Frailty and postoperative functional outcome

Preoperative evaluation in elderly cardiac surgery patients

Lisa Verwijmeren

Frailty and postoperative functional outcome

Preoperative evaluation in elderly cardiac surgery patients

Lisa Verwijmeren

Author: Lisa Verwijmeren

Cover design: Susanne van den Heuvel www.susannevandenheuvel.nl
Layout & printing: Guus Gijben www.proefschrift-aio.nl

ISBN: 978-94-93184-76-3

Paranymphs: Eefje Hendriks
Annemarie Brouwers

Committee: Prof. dr. J.J.M. Van Delden
Prof. dr. M. Muller
Prof. dr. P.A.F.M. Doevendans
Prof. dr. R.G. Hoff
Prof. dr. R.J.M. Klautz

Frailty and postoperative functional outcome

Preoperative evaluation in elderly cardiac surgery patients

Kwetsbaarheid en postoperatieve functionele uitkomsten

Preoperatieve evaluatie van oudere hartchirurgische patiënten

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus, prof.dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

dinsdag 19 januari 2021 des middags te 2.30 uur

door

Lisa Verwijmeren

geboren op 14 november 1987
te Tilburg

Promotor: Prof. dr. W.A. van Klei

Copromotoren: Dr. P.G. Noordzij
Dr. H.P.A. van Dongen

Dit proefschrift werd mede mogelijk gemaakt met financiële steun van de Afdeling *Research and Development* van de maatschap Anesthesiologie, Intensive Care en Pijnbestrijding van het Sint Antonius Ziekenhuis, Nieuwegein, de Nederlandse Hartstichting en de raad van bestuur van het Sint Antonius Ziekenhuis, Nieuwegein.

table of content

Chapter 1

General introduction

Ageing of the surgical population

Populations are rapidly ageing. In 2020, 14% of the Dutch population is aged 70 years or older. It is estimated that this number will increase over the next 20 years to a peak of 20% in 2040. The number of persons aged 70 year or older will increase with almost 1.4 million individuals during the next two decades.[1] In addition to population ageing, medical technology has advanced. Innovations in perioperative medicine have made surgical procedures safer and reduced postoperative mortality rates. Therefore, high-risk procedures, such as cardiac surgery, have become increasingly safe for elderly patients. However, older age remains associated with an increased risk for postoperative morbidity and mortality. Prior to surgery preoperative physicians weigh risks and benefits of a procedure to propose the most suitable treatment. Age alone is a poor predictor of surgical outcome. When comorbidities are taken into account, the association of age with postoperative adverse outcome is weak. And, even very old patients can benefit from surgery.[2,3] Currently there is an unmet need for a preoperative risk assessment tailored to the elderly patient that aids risk stratification and decision making.

A clinical case of an elderly patient referred for cardiac surgery is presented in Box 1 and will serve as an example throughout this introduction.

Prior to surgery, patients routinely visit the preoperative anaesthesia outpatient clinic. Preoperative anaesthesia assessment is aimed at revealing the presence and extent of comorbidity. This information, combined with procedure specific risk, is used to predict adverse postoperative outcomes. Especially in elderly patients, accurate preoperative risk stratification is important to make the right treatment decisions and fully inform the patient.[4] Additionally, high risk patients may benefit from prehabilitation.[5] In addition to clinical judgement, prognostic models are available to predict adverse events after cardiac surgery. Over the past two decades risk factors for poor outcome in elderly patients have been increasingly investigated in surgical populations to improve preoperative risk stratification. However, commonly used tools, i.e. EuroSCORE II, Parsonnet score, or Society of Thoracic Surgeons score (STS) are not specifically designed for older patients and often perform poorly.[6–9] Advanced age is associated with comorbidity and with limitations in somatic, physical, mental and social functioning which impair functional capacity. Reduced functional capacity leads to a loss of homeostasis (the ability of the body to maintain internal equilibrium after experiencing a stressor).[10–13] This process is highly variable between individuals and there is important heterogeneity of functional capacity in patients of similar chronological age. A routine preoperative screening (Box 1) properly assesses comorbidity but provides limited insight into functional capacity. Frailty screening can quantify this heterogeneity and addition of a frailty screening to preoperative screening could fill this void.

Box 1. Clinical scenario

A seventy-eight-year old patient visited the anaesthesia outpatient clinic, accompanied by his daughter, for a preoperative assessment prior to coronary artery bypass grafting and concomitant aortic valve replacement. His clinical signs were shortness of breath and chest pain with strenuous exercise (walking up two flights of stairs), receding after a short rest. He was living independently, with help from his daughter to manage his daily medication and household chores. Physical examination showed no abnormalities, besides a known cardiac murmur. His medical history included hypertension, severe aortic valve stenosis (peak gradient 65 mmHg, aortic valve area <1.0 $cm^{2)}$, diabetes mellitus (non-insulin dependent), and a reduced cardiac function (estimated left ventricular ejection fraction 25%). Medical therapy was aimed at managing his cardiac comorbidities and diabetes mellitus, and consisted of six different drugs (antiplatelet therapy, anti-hypertensive drug, statin, oral antidiabetic drugs, and a proton pump inhibitor). Laboratory results showed no signs of anaemia (haemoglobin 8.1 mmol/l) or renal dysfunction (estimated glomerular filtration rate 73 ml/min/1.73m^2).

The patient was approved for cardiac surgery and underwent combined coronary artery bypass grafting and aortic valve replacement four weeks after preoperative screening. Surgery was successful and the patient was transferred to the Intensive Care Unit for postoperative care. After two days he was transferred to the general ward for further recovery. Despite an uncomplicated postoperative course his hospital stay of 11 days was longer than average.

