis was performed with LogXact, version 4.1, Cytel Software Corporation.

RESULTS

1. Patient selection and characteristics

A total of 92 patients with critical limb ischemia having surgical treatment were included. The study population consisted of 58% males with a median age of 76 years. Baseline characteristics are summarized in Table 1.

Table 1 Characteristics of all included patients with critical limb ischemia receiving surgery

	Rutherford 4-6 *n*=92 (%)
Gender, male	53 (58)
Age, median (IQR)	76 (71-82)
Age 65-70 years	20 (22)
Age 70-79 years	37 (40)
Age ≥ 80 years	35 (38)
Living status	
Nursing home	21 (23)
Daily care at home	18 (20)
Home without care	53 (57)
Comorbidity	
Cardiac	55 (60)
Pulmonary	18 (20)
Renal impairment	10 (11)
Neurological	26 (28)
Diabetes mellitus	44 (48)
Operation	
Necrotectomy	11 (12)
Minor amputation	14 (15)
Major amputation	18 (19)
Femoral endarterectomy	10 (11)
Femoropopliteal bypass	24 (26)
Femorocrural bypass	9 (10)
Aortofemoral bypass	6 (7)

Data are presented as n and (%), unless otherwise specified. IQR=interquartile range.

2. Delirium

A total of 29 (32%) patients developed a delirium during admission (Table 2). Of all patients with a delirium, 17 (59%) developed a delirium prior to operation. All these patients continued to have a delirium post-operatively. In 12 patients delirium occurred post-operatively, most of them (67%) on the first postoperative day. The median duration of delirium was 3 days. Patients who developed a delirium pre-operatively had a significant longer duration of delirium (median 6 days) compared to patients who developed a delirium postoperatively (median 2 days; p=0.02).

Table 2 The onset and length of the delirium.

	Rutherford 4-6 *n*=92 (%)
Delirium	29 (32)
Pre-operative delirium	17 (59)
Postoperative delirium	12 (41)
Onset of postoperative delirium (*n*=12)	
Day 1 post-operative	7 (67)
Day 2 post-operative	3 (25)
Day 3 post-operative	- -
Day 4 or more	2 (8)
Length of delirium, Median (IQR)	3 (1-6)

Data are presented as n and (%)
IQR=interquartile range.

3. Pre-operative risk factors and factors on frailty related to delirium

Nineteen (66%) of the patients with a delirium were octogenarians (p<0.001). Identified factors related to delirium were cardiac comorbidity (p=0.010), delirium in medical history (p=0.010) and visual impairment (p=0.031). The daily use of alcohol (p=0.017) and hypercholesterolemia (p=0.028) were significantly more observed in the group without a delirium (Table 3).
Univariable analysis identified several factors on frailty associated with delirium, as physical impairment (p=0.007) and living in a nursing home prior to admission (p<0.001). Data are summarized in Table 3.

4.Peri-operative factors

A major amputation (p=0.003) and pre-operative anaemia (p=0.031) were significantly more present in patients with a delirium (Table 4). Bypasses procedures and a longer duration of anaesthesia were significantly more observed in patients without a delirium. (Table 4).

Table 3 Univariate analysis of possible risk factors in patients with critical limb ischemia in relation to the onset of delirium.

	No delirium *n*=63 (%)	Delirium *n*=29 (%)	*p*-value
Gender			
Male	36 (57)	17 (59)	0.894
Age			
Median age (IQR) ‡	75 (69-80)	81 (76-86)	0.001[b]
Age 65-70 years	17 (27)	3 (10)	
Age 70-79 years	30 (48)	7 (24)	
Age ≥ 80 years	16 (25)	19 (66)	0.003
Fontaine classification			
Fontaine 3	24 (38)	4 (13)	
Fontaine 4	39 (62)	25 (87)	0.019
Comorbidity			
Cardiac	32 (51)	23 (79)	0.010
Pulmonary	12 (19)	6 (21)	0.854
Renal impairment	5 (8)	5 (17)	0.278[a]
Neurological	16 (25)	10 (34)	0.369
Diabetes Mellitus	27 (43)	17 (59)	0.160
Hypertension	38 (60)	12 (41)	0.090
Hypercholesterolemia	28 (44)	6 (21)	0.028
Other predisposing factors			
Delirium in medical history	3 (5)	7 (24)	0.010[a]
Daily use of alcohol	18 (29)	2 (7)	0.017
Visual impairment	18 (29)	15 (52)	0.031
Hearing impairment	22 (35)	11 (38)	0.780
Frailty factors			
Physical impairment[#]	29 (46)	22 (76)	0.007
Undernourishment[*]	13/61 (21)	10/24 (42)	0.057
Daily nurse visits at home	11/55 (20)	7/16 (44)	0.093[a]
Living in nursing home	8 (13)	13 (45)	<0.001

Values in parentheses are percentages unless indicated otherwise; values are ‡ median (interquartile range)
p-value is calculated with Chi-squared test
a= Fisher exact test, b= Mann-Whitney U test
# physical impairment is defined as a KATZ-ADL score <6 [21]
*undernourishment is defined as a SNAQ-RC-score ≥3 [22]

Table 4 Peri-operative variables in relation to onset of postoperative delirium in patients with critical limb ischemia having surgery

	No delirium *n*=63 (%)	Delirium *n*=29 (%)	*p*-value
ASA-score ≥ 3	43 (68)	26 (90)	0.028
Duration of anaesthesia, median (IQR)	142 (27-211)	52 (26-100)	0.035[b]
Type of anaesthesia			
General anaesthesia	56 (89)	28 (96)	
Regional anaesthesia	7 (11)	1 (4)	0.226
Operation type			
Minor amputation	16 (25)	9 (31)	0.572
Major amputation	7 (11)	11 (38)	0.003
Bypass*	32 (51)	7 (24)	0.016
Femoral endarterectomy	8 (13)	2 (7)	0.714[a]
Hemoglobulin and transfusion			
Pre-operative anemia**	35/59 (60)	22/27 (81)	0.044
Pre-operative Hb, median (IQR)	7.7 (6.4-8.0)	6.8 (6.3-7.4)	0.075[b]
Post-operative anemia**	31/32 (97)	20/22 (91)	0.560[a]
Post-operative Hb, median (IQR)	6.45 (5.7-6.9)	6.2 (5.7-6.9)	0.832[b]
Packed Cells transfusion	18 (29)	5 (17)	0.244
≥ 3 Packed Cells transfused	9 (14)	2 (7)	0.492[a]

Data are presented as n and (%), unless otherwise specified.

Hb = hemoglobulin in mmol/L, IQR = interquartile range.

p-value is calculated with Chi-squared test, a= Fishers's Exact test, b= Mann-Whitney U test

* Femoropopliteal, femorocrural, ileofemoral and aortofemoral bypass.