Inquiries at three months after surgery revealed that his overall health had slightly decreased since the surgical procedure. He was able to perform ordinary daily activities, but his endurance was limited when performing more demanding activities, such as longer walks or walking stairs. He experienced difficulties with prolonged concentration (i.e. reading a newspaper). After his surgery he spend more time on maintaining his health. After one year, his physical performance had improved further, and he was able to complete long walks without physical complaints. Overall, he reported an improvement in physical health related quality of life and equal mental health related quality of life.

Frailty

Frailty can be described as "*a biologic syndrome of decreased functional reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, thereby causing vulnerability to adverse outcomes*".[13] The syndrome of frailty is closely related to comorbidity and disability, and often occurs simultaneously.[14] The aetiology of frailty is largely unknown, but contributing factors include malnutrition, muscle wasting, fatigue, sarcopenia, chronic inflammation, immuno-senescence, and hormonal deficits.[13,15]

Assessment of frailty can be performed in several ways. In surgical literature up to forty different methods have been described.[16] Choosing the most suitable method for preoperative practice is difficult. Currently, the gold standard to assess frailty is a full geriatric assessment. Accumulations of deficits on the somatic, physical, mental, and social domain lead to a diagnosis of frailty. *Figure 1* shows the four domains with examples of corresponding characteristics. However, a full geriatric assessment is time consuming. Given the rise in elderly patients, and the already high workload of medical professionals, this seems unfeasible for most clinics. In cardiac surgery, frailty is often measured with a single frailty characteristic (i.e. nutritional status, grip strength or gait speed) or a frailty scale (i.e. Clinical Frailty Scale, Fried Score, or Edmonton Frail Scale).[17–22] The measurement of a single frailty characteristic is efficient and easily performed. However, a single feature does no justice to the multidimensional aspect of frailty. Most frailty scales incorporate several frailty domains, but patient specific risk factors cannot be identified from a single score. Ideally, preoperative frailty screening is quick, inexpensive, and aimed at identifying risk factors that facilitate prehabilitation. For our patient described in box 1, regular anaesthesia screening offered no specific areas of prehabilitation. Screening for frailty could, for example, reveal nutritional deficits or mobility impairments which might be altered by a dietician or physical therapist.

In addition to traditional determinants of complications or mortality, frailty has become an established risk factor for adverse outcomes after cardiac surgery. For example, frail patients had almost two-fold increased odds for mortality after cardiac surgery, and 1.6 to 4.9 fold higher odds for major complications.[10,12,18,23,24] However, associations are dependent on the type of surgery and the tests that are used to diagnose frailty.

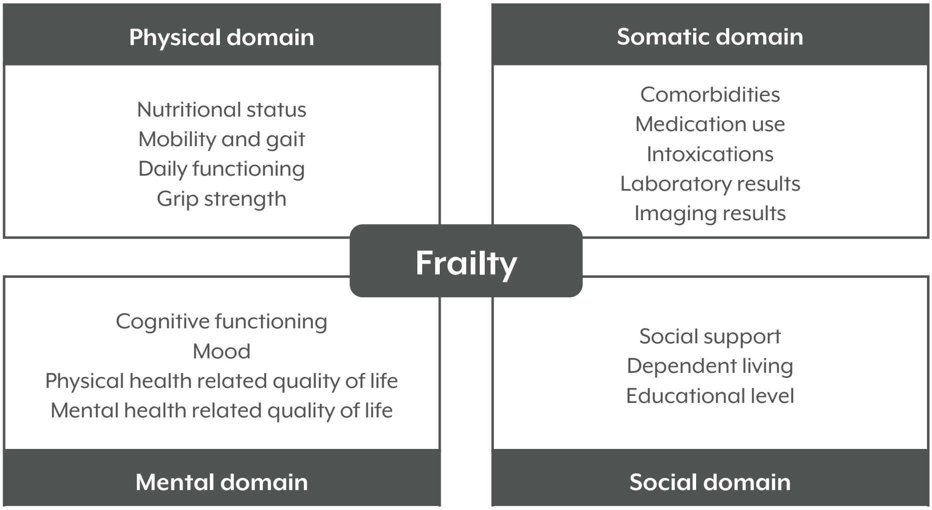


Figure 1. Frailty domains and several examples of characteristics.

Patient reported outcome measures

The general purpose of (cardiac) surgery is to improve survival and alleviate symptoms from chronic (cardiac) disease. However, apart from perioperative complications or mortality, a considerable proportion of patients experience a loss in health related quality of life (HRQL) or has difficulties in functioning after cardiac surgery. Loss in HRQL occurs in 8 to 20% of patients, and disabilities are present in 9 to 29% after one year.[24–29] For example, the patient in our clinical example reported an overall improvement of his health three months after his surgery, but still experienced some disability regarding mobility and concentration. Surveys among patients with cardiovascular disease revealed that four out of five patients value quality of life over longevity.[12] A loss in HRQL, or new disabilities should therefore be considered as an unfavourable outcome of surgery. Traditionally, research focussed on survival, length of stay or complications. Most risk scores were designed to predict mortality.[6,8] But, focussing on these outcomes creates an incomplete evaluation of a patients overall health after cardiac surgery. Some studies have attempted to identify preoperative determinants for long term HRQL or disability.[26,30–32] Unfortunately, readily available patient characteristic such as age, sex, comorbidities, laboratory values, or imaging results have not led to improved preoperative risk stratification for patient reported outcomes.[26,30–32] A knowledge gap still exists on functional outcomes of elderly patients after cardiac surgery and preoperative factors contributing to HRQL or disability.