** anemia is defined as a Hb <7.6 mmol/L for women and <8.2 mmol/L for men [23]

5.Multivariable analysis

All variables of Tables 3 and 4 with a p-value below 0.40 in relation to delirium entered simultaneously the conditional logistic regression model. Based on an asymptotic p-value above 0.40 the following variables were eliminated from the model during the stepwise backwards procedure: renal impairment, physical impairment, ASA ≥ 3, age, cardiac comorbidity and history of delirium. Continuing the stepwise backwards procedure using exact conditional regression analysis the following variables were additionally eliminated based on an exact p-value above 0.40: daily nurse visits at home, Fontaine 4, neurological comorbidity, living in a nursing home, operation time, pre-operative hemoglobulin and hypertension. Eventually, diabetes mellitus, SNAQ-RC ≥ 3, general anaesthesia, visual impairment, daily alcohol use, hypercholesterolemia and packed cells transfusion remained in the finally estimated model with exact p-values below 0.40, while operation type was adjusted for through conditioning. Only two factors were significantly associated with the onset of delirium: diabetes mellitus (OR = 6.23; 95% CI: 1.11-52.2; p = 0.035) and SNAQ_RC ≥ 3 (OR = 5.55; 95 % CI: 1.07-42.0; p = 0.039), adjusted for the other variables mentioned and presented in Table 6 and stratified by operation type. The only variable

selected for discriminating between pre and post-operative delirium in the delirium patients with an exact p-value below 0.40 was visual impairment, with a non-significant effect in favor of a pre-operative delirium (OR = 2.89; 95% CI: 0.55-17.9; p = 0.27).

Table 5. Results of an exact conditional logistic regression analysis of delirium, where the conditioning is on operation type (4 strata).

Variables	OR(95% CI)	*P*-value
Diabetes Mellitus	6.23 (1.11-52.2)	0.035
SNAQ-RC ≥ 3	5.55 (1.07-42.0)	0.039
General anesthesia	13.3 (0.96- ∞)	0.054
Visual impairment	3.72 (0.98-15.6)	0.055
Daily alcohol use	0.15 (0.01-1.07)	0.062
Hypercholesterolemia	0.30 (0.06-1.22)	0.10
Packed cells transfusion	0.68 (0.31-1.23)	0.27

Data presented as odds ratios (OR) and their 95 % confidence intervals (CI). Confidence limits and p-values are exact.

6. Secondary outcomes

The onset of a delirium during hospital stay was not significant related to more complications. The median hospital stay of patients with a delirium was 14 days (IQR 11) and was significantly longer compared to 8 days for patients without a delirium. (p=0.001) (Table 5).

The difference in survival between patients with and without a delirium was tested and illustrated using the Kaplan Meier method (Figure 1). Overall mortality was higher in the delirium group than in the non-delirium group (log-rank test p < 0.0005). Thirty-four percent of the patients with a delirium died within six months after surgery in contrast to 8% in the non-delirium group (p=0.005). There was no difference in new admissions to a nursing home between both groups (Table 5).

Occurrence of delirium was related to an increase in hospital stay of 4.4 days after adjustment for identified independent predictors for delirium (visual impairment and diabetes mellitus). The additional delirium-related hospital stay corresponded to an increase of healthcare costs of € 2195 [95% Confidence Interval €595 - €3794], per extra delirium. After correction for confounders (visual impairment and diabetes mellitus), the costs were an extra € 1519 [95% Confidence Interval -€717 - €3110] per delirium.

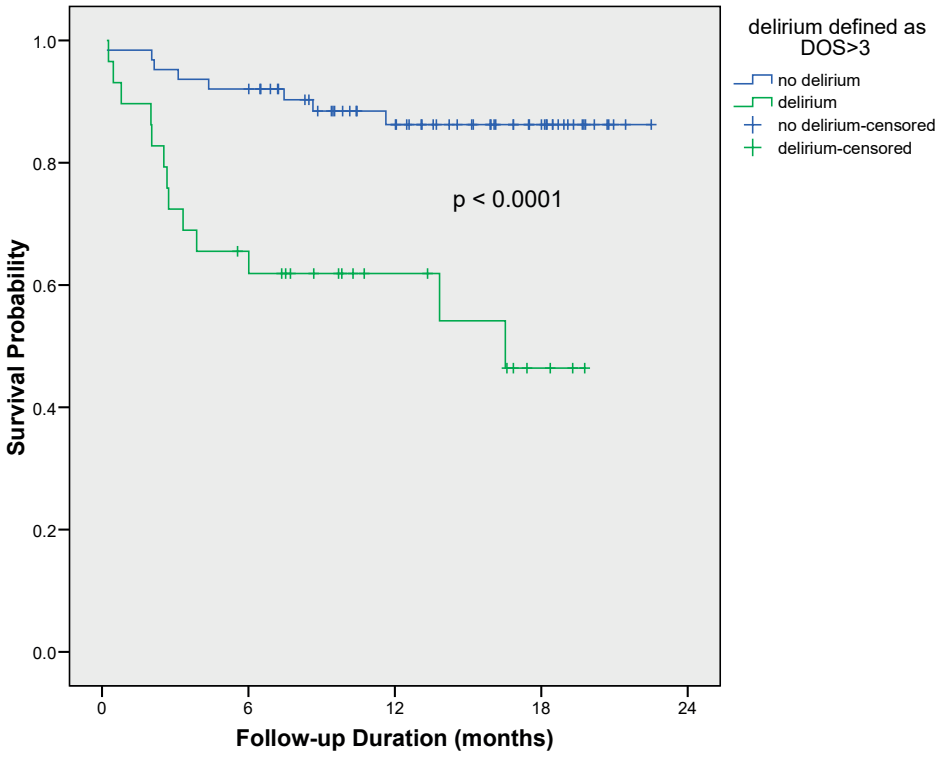

Figure 1. survival in relation to the onset of delirium in patients with critical limb ischemia

Table 6 Hospital length of stay, ICU stay and mortality in relation to onset of postoperative delirium in patients with critical ischemia.

	No delirium *n*=63 (%)	Delirium *n*=29 (%)	*p* value
Medical Adverse Events			
Cardiac	2 (3)	- -	1.0[a]
Pulmonary	2 (3)	2 (7)	0.588[a]
Neurological	- -	- -	
Renal/urinary	2 (3)	5 (17)	0.030[a]
Surgical Adverse Events			
Wound infection	4 (6)	3 (10)	0.674[a]
Re-bleeding requiring intervention	1 (2)	- -	1,0[a]
Wound dehiscence	1 (2)	1 (3)	0.533[a]
Length of stay			
Total Hospital stay in days, median (IQR)	8 (6-13)	14 (9-20)	0.001[b]
Admission to ICU	5 (8)	3 (10)	0.704[a]
ICU stay in days ≥ 2	- -	1 (3)	0.315[a]
Discharge destination			
New nursing home client after discharge	10 (16)	5 (17)	0.761[a]

Data are presented as n and (%), unless otherwise specified.
P-value is calculated with Chi-squared test
a= Fisher's exact test, b= Mann-Whitney U test
IQR=interquartile range.

DISCUSSION

In this longitudinal observational study, we attempted to find predictors for the onset of delirium in patients with critical limb ischemia and to explore the impact on the related outcomes. *Balasundaram et al.* reviewed the literature regarding the incidence and aetiology of delirium after elective vascular surgery. [12] Incidences rates between 29 and 39% are reported [9,13-15,27] However, only two of these studies reported data concerning patients with critical limb ischemia, with incidences rates of delirium between 42-44% after bypass surgery. [9,15] We reported a 32% incidence rate of delirium in elderly patients with critical limb ischemia with a tremendous mortality rate of 34% after six months.

The included potential risk factors for delirium influence each other and are often age related (i.e. visual impairment). The identified risk factors in this study are therefore related to the population studied and affected by the choice of potential confounders. After multivariable analysis,

diabetes mellitus and undernourishment were identified as independent risk factors for delirium in this study.

Preoperative delirium risk assessment is critical for identification of those patients who would most benefit from delirium prevention and surveillance protocols. Health care providers need to be aware of these identified risk factors for developing delirium. In these patients, non-pharmacological delirium prevention strategies should be initiated timely, with special attention for optimizing nutritional status.

An important finding of our study is that most patients with a delirium developed it in the pre-operative period (59%). This is the first study that reported that patients often develop a delirium in the pre-operative period. All of these patients continued to have a delirium postoperatively despite adequate treatment. For patients developing a delirium in the postoperative period, most developed delirium on the first postoperative day. This indicates the need for early preventive measures and maybe even standard preoperative consultation of a geriatrician in patients at risk for delirium.

In our study pre- and postoperative hemoglobulin levels were not related with the onset of delirium after exact conditional logistic regression analysis. However, this could be explained by the high overall incidence of anaemia in our study population (66%). Despite that anaemia could not be related to the onset of delirium in this study, it is still related to higher postoperative complication rates [28]. Therefore, preventive treatment of anaemia may lead to a better outcome in operatively treated patients.

Interestingly, we report a lower incidence of delirium after bypass surgery (19%) and bypass surgery was more frequently performed in the group without a delirium. In addition, duration of anaesthesia was longer in patients without a delirium. In a study performed by Sasajima et al, an incidence of 29% delirium after bypass surgery was reported[9,15]. These differences could be explained by a certain selection bias. The indication for surgical (bypass) therapy was discussed in a multidisciplinary consultation based on the patient's condition in our study. Patients condition and frailty were key factors in deciding whether a patient was eligible for a certain type of operation. Patients in a better condition were more likely to receive a bypass procedure than patients in a worse and frail condition. Patient deemed unfit for surgery (bypass or amputation) or endovascular treatment received a conservative treatment with antibiotics and analgesics or had a primary amputation.

Patients having an endovascular revascularisation were excluded in this study. Postoperative delirium may develop secondary to the extent of surgical trauma. Consequently, patients undergoing more invasive surgeries, such as bypass surgery, as well as major amputations may have higher rates of postoperative delirium. As Brosi et al reported, an endovascular-first revascularization strategy should be preferred in octogenarians whenever possible because of the high perioperative mortality associated with surgery. [29] Our finding may support this theory, especially for frail elderly who are at risk for delirium.

Sasajima et al, identified critical limb ischemia as an independent risk factor for the onset of delirium after bypass surgery. [9,15] To our knowledge this is the only study reported factors related to the onset of delirium in patients with critical limb ischemia receiving surgical treatment. The relation between critical limb ischemia and the onset of delirium is not yet fully known. However, critical limb ischemia is frequently associated with systemic atherosclerosis and its adverse effects on patient outcomes [18]. Besides systemic atherosclerosis contributes to cognitive decline among elderly patients and cognitive impairment is a well-known risk factor for the onset of delirium. [30,31]

Pol et al investigated the relation between systemic atherosclerosis and the onset of delirium and could not support this theory.[32] Our study even reported a reverse relation between delirium and hypercholesterolemia. However, in this study, hypercholesterolemia was noted based on the patient's medical record. This could explain the observed relation in our study. In addition, the reported daily use of alcohol had a reverse relation to the onset of delirium. In contrast to several other studies in which alcohol abuse is a predisposing factor for the onset of delirium. [27]. The results on self-reported alcohol consumption, in this study may have led to a biased estimate of use. Possibly, there is an underestimation of self-reported drinking among individuals who drank more heavily. This study brings into question the accuracy of self-report measures, especially since other studies reported that alcohol consumption is an independent risk factor for delirium. [33] Frail patients are more likely to develop a delirium. [14,34,35] Patients with critical limb ischemia are often burdened with multiple comorbidities and are care dependent due to physical and cognitive impairment leading to a frail condition. This statement was partially confirmed in our study on patients with critical limb ischemia receiving surgery.

Limitations

Most of our data were obtained by extracting data from electronic medical records. Therefore, some data were missing and could not be obtained otherwise.

Several earlier studies confirmed medication as a risk factor for postoperative delirium and therefore should be included in further research. By using the DOSS as screening tool for delirium in hospitalized patients we might have missed the hypoactive type of delirium. Therefore our incidence could be an underestimation of the real incidence of delirium in patients with critical limb ischemia.

CONCLUSION

Delirium is a common adverse event in patients with critical limb ischemia having surgery with a devastating outcome on the long term. Most patients developed a delirium pre-operatively which indicates the need for early recognition and preventive strategies in the pre-operative

period. This study identified undernourishment and diabetes mellitus as independent risk factors for delirium.

Acknowledgment:

We would like to thank A.J. van Gammeren, M.D. PhD, Department of Clinical Chemistry and Haematology, Amphia Hospital for providing the blood transfusion data.

Addendum 1 DOSS: Delirium Observation Screening Scale	
1	Dozes during conversation or activities
2	Is easy distracted by stimuli form the environment
3	Maintains attention to conversation or answer
4	Does not finish question answer
5	Gives answers which do not fit the question
6	Reacts slowly to instructions
7	Thinks to be somewhere else
8	Knows which part of the day it is
9	Remembers recent event
10	Is picking, disorderly, restless
11	Pulls iv tubes, feeding tubes, catheter
12	Is easy or sudden emotional
13	Additive or visual hallucinations

If present 1 point.
Rate three times per day.

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Chapter 9

General discussion and conclusion

GENERAL DISCUSSION AND CONCLUSION

This thesis underlines that frailty and delirium are important issues influencing the outcome of care for elderly surgical patients. Up to now, very few studies have focused on delirium and its prevention in vascular and general surgery patients. In addition, an accurate screening tool on frailty is lacking. Although specialized geriatric wards and multicomponent interventions have been proven to prevent delirium and improve outcome, in many hospitals this is probably not feasible. The aims of the research in this thesis were to explore the role of conservative therapies in frail elderly patients in need for (extensive) surgery. Also, delirium incidence and predictive factors of delirium in elderly patients having surgery were examined. In this chapter results of these studies will be discussed as well as future directions for research.

The role of conservative treatment in the elderly

First, we studied the role of conservative treatment in selected elderly patients where surgical treatment might have been preferred. The results of conservative treatment in patients with several acute and less acute diseases that requires surgical interventions are described.

The results of conservative treatment for selected patients with severe critical limb ischemia (CLI) are reported in **Chapter 2**. The preferred therapy for CLI is either endovascular revascularization or bypass surgery. Particular, since amputation leads to decreased mobility, higher health care costs and a reduced quality of life[3]. We describe a retrospective study reporting on the results of conservative treatment in 38 selected patients with severe CLI. Conservative treatment was started in patients who were deemed unfit for revascularization, either because of poor general health or because of anatomical unsuitability. The limb survival rate was 84% during 2-year follow-up. Complete wound regression was attained in 58% of the patients. Although the mortality rate was high (58%), a minor part of the patients died due to sepsis caused by progressive gangrene. This study suggests that conservative treatment could be a viable alternative to primary amputation for selected patients with severe CLI deemed unfit for surgical or endovascular revascularization.