Thesis objective

The aim of this thesis is to assess the associations of frailty characteristics and functional outcomes after cardiac surgery in elderly patients. More specifically, the aim is to identify which frailty characteristics are associated with worse HRQL or disability after one year. Additionally, the preoperative determinants of common postoperative complications (cardiac surgery associated acute kidney injury (CSA-AKI) and delirium), and their impact on functional outcome after cardiac surgery are investigated.

Outline of this thesis

The next three chapters of this thesis focus on predicting postsurgical functional outcomes. **Chapter 2** describes how a change in HRQL after surgery can be predicted by using preoperative information. In **Chapter 3** the association of frailty characteristics on worse HRQL or disabilities was studied. **Chapter 4** describes how the association of frailty with disability after surgery can be used to guide preoperative multi-disciplinary team care. The following two chapters focus on postoperative complications after cardiac surgery. In **Chapter 5** the association of preoperative biomarkers and CSA-AKI is described. And, the influence of CSA-AKI on patient reported disability after one year. Frailty as a predictor for postoperative delirium and the long term effect of delirium on HRQL is investigated in **Chapter 6**. Finally, **Chapter 7** summarizes the overall conclusions and provides recommendations for clinical practice and further research.

References

1. Statline. Prognose bevolking; geslacht en leeftijd, 2020-2060. 17-12-2019. https://opendata.cbs.nl/statline/#/CBS/nl/dataset/84646NED/table?ts=1591866408680. Published 2019. Accessed June 11, 2020.
2. Fruitman DS, MacDougall CE, Ross DB. Cardiac surgery in octogenarians: can elderly patients benefit? Quality of life after cardiac surgery. *Ann Thorac Surg*. 1999;68(6):2129-2135.
3. Huber CH, Goeber V, Berdat P, Carrel T, Eckstein F. Benefits of cardiac surgery in octogenarians - a postoperative quality of life assessment. *Eur J Cardio-thoracic Surg*. 2007;31(6):1099-1105.
4. Whiteman AR, Dhesi JK, Walker D. The high-risk surgical patient: A role for a multi-disciplinary team approach? *Br J Anaesth*. 2016;116(3):311-314.
5. Chan SP, Ip KY, Irwin MG. Peri-operative optimisation of elderly and frail patients: a narrative review. *Anaesthesia*. 2019;74:80-89.
6. Nashef SAM, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg*. 1999;16(1):9-13.
7. Gogbashian A, Sedrakyan A, Treasure T. EuroSCORE: a systematic review of international performance. *Eur J Cardio-Thoracic Surg*. 2004;25(5):695-700.
8. Parsonnet V, Dean D, Bernstein AD. A method of uniform stratification of risk for evaluating the results of surgery in acquired adult heart disease. *Circulation*. 1989;79(6 Pt 2):I3-12.
9. O'Brien SM, Feng L, He X, et al. The Society of Thoracic Surgeons 2018 Adult Cardiac Surgery Risk Models: Part 2—Statistical Methods and Results. *Ann Thorac Surg*. 2018;105(5):1419-1428.
10. Lee DH, Buth KJ, Martin BJ, Yip AM, Hirsch GM. Frail patients are at increased risk for mortality and prolonged institutional care after cardiac surgery. *Circulation*. 2010;121(8):973-978.
11. Sepehri A, Beggs T, Hassan A, et al. The impact of frailty on outcomes after cardiac surgery: A systematic review. *J Thorac Cardiovasc Surg*. 2014;148(6):3110-3117.
12. Kim SW, Han HS, Jung HW, et al. Multidimensional frailty score for the prediction of postoperative mortality risk. *JAMA Surg*. 2014;149(7):633-640.
13. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: Evidence for a phenotype. *J Gerontol Med Sci*. 2001;56(3):146-164.
14. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the Concepts of Disability, Frailty, and Comorbidity: Implications for Improved Targeting and Care. *Journals Gerontol Ser A Biol Sci Med Sci*. 2004;59(3):M255-M263.
15. Betelli G. Chapter 2 Preoperative evaluation from Traditional Consultation to Comprehensive Geriatric Assessment: A 360 Perspective. In: Betelli G, ed. *Perioperative Care of the Elderly. Clinical and Organizational Aspects*. First. Cambridge: Cambirdge University Press; 2018:18.
16. McIsaac DI, Macdonald DB, Aucoin SD. Frailty for Perioperative Clinicians: A Narrative Review. *Anesth Analg*. 2020;130(6):1450-1460.
17. Unosawa S, Taoka M, Osaka S, et al. Is malnutrition associated with postoperative complications after cardiac surgery? *J Card Surg*. 2019;34(10):908-912.
18. Afilalo J, Mottillo S, Eisenberg MJ, et al. Addition of frailty and disability to cardiac surgery risk scores identifies elderly patients at high risk of mortality or major morbidity. *Circ Cardiovasc Qual Outcomes*. 2012;5(2):222-228.
19. Afilalo J, Eisenberg MJ, Morin J-F, et al. Gait speed as an incremental predictor of mortality and major morbidity in elderly patients undergoing cardiac surgery. *J Am Coll Cardiol*. 2010;56(20):1668-1676.

20. Reichart D, Rosato S, Nammas W, et al. Clinical frailty scale and outcome after coronary artery bypass grafting. *Eur J Cardio-Thoracic Surg*. 2018;54(6):1102-1109.

21. Nakano M, Nomura Y, Suffredini G, et al. Functional Outcomes of Frail Patients After Cardiac Surgery. *Anesth Analg*. 2020;130(6):1534-1544.

22. Amabili P, Wozolek A, Noirot I, et al. The Edmonton Frail Scale Improves the Prediction of 30-Day Mortality in Elderly Patients Undergoing Cardiac Surgery: A Prospective Observational Study. *J Cardiothorac Vasc Anesth*. 2019;33(4).