In **Chapter 3** we describe a retrospective observational study on patients diagnosed with ruptured abdominal aortic aneurysm (rAAA). The current clinical outcomes of emergency endovascular aneurysm repair (eEVAR), conventional open repair, and conservative treatment were evaluated. The selection to intervene and perform an emergency procedure (eEVAR or open repair) or to initiate conservative treatment was made on the expertise of the vascular surgeon on call. Twelve patients (mean age 87 years) did not undergo a surgical intervention and were treated conservatively. Practically all these patients died within 48 hours (median 27 hours). In this study, advancing age in combination with frailty was mentioned most frequently as the reason for conservative treatment. No significant difference in 30-day mortality rate was detected between eEVAR (30%) and open repair (26%). During five-year follow-up the mortality rate was 76% after eEVAR as well as after open repair. Remarkably, age was not related to an

increase in 30-day mortality after emergency surgery, most likely as a result of the selection of elderly judged as fit for emergency repair.
This study supports the concept that the selection as whether to intervene in case of rAAA or not should not be made based on age alone, but also on the existence of comorbidity and patient preference.

Delirium

Postoperative delirium is a common and serious adverse event in the elderly patient and is associated with significant morbidity and mortality. Delirium care is of importance because the number of elderly requiring surgery is expected to increase in numbers in the near future. As a result, the incidence of delirium will also rise the coming years.
Post-operative delirium and the associated risk factors have been studied quite extensively in patients having orthopedic or cardiac surgery. Research is lacking concerning the true incidence rates, risk factors and outcomes for patients that underwent major general surgery.
In case of planned, major elective surgery identification of high risk patients is most effective, since pre-operative optimization of the patient could significantly reduce postoperative delirium and the related detrimental outcome. Post-operative delirium and the associated risk factors have been studied quite extensively in patients having orthopedic or cardiac surgery. We systematically reviewed the existing literature in order to identify the risk factors for delirium after elective vascular surgery in the elderly, based on solid evidence **(Chapter 4)**. A systematic literature search was conducted using PubMed and EMBASE, using the MeSH terms and key words "delirium", "surgery" and "risk factor". Ten articles were selected for inclusion, incidence of delirium across the studies ranged from 5 to 39%. The highest delirium incidence was observed after open aortic surgery as well as after surgery for critical limb ischemia. The leading risk factors consistently identified were advanced age and cognitive impairment. There was a significant heterogeneity between the included studies, because of differences in patient selection as well as variety in selection of possible risk factors for delirium analyzed.
In **Chapter 5** a study is described on the incidence and outcome of delirium in elderly patients (≥ 65 years) having acute or elective colorectal surgery for colorectal carcinoma or diverticulitis. Of the included patients, 83 (75%) received elective surgery and 28 (25%) acute surgery. No significant difference was observed in delirium incidence after acute (29%) and elective surgery (18%; p=0.24). Half of the octogenarian patients (5/10) who received acute colorectal surgery developed a delirium episode during hospitalization. Patients suffering delirium had higher incidence of adverse events, longer hospital stay and were more frequently discharged to a nursing home. Mortality after 30-days was significant higher in patients with a delirium (17% vs 1%; p=0.01), as well as six-month mortality rate (26% vs. 9%; p=0.07).
In **Chapter 6** we report on a study to evaluate predictive factors for delirium for patients having elective major abdominal surgery. Elderly patients (≥ 65 years) who had surgery for AAA (n=51) or colorectal cancer (n=181) were analyzed on potential risk factors and outcome after delirium.

Postoperative delirium occurred in 15% of patients. Independent predictive factors identified included: delirium in medical history, advancing age and ASA-score, pre-operative hemoglobin, anemia and packed cells during admission.
Delirium related outcomes in this study were the number of adverse events, length of hospital stay, institutionalization following discharge and mortality. Delirium was observed in 7 patients after open repair (27%) and in one patient after Endovascular Aneurysm Repair (EVAR) (4%; p=0.050). Patients developed a delirium more frequently after laparotomy (20%) compared to patients having laparoscopic surgery (8%; p=0.024).
Despite the minimal invasive nature of the EVAR technique, previous RCT studies reported similar results of EVAR and open repair for elective AAA surgery [4, 5]. Interestingly, delirium-related costs were not included in previous cost-analysis studies that indicated EVAR not to be cost-effective as compared with open repair [6]. For elderly patients at risk for delirium, less invasive procedures as EVAR and laparoscopic surgery could be preferable to more invasive surgery as it offers a better outcome.
Vascular surgery patients are frequently in a frail clinical condition and at risk for delirium. We evaluated the incidence and independent risk factors in the various vascular disease groups of our current clinical vascular practice **(Chapter 7)**. Patient admitted for critical limb ischemia, diabetic foot ulcer, AAA surgery, and patients having carotid artery surgery were included for this observational study. We identified patients with critical limb ischemia as the most frail and vulnerable ones. Of those patients with critical limb ischemia and delirium (incidence 24%), 53% were octogenarians.
Evidence is growing that suggests a relationship between systemic and cerebrovascular atherosclerosis and the development of delirium [7].
Micro-vascular changes in the brain caused by atherosclerosis can lead to impaired cognitive functioning and reserve and subsequently increase the risk for delirium [8]. However, in our study results could not support this hypothesis. A lower incidence of delirium was observed in the patients having carotid surgery compared to the patients with critical limb ischemia (24 vs. 8%).
A study was performed on patients with critical limb ischemia as described in **Chapter 8**. Briefly, 92 elderly patients (≥ 65 years), with critical limb ischemia having surgery were included in this study with the aim to identify predictive factors for delirium occurrence. The incidence of delirium was 32%, of which 59% started pre-operatively. We identified undernourishment and diabetes mellitus as independent risk factors for delirium. Delirium was related to longer hospital stay and mortality after 6 months (34% after delirium vs. 8% no delirium; p<0.01. Delirium-related hospital stay corresponded to an increase in healthcare costs of €1519 per delirium.

FUTURE PERSPECTIVES

Frailty

The demographic trends towards an ageing population in the Western world and an increasing incidence of frail elderly with significant comorbidities are important considerations for all healthcare professionals. We reported on the outcome of conservative treatment for several disease that may have been treated with surgery as well and our data indicate a beneficial effect. The key for clinical decision making to perform surgery or not is the selection of patients, including age as well as comorbidity and patient preference in treatment options. In addition, the expediency of comprehensive interventions in the fragile elderly should be studied in more detail with the outcome of conservative management, thereby taking into account the impact on quality of life of frail elderly after operative and non-operative case management. Capturing and measuring factors on frailty are necessary to identify patients, to predict outcome of treatment and to help in clinical decision making.

Delirium

Research in the pathogenesis of delirium is required to better understanding the disease and to identify predisposing and precipitating factors. Prevention and risk-assessment need refining and testing in other surgical patient populations. To get a better understanding of the long-term outcomes after delirium, studies with a longer follow-up period are required.

In current research, available literature and practice, 30-day mortality is an important outcome parameter. The 6-month mortality rates after delirium presented in this thesis are impressive. Short-term outcomes are of less importance when considering invasive procedures in patients with significant limited life expectancies. Therefore, 6-month mortality may be a more appropriate parameter, especially in case of frail elderly patients, at risk for delirium having a limited life-expectancy.

Because delirium incidence is high in elderly having surgery, and will probably increase in future because of demographic ageing, education and knowledge on delirium should be extended on all concerning health care professionals.

The most effective and expedient method in delirium care is prevention of its occurrence. Several studies demonstrated that delirium is preventable by performance of multicomponent interventions during admission. However, in current clinical practice, patients are often admitted on the day of surgery, and at that moment screened for frailty and delirium risk. Preventive actions started in this timeframe will probably have no or only little effect.

When high risk patients are identified earlier, during the preoperative outpatient period, appropriate preventive arrangements can be implemented at a more convenient time and most likely will result in a lower delirium rate and related outcomes as hospital stay, morbidity and mortality may improve significantly. Outpatient consultation of a multidisciplinary coordinated team of healthcare professionals can screen patients on frailty and risk for delirium. Instantly the modifiable risk factors could be optimized. Proactive geriatric consultation with early pre- and

postoperative interventions and optimization of polypharmacy has been proven to reduce both incidence and severity of surgery related delirium[9-11]. Early screening and treatment of undernutrition and physical impairment can be started with the help of dieticians and physiotherapists. Actions to elevate hemoglobin levels pre-operatively could potentially decrease delirium incidence. Since the rate of pre-operative anemia is high in elderly, more research should be performed in patients with increased risk for delirium [12].

Thus, more research has to be focused on the results of a multi-disciplinary approach of the elderly frail patients at risk for delirium and its related problems. By improving our knowledge in this areas we develop new insights in decision making and may act more appropriately and successfully in the treatment of high-risk elderly patients presenting with a surgical disease.

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Chapter 10

Samenvatting in het Nederlands
Summery in Dutch

SUMMARY IN DUTCH

Dit proefschrift bevestigt dat kwetsbaarheid en delier belangrijk zijn bij de behandeling van de oudere chirurgische patiënt. Helaas zijn er weinig studies die zich richten op preventie van het delier en het ontbreekt aan een screenings instrument. Ondanks resultaten van studies waarin is aangetoond dat gespecialiseerde geriatrische betrokkenheid en multidisciplinaire interventies bewezen effectief zijn in het voorkomen van delier, is het niet haalbaar dit in de dagelijkse praktijk voor alle patiënten uit te voeren. Het doel van dit proefschrift was om de rol van conservatieve behandeling te onderzoeken bij kwetsbare patiënten die anders (uitgebreide) chirurgie zouden moeten ondergaan. Daarnaast worden de incidentie en voorspellende factoren voor delier nader gedefinieerd.

De rol van conservatieve behandeling van ouderen

De rol van conservatieve behandeling bij geselecteerde oudere patiënten waarbij het verrichten van een operatie de meest logische behandeling lijkt, wordt nader onderzocht. Terwijl er veel bekend is over de resultaten van operaties bij oudere patienten, zijn publicaties over conservatieve behandelingen voor dezelfde aandoeningen schaars. Derhalve wordt in dit proefschrift nadruk gelegd op de beschrijving van resultaten van de conservatie behandeling van patiënten met acute en minder acute ziekten, die eveneens met een (uitgebreide) operatie behandeld hadden kunnen worden.

De resultaten van conservatieve behandeling van geselecteerde patiënten met ernstige kritieke ischemie van de onderste extremiteiten zijn beschreven in **Hoofdstuk 2.** De behandeling van voorkeur bij kritieke ischemie bestaat uit endovasculaire- of chirurgische revascularisatie. Deze benadering wordt gezien als eerste keuze, omdat amputatie gepaard gaat met morbiditeit, hoge kosten en een vermindering in de kwaliteit van leven[3]. Hoofdstuk 2 beschrijft een retrospectieve studie waarbij de resultaten van conservatieve behandeling van 38 geselecteerde patiënten met ernstige kritieke ischemie worden beschreven. Conservatieve behandeling werd gestart omdat patiënten iet fit genoeg geacht werden voor revascularisatie vanwege een te slechte algemene conditie, of omdat het vaatlijden anatomisch niet geschikt was voor revascularisatie. Het been kon in 84% van de gevallen, gedurende 2 jaar follow-up worden behouden. Complete regressie van de wond die het gevolg was van de kritieke ischemie werd bereikt in 58% van de patiënten. Ondanks dat de mortaliteit hoog was (58%), kon slechts een klein deel verklaard worden door sepsis ten gevolge van progressie van gangreen. Deze studie toont aan dat conservatieve behandeling in bepaalde situaties een geschikt alternatief kan zijn, vergeleken met een primaire amputatie bij geselecteerde patiënten met ernstige kritieke ischemie waarbij revascularisatie niet mogelijk is.

Hoofdstuk 3 is een retrospectieve observationele studie van patiënten met een geruptureerd Aneurysma van de Abdominale Aorta (AAA). De uitkomsten van de huidige behandelingen: "emergency endovascular aneurysm repair" (eEVAR), open chirurgisch herstel en conservatieve behandeling werden geëvalueerd. De besluitvorming om een spoedoperatie (eEVAR of open

chirurgisch herstel) of conservatieve behandeling uit te voeren werd verricht door de vaatchirurg van dienst. Twaalf patiënten (gemiddelde leeftijd 87 jaar) werden niet geopereerd en kregen een conservatieve behandeling. Deze patiënten overleden binnen 48 uur (mediaan: 27 uur). Hoge leeftijd in combinatie met fragiliteit werden het meest genoemd als motivatie voor de keuze van een conservatieve behandeling. Er werden geen verschillen in de 30-dagen mortaliteit gedetecteerd tussen eEVAR (30%) en open chirurgisch herstel (26%). Gedurende vijf jaar follow-up was de mortaliteit 76%, zowel na eEVAR als na open chirurgisch herstel. Toename van leeftijd was niet gerelateerd aan stijging van de 30-dagen mortaliteit na spoedoperatie, meest waarschijnlijk als resultaat van de selectie van patiënten.
Deze studie ondersteunt de gedachte dat selectie van patiënten met een geruptureerd AAA voor spoedoperatie niet gemaakt moet worden op basis van leeftijd op zich, maar op basis van comorbiditeit en de wensen van de patiënt.

Delier

Het delier is geassocieerd met een hoge mortaliteit, comorbiditeit, hoge afhankelijkheid van verpleegkundige zorg, langdurige opname in het ziekenhuis, en een hoge frequentie van overplaatsing naar verpleeghuis. De impact van delier op patiënten en de naaste familie is groot en het delier brengt hoge kosten met zich mee. Daarnaast kan het delier zorgen voor blijvende cognitieve stoornissen.
Onderkenning van het probleem is van groot belang aangezien het aantal kwetsbare ouderen die operaties zullen moeten ondergaan in de toekomst zal toenemen. Het valt dan ook te verwachten dat de incidentie van het delier zal gaan toenemen de komende jaren.
Het post-operatieve delier en de risicofactoren zijn eerder door anderen onderzocht bij patiënten die orthopedische of hart-operaties ondergingen. Data over het delier bij patienten binnen de algemene chirurgie zijn slechts in zeer beperkte mate aanwezig in de literatuur.
Waarschijnlijk heeft de identificatie van hoog risicopatiënten het meeste zin bij patiënten die grote electieve operaties ondergaan, omdat pre-operatieve optimalisatie van de patiënt kan leiden tot een afname van het aantal delier en de daaraan gerelateerde nadelige uitkomsten. Wij hebben een systematisch review verricht om risicofactoren op delier na uitgebreide vasculaire electieve chirurgie bij ouderen vast te stellen **(Hoofdstuk 4)**. Een systematische literatuurstudie werd verricht in PubMed en EMBASE, met de MeSH termen en keywords “delirium”, “surgery” en “risk factor”. Tien artikelen werden geselecteerd voor inclusie. De incidentie van delier varieerde per studie van 5 tot 39%. De hoogste incidentie werd beschreven bij patiënten die open aneurysma chirurgie onderingen en bij patienten die kritieke ischemie van de onderste extremiteiten hadden. De belangrijkste risicofactoren die het meest werden beschreven waren hoge leeftijd en cognitieve stoornissen. Er was een aanzienlijke heterogeniteit tussen de studies door verschillen in patiëntpopulaties, de gebruikte diagnostische middelen en de combinatie van potentiële risicofactoren. Hierdoor is het stellen van eenduidige conclusies niet mogelijk.