23. Sündermann S, Dademasch A, Praetorius J, et al. Comprehensive assessment of frailty for elderly high-risk patients undergoing cardiac surgery. *Eur J Cardiothorac Surg*. 2011;39(1):33-37.

24. Afilalo J, Lauck S, Kim DH, et al. Frailty in Older Adults Undergoing Aortic Valve Replacement. The FRAILTY-AVR Study. *J Am Coll Cardiol*. 2017;70(6):689-700.

25. Hosler QP, Maltagliati AJ, Shi SM, et al. A Practical Two-Stage Frailty Assessment for Older Adults Undergoing Aortic Valve Replacement. *J Am Geriatr Soc*. 2019;67(10):2031-2037.

26. Sun LY, Tu J V., Lee DS, et al. Disability-free survival after coronary artery bypass grafting in women and men with heart failure. *Open Hear*. 2018;5(2):1-12.

27. Blokzijl F, van der Horst ICC, Keus E, Waterbolk TW, Mariani MA, Dieperink W. Quality of life in elder adults one-year after coronary bypass. *J Vasc Nurs*. 2016;34(4):152-157.

28. Hoogerduijn JG, Buurman BM, Korevaar JC, Grobbee DE, De rooij SE, Schuurmans MJ. The prediction of functional decline in older hospitalised patients. *Age Ageing*. 2012;41(3):381-387.

29. Shan L, Saxena A, McMahon R, Newcomb A. Coronary artery bypass graft surgery in the elderly: A review of postoperative quality of life. *Circulation*. 2013;128(21):2333-2343.

30. Kurfirst V, Mokráček A, Krupauerová M, et al. Health-related quality of life after cardiac surgery - the effects of age, preoperative conditions and postoperative complications. *J Cardiothorac Surg*. 2014;9(1):1-8.

31. Grady KL, Lee R, Subačius H, et al. Improvements in Health-Related Quality of Life Before and After Isolated Cardiac Operations. *Ann Thorac Surg*. 2011;91(3):777-783.

32. Rumsfeld JS, Ho PM, Magid DJ, et al. Predictors of health-related quality of life after coronary artery bypass surgery. *Ann Thorac Surg*. 2004;77(5):1508-1513.

Chapter 2

Preoperative determinants of quality of life a year after coronary artery bypass grafting: a historical cohort study

Lisa Verwijmeren
Peter G Noordzij
Edgar J Daeter
Bas van Zaane
Linda M Peelen
Eric P A van Dongen

J Cardiothorac Surg. 2018; 13: 118

Abstract

Background: Health related quality of life (HRQL) is an important patient related outcome measure after cardiac surgery. Preoperative determinants for postoperative HRQL have not yet been identified, but could aid in preoperative decision making. The aim of this article is to identify associations between preoperative determinants and change in HRQL one year after coronary artery bypass grafting (CABG).

Methods: Single centre retrospective cohort study in 658 patients. Change in HRQL was defined as a decrease or increase of ≥5 points on the physical or mental domain of the Short Form 12 (SF-12) questionnaire. Patients were stratified in three groups according to worse, unchanged, or better HRQL. Multinomial logistic regression analysis was used to investigate the association between preoperative risk factors and postoperative change in HRQL.

Results: Physical HRQL improved in 22.8% of patients, did not change in 61.2% of patients and worsened in 16.0% of patients. Comorbidities associated with change in physical HRQL were a history of stroke, atrial fibrillation, vascular disease or pulmonary disease. Most important risk factor for change in physical HRQL was preoperative HRQL. Higher preoperative SF-12 score decreased the odds for worse physical HRQL and increased the odds for better physical HRQL. Mental HRQL improved in 49.8% of patients, remained unchanged in 34.5% of patients and worsened in 15.7% of patients. Preoperative HRQL was an important risk factor for a change in mental HRQL. Higher preoperative physical HRQL increased the odds for improved mental HRQL. Lower preoperative mental HRQL increased the odds for better mental HRQL.

Conclusions: One year after CABG the majority of patients experiences equal or improved HRQL compared to before surgery. Most important preoperative risk factor for change in HRQL is preoperative HRQL.

Introduction

In the past years the population of patients referred for coronary artery bypass grafting (CABG) changed to an older and more complex population.[1–3] Assumed causes are an increased life expectancy and improvements in surgical and anaesthetic techniques, making it possible for elderly high risk patients to undergo surgery.[1,2] Even though CABG is considered safe for elderly patients, a considerable risk for complications or mortality remains.[4] Especially in more complex patients a tailored approach is needed in which health benefits are weighed against risk of complications. Risk stratification tools like the European System for Cardiac Operative Risk Evaluation (euroSCORE), Parsonnet score or the American College of Surgeons Risk Calculator can aid in estimating outcome after surgery.[5–7] However, these tools were developed to predict morbidity or mortality, not health related quality of life (HRQL).[8] In general, HRQL improves after cardiac surgery, but it is known that 8-19% of patients experiences a decrease in HRQL.[9] In addition to the traditional outcome parameters of major morbidity or mortality, information on patient-perceived postoperative HRQL is crucial for full informed consent prior to surgery. To optimize preoperative risk-assessment and facilitate shared decision making, more accurate data on risk factors that influence postoperative HRQL are needed. This study aims to identify which preoperative determinants are associated with a clinically relevant change in HRQL one year after CABG.