Hoofdstuk 5 omvat een studie naar de incidentie en de gevolgen van delier bij ouderen (≥ 65 jaar) die acute of electieve colorectale chirurgie ondergingen voor colorectaal carcinoom of diverticulitis. Van de geïncludeerde patiënten ondergingen er 83 (75%) electieve chirurgie en 28 (25%) acute chirurgie. Er werd geen significant verschil gevonden in de incidentie van delier tussen acute (29%) en electieve chirurgie (18%) *p*=0.24. De helft van de 80-plussers (5/10) die acute colorectale chirurgie ondergingen ontwikkelde een delier tijdens opname. Patiënten die een delier ontwikkelden hadden vaker complicaties, waren langer in het ziekenhuis opgenomen, en werden vaker overgeplaatst naar een het verpleeghuis. De 30-dagen mortaliteit was significant hoger bij patiënten met een delier (17% vs 1%; p=0.01), evenals de 6-maanden mortaliteit (26% vs. 9%; *p*=0.07).

Hoofdstuk 6 beschrijft een studie waarin voorspellende factoren voor delier werden bepaald bij patiënten die een uitgebreide abdominale operatie ondergingen. Ouderen (≥ 65 jaar) die een operatie ondergingen voor een AAA (*n*=51) of colorectale maligniteit (*n*=181) werden geanalyseerd om potentiële risicofactoren en uitkomsten van het delier te kunnen vaststellen. Het postoperatieve delier trad op bij15% van de patiënten en geïdentificeerde, onafhankelijke risicofactoren waren: delier in de voorgeschiedenis, hogere leeftijd en een hogere ASA-score. Het pre-operatieve hemoglobinegehalte, anemie en het aantal bloedtransfusies gedurende opname waren geassocieerd met het optreden van het delier. De uitkomsten na delier waren indrukwekkend door het optreden van complicaties, langere opnameduur, ontslag naar het verpleeghuis na opname, en een toename van de mortaliteit.

Delier trad op in 7 patiënten die een open herstel ondergingen (27%) en in een enkele patiënt die een Endovascular Aneurysm Repair (EVAR) onderging (4%; *p*=0.050). Patiënten ontwikkelde een delier vaker na een laparotomie (20%) vergeleken met patiënten die een laparoscopische operatie ondergingen (8%; *p*=0.024).

Ondanks het minimale invasieve karakter van de EVAR werden in de grote RCT-studies geen superioriteit aangetoond voor geplande AAA-chirurgie. Echter, er werd geen rekening gehouden met de delier-gerelateerde kosten in de kosten analyse in deze studies. Bij oudere patiënten is duurdere, minder invasieve chirurgie als EVAR en laparoscopie verdedigbaar als eerste keuze vergeleken met meer invasieve procedures.

Vaatpatiënten worden vaak gezien als kwetsbaar en als hoog risicopatiënten voor delier. Wij evalueerden de incidentie van delier en onderzochten onafhankelijke risicofactoren in de verschillende patiëntgroepen in de dagelijkse vaatpraktijk **(Hoofdstuk 7)**. Patiënten opgenomen met kritieke ischemie, diabetische voet, AAA en patiënten die een carotis desobstructie ondergingen werden geïncludeerd voor deze studie. Patiënten met kritieke ischemie werden in deze studie geïdentificeerd als het meest kwetsbaar. Van de patiënten met kritieke ischemie die een delier ontwikkelde (indidentie 24%) was 53% 80-plusser.

Aanvullend werd een gedetailleerd onderzoek verricht naar delier bij patiënten met kritieke ischemie **(Hoofdstuk 8)**. Tweeënnegentig oudere patiënten (≥65 jaar) die een operatie ondergingen werden geïncludeerd in deze studie met als doel onafhankelijke voorspellende factoren te

identificeren voor het optreden van delier. De incidentie van delier was 32% en bij 59% van deze patiënten ontwikkelde delier zich reeds in de pre-operatieve fase. Ondervoeding en diabetes mellitus werden geïdentificeerd als onafhankelijke risicofactoren. Delier was gerelateerd aan een langer ziekenhuisverblijf en een verhoogde mortaliteit na zes maanden (34% met delier versus 8% zonder delier). De delier-gerelateerde extra opnameduur leidde tot een toename van de zorgkosten van €1519 per delier.

ONDERZOEK IN DE TOEKOMST

Kwetsbaarheid en de rol van conservatieve behandeling bij ouderen

Op alle fronten is meer onderzoek nodig naar de rol van conservatieve behandeling bij chirurgisch kwetsbare patiënten en de behandeling en preventie van delier. De vergrijzing in de westerse wereld en de toename van het aantal kwetsbare ouderen met ernstige comorbiditeit zijn belangrijke uitdagingen voor zorgverleners. De resultaten van conservatieve behandeling voor verschillende ziekten waarvoor in niet-belaste patiënten chirurgisch ingrijpen zou worden verricht, zijn beschreven in dit proefschrift. De sleutel in de besluitvorming om een operatie uit te voeren is de juiste selectie van patiënten. Deze keuze moet niet worden gemaakt op basis van de leeftijd van de patiënt alleen, maar moet mede worden gemaakt door comorbiditeit- en de wensen van de patiënt te betrekken. Daarnaast moet bij oudere, kwetsbare patiënten de doelmatigheid van een uitgebreide operatie worden afgewogen. Het verdient aanbeveling om een conservatieve, of palliatieve behandeling, altijd te overwegen als behandelingsmogelijkheid. Dit geldt met name bij kwetsbare oudere patiënten, waarbij herstel na een uitgebreide operatie onwaarschijnlijk wordt geacht. Meer onderzoek is nodig om de uitkomsten van conservatieve behandeling vast te stellen en het inzicht te verbeteren op de impact van de kwaliteit van leven. Het vastleggen en meten van factoren die de kwetsbaarheid van de patiënten omvatten zijn nodig om risicopatiënten te identificeren. Uitkomsten kunnen dan beter worden voorspeld en de klinische besluitvorming kan worden onderbouwd

Delier en chirurgie

Meer wetenschappelijk onderzoek naar het concept en de pathogenese van delier is nodig en zal mogelijk leiden tot een beter begrip hoe de verschillende risicofactoren met elkaar samenhangen bij het ontstaan van delier. Preventie en risicobepaling moet worden verfijnd en getest in andere chirurgische populaties. Om beter inzicht te krijgen in de lange termijneffecten van delier zijn studies met een langere follow-up duur noodzakelijk.

In de huidige wetenschap, literatuur en dagelijkse praktijk is de 30-dagen mortaliteit een belangrijke parameter. De 6-maanden mortaliteit na delier die worden beschreven in de proefschrift is aanzienlijk. De korte termijn resultaten zijn van minder belang indien uitgebreide interventies

bij kwetsbare ouderen wordt overwogen. De 6-maanden mortaliteit is waarschijnlijk een betere uitkomstmaat bij kwetsbare ouderen met een beperkte levensverwachting.
Aangezien de incidentie van delier hoog is bij ouderen die chirurgie ondergaan, valt te verwachten dat er in de toekomst delier een groter probleem zal worden. Onderwijs en kennis over het delier zal uitgebreid moeten worden bij alle betrokken zorgverleners.
De meest effectieve en doelmatige methode in de behandeling van delier is gericht op preventie. Meerdere studies hebben aangetoond dat delier te voorkomen is door het uitvoeren van preventieve niet-medicamenteuze maatregelen gedurende opname. Echter, patiënten worden in de dagelijkse praktijk vaak opgenomen op de dag van de operatie, en op dat moment gescreend op kwetsbaarheid en risico op delier. Het effect van preventieve acties die dan worden genomen is logischerwijs klein door de korte periode die resteert voor de operatie.
Het identificeren van patiënten met een hoog risico voor delier tijdens de poliklinische fase kan effectiever zijn. Preventieve maatregelen kunnen dan eerder worden uitgevoerd en mogelijk zal dit leiden tot een afname in de incidentie van delier. Verder zullen delier-gerelateerde uitkomsten als morbiditeit, mortaliteit en opnameduur verbeteren.
Een multidisciplinair team van specialisten kan in de poliklinische setting patiënten screenen op kwetsbaarheid en het risico voor delier inschatten. Vervolgens kunnen beïnvloedbare risicofactoren voor het delier worden behandeld. Proactieve consultatie van de geriater hebben bewezen de ernst en de incidentie van het delier te verminderen. Dit werd bewerkstelligd door pre- en postoperatieve adviezen te geven, en medicatie te saneren[11, 42, 43]. Vroege detectie en behandeling van ondervoeding, en het in een betere fysieke conditie brengen van de patiënt in de pre-operatieve fase kan worden bereikt door diëtisten en fysiotherapeuten in te zetten. Pre-operatieve anemie komt veel voor bij ouderen die een operatie moeten ondergaan, en er lijkt een relatie met het delier[44]. Het effect van pre-operatief verhogen van hemoglobine gehalte moet worden onderzocht, dit zou mogelijk een bedrage kunnen leveren in delierpreventie.

Chapter 11

List of publications
PhD Portfolio
Acknowledgements (dankwoord)
Curriculum Vitae Auctoris
List of publications
Publications (this thesis):

LIST OF PUBLICATIONS

- Conservative treatment in selected patients with severe critical limb ischemia.
  AR Thomas, **JW Raats**, MMA Lensvelt, HGW de Groot, GH Ho, EJ Veen, L van der Laan
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PhD Portfolio

Name PhD student: Jelle Raats
Erasmus MC Department: Surgery

PhD period: 2013-2016
Promotor: Prof. dr. J.N.M. IJzermans
Supervisors: dr. L. van der Laan

1. PhD training

	Year	Workload (Hours/ECTS)
General academic skills		
Monthly research meeting, Breda	2013-2015	2
Seminars		
Vascular rounds	2015	1
Presentations poster		
National scientific poster presentations	2014	1
Presentations oral		
National scientific presentations	2014	5
National scientific presentations	2015	2
International scientific presentations	2014,2016	5
Specific courses		
International Summer Course - Biology of Ageing	2014	3
(Inter)national conferences		
National conferences	2013	2
National conferences	2014	3
National conferences	2015	2
International conferences	2014, 2016	5
National conferences	2016	1

2. Teaching activities

	Year	Workload (Hours/ECTS)
Supervising practicals and excursions, tutoring		
Supervising/teaching medical students	2013-2016	1
Supervising:		
S.L. Steunenberg	2015-2016	2

ACKNOWLEDGEMENTS (DANKWOORD)

Allereerst mijn promotor, Prof. dr. J.N.M. IJzermans. Bedankt voor uw vertrouwen in mij en bedankt voor uw steun en bijdrage aan dit proefschrift. Ik hoop dat de samenwerking in de toekomst kan worden voortgezet hetzij op wetenschappelijk gebied dan wel tijdens mijn opleiding in het Erasmus MC.

Mijn copromotor, Dr. L. van der Laan. Beste Lijckle, voor het eerst heb ik u ontmoet tijdens mijn sollicitatiegesprek voor een baan als ANIOS in het Amphia ziekenhuis. Een gesprek waar mij al snel duidelijk werd dat er mogelijkheden waren voor het verrichten van wetenschappelijk onderzoek. "Welkom bij de club" waren uw woorden toen u mij belde en vertelde dat ik was aangenomen. Na de eerste maanden gewerkt te hebben als ANIOS kwam u met een mooi voorstel voor een promotietraject. Er volgde een periode waarin ik mijzelf wetenschappelijk kon ontwikkelen, wat uiteindelijk heeft geresulteerd in dit proefschrift. Dit is gelukt mede door uw inspanningen, waarin u een omgeving heeft gecreëerd waarin ik optimaal kon presteren. Mijn dank hiervoor is groot. Ook bedankt voor alle momenten waarop wij van gedachten konden wisselen onder het genot van een kopje Nespresso. Bedankt voor alle roosterkunsten die we hebben uitgehaald om mij vrij te plannen voor het verrichten van wetenschappelijk onderzoek gedurende mijn ANIOS-periode. Bedankt voor alle (on)mogelijke deadlines waardoor de vaart er goed in bleef. De mooiste momenten blijven toch de presentaties op de internationale congressen waar ik de wetenschappelijke resultaten van de onderzoeken mocht presenteren. Zowel in Zuid-Afrika als in Londen voelde ik mij bijzonder gesteund door uw aanwezigheid. Op deze reizen hebben we veel plezier gehad en hebben wij elkaar beter leren kennen. Ondertussen ben ik begonnen aan de opleiding tot chirurg, het mooiste vak ter wereld. In de toekomst hoop ik nog veel te mogen leren, en ik kijk uit naar verdere samenwerking op wetenschappelijk terrein en in de operatiekamer. Ik wil u bedanken voor alle kansen die ik heb gekregen en de steun die ik heb gevoeld gedurende de promotie.

Ook wil ik de leescommissie, Prof. dr. D.A.M.P.J. Gommers, Prof. dr. C. Verhoef en prof. dr. H. van Goor, bedanken voor het beoordelen van dit proefschrift en het zitting nemen in de oppositie.

Tevens dank ik Prof. dr. J.A.M. Zeebregts, Dr. R.J. Osse en Dr. F.U.S. Mattace Raso voor hun zitting als opponent in de promotiecomissie.

Beste Prof. dr. E.W. Steyerberg. Bedankt voor uw bijdrage aan mijn proefschrift. Ik ben erg onder de indruk van uw statische kennis en het feit dat u uit het hoofd schattingen kan maken van p-waarden met een indrukwekkende precisie.