Materials and Methods

Design

This was a single centre retrospective cohort study. Since patients were not subjected to investigational actions and were treated according to standard guidelines the need for informed consent was waived by the local review board of the ethical committee (Medical research Ethics Committee United, number W15.069). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Population

All patients older than 18 years who underwent elective isolated CABG between the first of July 2011 and the first of May 2014 were eligible for inclusion. Inclusion criteria were a completed medical outcomes study Short Form (SF) 12 version 2 questionnaire at baseline and at twelve months after CABG. Surgical procedures were performed by multiple cardiothoracic surgery consultants and their supervised trainees in a tertiary referral hospital (St. Antonius Hospital, Nieuwegein, The Netherlands). Perioperative care was carried out according to standard clinical practice and based on international guidelines for all patients.[10]

Clinical characteristics and data collection

As potential determinants for postoperative HRQL patient characteristics, medical history and comorbidities, preoperative laboratory tests and preoperative HRQL were considered.

Data on age, gender, body mass index and preoperative laboratory tests were collected from the routine preoperative anaesthesia visit. Medical history, additive euroSCORE and postoperative complications were collected from the hospital's electronic database for cardiac surgery patients. Registration of postoperative complications was conducted in the context of a national registry of cardiac interventions in The Netherlands (Supervisory Committee for Cardiac Interventions (Begeleidingscommissie Hartinterventies Nederland).[11] Intraoperative data was collected from the computerized medical record (MetaVision 5.46.44, iMDsoft®, Düsseldorf, Germany). A manual review of the data was performed to check for accuracy and missing values by a member of the research team (LV). Missing data on laboratory values, medication use and surgical characteristics were fully completed by manually checking electronic patient records.

Outcomes

Primary outcome was change in HRQL 12 months after surgery measured with the SF-12 before surgery and at one year after surgery. The SF-12 is derived from the SF-36, a widely validated questionnaire including 36 questions on physical and mental well-being.[12] The SF-12 is a validated shorter version with 12 questions.[13] Questions include, but are not limited to items relating to overall health perception, being able to exercise, feeling at ease or feeling full of energy. Answers on these twelve items are converted into two norm-based scores ranging from 0 to 100, representing physical and mental HRQL[14] Higher scores represent better HRQL. Additional file, table 1 presents reference scores for the Dutch population.

Secondary outcome was a composite endpoint of any complication and defined as one or more of the following; new atrial fibrillation defined as rhythm disturbance requiring treatment including reanimation, defibrillation or medication; re-sternotomy, defined as reoperation requiring opening of the sternum; myocardial infarction, defined as presence of ≥2 of the following symptoms: prolonged typical chest pain, ≥ten-fold increase of cardiac enzyme levels, and new wall motion abnormalities and/or changes in two or more leads in at least two consecutive ECGs; deep sternal wound infection, defined as requiring surgical drainage or fixation, positive wound cultures or antibiotic therapy; and ischemic stroke, defined as an acute episode of cerebral, spinal or retinal dysfunction caused by infarction of the central nervous system lasting >72 hours.

Procedures

As part of routine care, SF-12 questionnaires were sent by mail to all patients before surgery and were collected at the time of hospital admission. Twelve months after the operation a questionnaire was sent by email to each surviving patient. This study was carried out as a retrospective analysis of data collected for quality assessment purposes. In this process no second request was made to retrieve a missing questionnaire when a patient did not respond.

Statistical analysis

Data are presented as frequencies and percentages of total for categorical data, as mean ± standard deviation (SD) for normally distributed continuous data and as median and interquartile range (IQR) for non-normally distributed continuous data. Normality was tested using visual inspection of histograms and Kolmogorov-Smirnov test. Scores for preoperative HRQL were compared to the Dutch population mean using a one sample t-test. A paired sample t-test was used to compare preoperative HRQL to scores at one year after surgery. A delta score was calculated for change in HRQL by subtracting preoperative SF-12 scores from postoperative SF-12 scores. A positive delta score represents an improvement in HRQL. To study the clinical relevance of the difference in HRQL a threshold value was used to compare groups. As standard threshold values are lacking in CABG surgery for the SF-12 questionnaire, we based our threshold value on two articles using the SF-36 in elderly patients undergoing CABG or aortic valve surgery. Welke et al. defined a clinically relevant change as a difference of ≥5.42 points in physical or ≥6.33 in mental HRQL.[15] Jansen-Klomp et al. used a cut-off point of ≥2.5 points.[16] As with the SF-12 questionnaire the HRQL could increase or decrease as much as four points by changing the results of a single question, we set the threshold value at 5 or more points decrease or increase to ensure a clinically relevant change. Subsequently, the study cohort was stratified in three groups according to change in HRQL: worse, no change or better HRQL. Differences between the three groups were tested using Chi square test for dichotomous or categorical variables and one way ANOVA or Kruskal Wallis test for continuous data depending on normality.

To analyse the independent effects of all risk factors a multivariable model was built using multinomial logistic regression analysis. This analysis allows for a dependent variable with more than two categories. Patients with no clinically relevant change in HRQL were used as reference category to which the outcomes 'worse HRQL' and 'better HRQL' were compared. No variable selection took place and all variables were added simultaneously. To prevent multicollinearity, correlations between all variables were tested using Pearson's correlation coefficient. Of variables with a correlation >0.8 one variable was excluded from the model. Non-linearity of the continuous variables regarding preoperative physical and mental HRQL was investigated by adding various transformations and assessing model fit in terms of log likelihood. If model fit improved, the transformations were retained in the multivariable model. Results are presented as odds ratios with their accompanying confidence intervals. For statistical analysis IBM SPSS version 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) was used. A p-value <0.05 was considered as statistically significant for all analyses.

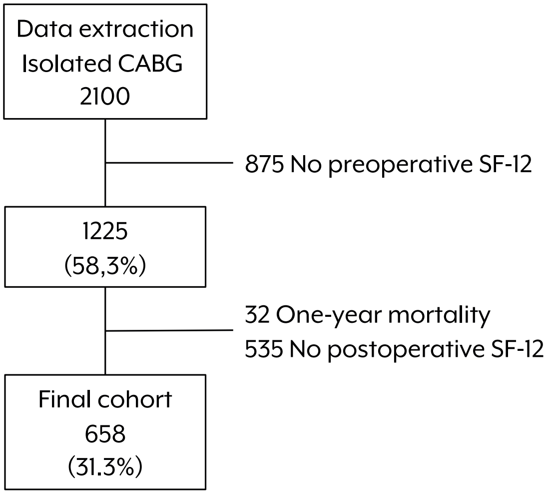


Figure 1. Flowchart of patient selection. CABG: coronary artery bypass graft, SF: Short Form

Results

Study population

In total, 2100 patients underwent elective isolated CABG. Of these patients, 1225 completed a baseline SF-12. Thirty-two patients died within one year. 658 (31.3% of total, 53.7% of 1225) patients returned the 12 month follow up questionnaire and were included in the final cohort (figure 1). Overall, non-responders had more comorbidities compared to responders. This was expressed by significant differences in age, incidence of male gender, diabetes mellitus, prior myocardial infarction, LVEF and euroSCORE. Supplementary table 2 shows other baseline variables for responders and non-responders [see Additional file 1].

Patient characteristics and outcome

Mean age was 66 years (SD ±9) minimum age was 47 and maximum age was 87 years old. The majority of patients was male (82.4%). Baseline characteristics including preoperative HRQL are presented in table 1. In-hospital complications occurred in 41 (6.2%) patients. Postoperative atrial fibrillation was most common and occurred in 19 (2.9%) patients. Median length of stay was 6 (IQR 4-7) days. Mean preoperative physical HRQL in the study cohort was lower compared to the Dutch population mean (39.2 (SD ±5.4) vs 50.6 (SD ±9.2) p<0.001 respectively, difference: -11.4; 95%CI -11.8 to -11.0). One year after surgery mean physical HRQL increased slightly to 39.9 (SD ±4.6) (p=0.007) but remained below the population mean (difference -10.7; 95%CI -11.0 to -10.3). Mean preoperative mental HRQL was lower compared to the population mean (48.9 (SD ±13.1) vs 50.2 (SD ±9.2) p=0.001 respectively, difference: -1.7; 95%CI -2.7 to -0.7). Mean mental HRQL improved to 54.4 (SD ±12.6) (p<0.001) after surgery and rose above population mean (difference 3.8; 95%CI 2.8 to 4.8).

Determinants of a clinically relevant change in physical HRQL

Physical HRQL one year after surgery improved in 150 (22.8%) patients, did not change in 403 (61.2%) patients and got worse in 105 (16.0%) patients. Preoperative median EuroSCORE was 3 (IQR 1 - 4), 3 (IQR 1 - 4), and 3 (IQR 1 - 5) for worse, no change or better physical HRQL respectively (p=0.802). Median preoperative physical HRQL was 45.3 (IQR 41.5 - 48.5) for patients with worse physical HRQL; 39.7 (IQR 37.1 - 42.1) for patients with no change in physical HRQL and 34.8 (IQR 31.3 - 37.2) for patients with better HRQL (p<0.001). Median preoperative mental HRQL was 47.2 (IQR 35.9 - 54.1); 50.5 (IQR 40.8 - 59.2) and 52.6 (IQR 43.1 - 60.8) for patients with worse, no change or better HRQL respectively (p=0.001). Postoperative complications occurred in 6.7% of patients with worse physical HRQL, in 5.5% of patients with no change in physical HRQL and in 8.0% of patients with better physical HRQL (p=0.536).

Table 1. Baseline

	N = 658
Patient characteristics	
Age (years)	65.5 ±9.0
Male gender	542 (82.4%)
Current smoking	191 (29.0%)
Body mass index (kg/m2)	26.8 (24.6-29.8)
Hypertension	338 (51.4%)
Myocardial infarction	75 (11.4%)
Stroke	54 (8.2%)
Pulmonary disease	50 (7.6%)
Atrial fibrillation	26 (4.0%)
Peripheral vascular disease	68 (10.3%)
Unstable angina	65 (9.9%)
Diabetes mellitus	133 (20.2%)
Left ventricular ejection fraction	
Good (≥50%)	54 (83.0%)
Moderate (30-50%)	94 (14.3%)
Poor (<30%)	18 (2.7%)
Additive EuroSCORE	3 (1-4)
Preoperative hemoglobine (mmol/l)	8.8 (8.2-9.3)
Preoperative creatinine (µmol/)	82 (73-95)
Health related quality of life	
Preoperative physical HRQL	39.2 ±5.4 39.0 (36.0–42.6)
Preoperative mental HRQL	48.9 ±13.1 50.3 (40.2–59.0)
Surgical characteristics	
Duration of surgery (min)	189 (163-226)
Extra corporeal circulation time(min)	83 (68-101)
Mini extra corporeal circulation	485 (73.7%)
Use of internal mammary artery	626 (95.1%)
Packed red blood cell transfusion*	54 (8.2%)
Blood loss (ml)**	660 (519-850)

Data are presented as mean (±standard deviation), medians (interquartile range) or frequencies (%).
HRQL: health related quality of life
* Intraoperative packed red blood cell transfusion
** Blood loss at 24 hours after surgery

Table 2 shows the independent odds ratios of preoperative risk factors for a change in physical HRQL. Clinical features significantly associated with a change in physical HRQL were a history of stroke, atrial fibrillation, vascular disease or pulmonary disease. Patients with a prior stroke showed increased odds for worse physical HRQL. A history of atrial fibrillation or vascular disease decreased the odds for a worse physical HRQL and a history of pulmonary disease increased the odds for improved HRQL. Preoperative physical HRQL was significantly associated with a change in physical HRQL. A higher preoperative value on the SF-12 decreased the odds for worse HRQL and increased the odds for better HRQL.