Beste Dr. G.H. Ho. Bedankt voor alle tips en trucs die ik heb mogen leren over het visite lopen, het presenteren van wetenschappelijke artikelen, en het schrijven van een korte logische Engelstalige zin.

Beste Hans Flu, Rutger Thomas en Wilbert van Eijsden, beste medeauteurs, bedankt voor jullie bijdrage aan de wetenschappelijke artikelen die wij onder een zeer prettige samenwerking hebben mogen schrijven. We hebben veel gelachen en plezier gehad gedurende het schrijven.

Beste chirurgen van het Amphia, allen bedankt voorn jullie steun en ondersteuning. Ik ben dankbaar voor de mooie samenwerking die wij hebben.

Beste Jan van Trier, bedankt voor je ondersteuning bij het vinden van wetenschappelijke artikelen. Ik wil je bedanken voor de gesprekken onder het genot van een kopje koffie, die wat afleiding gaven op de momenten waarop ik het helemaal zat was in de medische bibliotheek.

Beste secretaresses, beste Jaqueline, beste Carola, dank voor jullie hulp bij de vele dingen die geregeld moesten worden gedurende het schrijven en afronden van dit proefschrift.

Beste Nathalie Verbogt, bedankt voor al je hulp tijdens het verzamelen van data en gegevens voor de KOP-studie.

Beste assistenten uit het Amphia ziekenhuis. Bedankt voor alle momenten van ontspanning en vertier gedurende mijn periode in Breda. Dankzij jullie collegialiteit heb ik hard kunnen werken aan dit proefschrift.

Beste verpleegkundigen van afdeling 46 uit het Amphia Ziekenhuis. Ik ben jullie bijzonder dankbaar voor het geduld en bemoedigende woorden op de momenten dat ik het niet meer zag zitten tijdens de ochtendvisite. Dankzij jullie inzet en medewerking heeft mijn onderzoeksperiode geresulteerd in dit proefschrift.

Beste wond&decubitus-verpleegkundigen van het Amphia ziekenhuis, bedankt voor al jullie ondersteuning op de afdeling gedurende mijn periode in het Amphia ziekenhuis.

Beste voetbalvrienden. De gesprekken in de kleedkamer zijn kansloos en gaan helemaal nergens over. Dit relativeert en is gymnastiek voor het brein waardoor er vervolgens beter gepresteerd kan worden. Nogmaals excuus voor alle momenten dat ik er niet heb kunnen zijn waardoor wij die wedstrijden natuurlijk hebben verloren.

Beste vrienden en stapmaten. Het schrijven van dit proefschrift is voor een groot deel geschreven in mijn vrije tijd. Bedankt voor alle momenten van ontspanning en steun die ik van jullie heb gekregen.

Beste Paranimfen, Jasper en Karel.
Jasper, voor het eerst heb ik je ontmoet in Zuid-Afrika toen wij daar stage liepen op de trauma afdeling in Kaapstad. We waren beide enthousiast over de heelkunde en kwamen toevallig beide in het Amphia terecht. Daar zijn wij goede collega's en vrienden geworden. Er is geen enkele twijfel dat jij mijn paranimf moest worden. We hebben elkaar door weer en wind gesteund in onze promotietrajecten en ons doel om chirurg te worden.
Karel, vanaf het eerste jaar Geneeskunde mijn vriend. Wie had ooit gedacht dat wij het zouden schoppen tot anesthesist en chirurg in spe. De surfvakanties die wij hebben gehad tijdens mijn promotie-traject waren een welkom moment van ontspanning. Geweldig dat jij altijd voor mij klaar staat.

Beste Koen, Rens en Jochem. Broeders, wat ben ik blij met jullie. Wat kunnen lachen met elkaar en staan altijd voor elkaar klaar. Door jullie blijf ik met beide benen aan de grond staan.

Beste Pa en Ma, wat heb ik toch geluk met jullie als mijn ouders. Onvoorwaardelijke liefde en steun. Ik kan werkelijk altijd bij jullie terecht, altijd staan jullie voor mij klaar. Ik hou van jullie.

Mijn allerliefste Liz. Het slotwoord is voor jou. Tijdens het schrijven van dit proefschrift heb ik ongelofelijk veel van je gevraagd. Zonder jouw steun was mij dit niet gelukt. Altijd sta jij voor mij klaar. Ondanks je drukke werk als advocaat weet jij je weg te cijferen voor mij. Ik hou van jou met heel mijn hart, en kijk uit naar alle mooie momenten in de toekomst die wij met elkaar gaan beleven.

CURRICULUM VITAE AUCTORIS

The author of this thesis, Jelle Raats, was born on the 17th of September 1988 in Oosterhout, the Netherlands. During his childhood he lived in Amersfoort where he graduated high school at the "t Hooghe Landt College" in 2006. After graduation, he continued to at the Erasmus University Rotterdam where he studied Medicine. During his studies and internships he developed an interest in surgery. After a surgical internship in South-Africa he completed his medical degree in 2013 and started his career as an uncredited surgical resident (ANIOS) at the Amphia Hospital in Breda. In this period he started his research projects in surgery which laid the foundation of this thesis. His work was conducted under the supervision of Prof. dr. J.N.M. IJzermans and dr. L. van der Laan. Within this project he conducted studies on elderly surgical patients. The role of conservative therapies in frail elderly patients in need for (extensive) surgery were explored. Also, delirium incidence and predictive factors of delirium in elderly patients having surgery were examined. In January 2016 he was admitted to the surgical training program of the Erasmus Medical Centre in Rotterdam and started his training in the Maasstad hospital in Rotterdam.

De auteur van dit proefschrift, Jelle Raats, werd op 17 september 1988 geboren in Oosterhout, Nederland. Zijn jeugd en middelbare schoolperiode bracht hij door in Amsersfoort waar hij uiteindelijk in 2006 zijn diploma behaalde aan t Hooghe Landt College. Aansluitend ging hij Geneeskunde studeren aan de Erasmus Universiteit in Rotterdam. Tijdens zijn studie en coschappen ontwikkelde hij een sterke interesse in de Heelkunde. Na een coschap in Zuid-Afrika behaalde hij zijn artsendiploma in 2013 en startte hij zijn carrière als arts-assistent niet in opleiding tot specialist (ANIOS) in het Amphia ziekenhuis in Breda. In deze periode startte hij zijn onderzoek naar kwetsbaarheid en ouderen bij chirurgische patiënten, wat de basis is van dit proefschrift. Zijn werk is verricht onder supervisie van Prof. dr. J.N.M. Ijzermans en dr. L. van der Laan. Binnen dit onderzoeksproject evalueert hij de rol van een conservatieve behandelingen bij fragiele oudere patiënten die een operatie zouden moeten ondergaan. Daarnaast wordt het delier en de gerelateerde risicofactoren geëvalueerd bij oudere chirurgische patiënten. De resultaten hiervan worden gepresenteerd in dit proefschrift. In 2014 vervolgde hij zijn assistentschap in het Erasmus Medisch Centrum in Rotterdam waarna hij solliciteerde voor de opleiding tot chirurg. In januari 2016 werd hij aangelopen in het Eramus Medisch Centrum vanwaar hij zijn opleiding startte in het Maasstad Ziekenhuis in Rotterdam.