Determinants of a clinically relevant change in mental HRQL

Mental HRQL improved in 328 (49.8%) patients at one year after surgery, remained unchanged in 227 (34.5%) patients and worsened in 103 (15.7%) patients. Preoperative median euroSCORE was 3 (IQR 1 - 5) for patients with worse mental HRQL, 3 (IQR 1 - 4) for patients with no change in mental HRQL, and 3 (IQR 1 - 4) for patients with better mental HRQL (p=0.887). Prior to surgery, physical HRQL was 37.9 (IQR 35.0 - 41.7); 37.9 (IQR 35.1 - 41.4) and 40.5 (IQR 37.0 - 43.9) for patients with worse, no change or better HRQL respectively (p<0.001). Preoperative mental HRQL was 55.2 (IQR 46.9 - 63.7); 55.6 (IQR 46.6 - 63.6) and 45.1 (IQR 34.7 - 53.4) for patients with worse, no change or better HRQL respectively (p<0.001). Postoperative complications were seen in 8.7% of patients with worse mental HRQL, in 5.3% of patients with no change in mental HRQL and in 6.1% of patients with better mental HRQL (p=0.481).

Independent odds ratios of preoperative risk factors for a change in mental HRQL are shown in table 3. No significant associations were seen between clinical risk factors and worse or better mental HRQL one year after CABG. Higher preoperative physical HRQL increased the odds for improved mental HRQL. Lower preoperative mental HRQL increased the odds for better mental HRQL.

Table 2. Multinomial regression analysis for change in physical HRQL

	Worse physical HRQL		Better physical HRQL	
	Beta	**OR (95%CI)**	**Beta**	**OR (95%CI)**
Age (per year)	-0.03	0.97 (0.92 – 1.01)	-0.00	1.00 (0.95 – 1.04)
Body mass index (per point)	0.02	1.02 (0.94 – 1.09)	-0.04	0.96 (0.91 - 1.02)
EuroSCORE (per point)	0.16	1.18 (0.95 – 1.46)	-0.03	0.98 (0.81 – 1.18)
LVEF >50%	0	1.00	0	0
LVEF 30-50%	1.67	5.32 (0.41 – 69.61)	0.60	1.82 (0.43 – 7.65)
LVEF <30%	1.15	3.16 (0.25 – 39.56)	0.66	1.94 (0.50 – 7.61)
Hemoglobin (per point)	-0.03	0.97 (0.65 – 1.44)	-0.24	0.79 (0.56 – 1.10)
Creatinine (per point)	-0.01	0.99 (0.98 – 1.01)	-0.00	1.00 (0.99 – 1.01)
Preoperative physical HRQL (per point)				
Singular	-1.25***	†	0.54	†
Quadratic	0.02***		-0.01*	
Preoperative mental HRQL (per point)	0.00	1.00 (0.98 – 1.03)	0.01	1.01 (0.99 – 1.03)
Male gender	0.07	1.07 (0.43 – 4.47)	0.11	1.12 (0.52 – 2.41)
Active smoking	0.41	1.51 (0.79 – 2.88)	0.45	1.57 (0.91 – 2.69)
Hypertension	0.51	1.67 (0.91 – 3.06)	-0.04	0.96 (0.60 – 1.55)
Myocardial infarction	0.18	1.19 (0.50 - 2.84)	0.37	1.45 (0.69 – 3.04)
Stroke	0.99*	2.68 (1.04 – 6.88)	0.47	1.60 (0.98 – 3.79)
Pulmonary disease	0.44	1.56 (0.55 - 4.43)	0.86*	2.36 (1.05 – 5.31)
Atrial fibrillation	-3.17*	0.04 (0.00 – 0.97)	-1.50	0.22 (0.05 - 1.10)
Peripheral vascular disease	-1.23*	0.29 (0.10 – 0.90)	0.20	1.23 (0.57 - 2.64)
Unstable angina	-0.47	0.62 (0.24 – 1.63)	0.22	1.25 (0.57 – 2.75)
Diabetes mellitus	0.22	0.25 (0.59 – 2.65)	-0.13	0.88 (0.49 – 1.60)

LVEF: left ventricular ejection fraction HRQL: health related quality of life. Unchanged HRQL was the reference category. Worse and Better HRQL were defined as ≥5 points change in delta HRQL.
*=p<0.050, **p=<0.005, ***=p<0.001
† Since clinical interpretation of odds ratios is limited for quadratic equations this is not presented.

Table 3. Multinomial regression analysis for change in mental HRQL

	Worse mental HRQL		Better mental HRQL	
	Beta	**OR (95%CI)**	**Beta**	**OR (95%CI)**
Age (per year)	-0.02	0.98 (0.93 – 1.02)	0.01	1.01 (0.97 – 1.04)
Body mass index (per point)	0.02	1.02 (0.96 - 1.08)	0.01	1.01 (0.96 – 1.06)
EuroSCORE (per point)	0.02	1.02 (0.85 – 1.23)	-0.07	0.94 (0.80 – 1.10)
LVEF >50%	0	0	0	0
LVEF 30-50%	-0.36	0.84 (0.21 – 3.39)	1.13	3.09 (0.60 – 15.83)
LVEF <30%	-0.18	0.70 (0.19 - 2.63)	0.66	1.93 (0.40 – 9.36)
Hemoglobin (per point)	-0.15	0.86 (0.61 – 1.23)	0.03	1.07 (0.80 - 1.43)
Creatinine (per point)	0.01	1.01 (1.00 – 1.02)	-0.00	1.00 (0.99 – 1.01)
Preoperative physical HRQL (per point)	-0.00	1.00 (0.95 – 1.05)	0.08***	1.08 (1.04 - 1.13)
Preoperative mental HRQL (per point)				
Singular	0.02	†	-1.07**	†
Quadratic	-0.01		0.02**	
Cubic	0.00		0.00**	
Male gender	0.15	1.17 (0.52 – 2.61)	-0.04	0.96 (0.50 – 1.85)
Active smoking	-0.09	0.92 (0.51 – 1.65)	0.03	1.04 (0.65 – 1.65)
Hypertension	0.16	1.18 (0.71 – 1.95)	0.12	1.13 (0.75 – 1.71)
Myocardial infarction	0.20	1.23 (0.60 – 2.51)	-0.56	0.57 (0.29 – 1.11)
Stroke	-0.03	0.97 (0.37 – 2.50)	0.18	1.19 (0.57 – 2.52)
Pulmonary disease	0.37	1.45 (0.63 – 3.34)	-0.62	0.54 (0.25 – 1.14)
Atrial fibrillation	0.39	1.48 (0.44 – 4.99)	-0.35	0.71 (0.23 – 2.15)
Peripheral vascular disease	0.00	1.00 (0.41 – 2.44)	0.34	1.41 (0.72 – 2.77)
Unstable angina	0.17	1.12 (0.52 – 2.74)	0.20	1.22 (0.62 – 2.41)
Diabetes mellitus	-0.6	0.94 (0.49 – 1.81)	0.02	1.02 (0.60 – 1.74)

LVEF: Left ventricular ejection fraction. HRQL: health related quality of life. Unchanged HRQL was the reference category. Worse and Better HRQL were defined as ≥5 points change in delta HRQL respectively.
*=p<0.050, **p=<0.005, ***=p<0.00
† Since clinical interpretation of odds ratios is limited for quadratic and cubic equations this is not presented.

Discussion

In this study the most important determinant for a change in HRQL one year after CABG was preoperative HRQL. Higher preoperative physical HRQL led to improved outcomes regarding physical and mental HRQL at one year after surgery considering other clinical risk factors. Lower mental HRQL before surgery increased the chance to improve in mental HRQL at one year after surgery. The influence of preoperative HRQL on a change after surgery illustrates the vital importance of acquiring information on HRQL in the preoperative setting in order to fully inform patients on expected patient-centred outcomes.

Change in HRQL

In the majority of patients physical HRQL hardly changed, as was reflected by a mean increase of 0.7 points. Mental HRQL increased in half of patients, with a mean increase of 5.5 points. Contrasting to our findings, other studies using the SF-36, showed a mean increase in physical HRQL ranging from 4.8 to 5.3 points and a mean increase in mental HRQL of 1.2 to 1.9 points.[17,18] In a cohort of 1744 patients, Rumsfeld et al. assessed SF-36 before and six months after CABG surgery. Health related quality of life increased 5.3 and 1.9 points for physical and mental HRQL respectively. Comparable to our results, preoperative physical HRQL was identified as the most important risk factor for a change in HRQL after taking other preoperative cardiac and non-cardiac risk factors into account.[19]

Deutsch et al. performed a study in 106 octogenarians undergoing CABG, valve surgery or CABG combined with valve surgery.[18] They assessed HRQL by SF-36 three and 12 months after surgery and compared it to preoperative scores. At three months physical HRQL significantly increased with 5.1 points and mental HRQL was comparable to preoperative levels. Cardiac and non-cardiac comorbidities and procedural data were not identified as relevant risk factors for change in HRQL. Unfortunately, baseline HRQL was not considered as possible risk factor for a change in HRQL in their study. In contrast to other literature reports, physical HRQL at one year after surgery increased to a lesser extent in our study, while the increase in mental HRQL was more eminent.[15,18,19]

These differences could be due to the moment of measuring HRQL. At one year after surgery, which was the moment of measurement in our study, HRQL could have been affected by other factors as well, resulting in lower scores. Furthermore, CABG is mainly performed to relieve complaints of angina, which is likely to result in improved physical functioning. In our cohort less than 10% of patients suffered from unstable angina while this was present in up to 28-61% in patients in other articles.[19,20] It is conceivable that patients in this study suffered from fewer complaints before surgery and therefore did not notice a relevant increase in physical HRQL. Also, questions regarding mental HRQL in the SF-12 include items as feeling full of energy, calm and peaceful or feeling downhearted. Although patients did not report an improvement in questions on physical functioning, CABG surgery may have improved mental status by relieving anxiety and enhancing feelings of security and self-esteem. The increase in mental HRQL in our study could reflect the overall benefit of the surgery.

Risk factors for change in HRQL after cardiac surgery

Preoperative risk stratification based on patient-centered outcomes, such as HRQL, could have great additional value in cardiac surgery but remains challenging as well designed risk models are lacking. Possible risk factors for change in HRQL that are readily available such as comorbidities, laboratory values or LVEF have been considered by others but resulted in conflicting results. Female gender [21,22], older age [23], diabetes mellitus[15,22,24], body mass index >35[15], low LVEF [22], pulmonary disease[15], vascular disease [15], EuroSCORE >3[8], deprived socio-economic status[24] and smoking[24] have been associated with worse HRQL following cardiac surgery. Older age[15], high social support [24], and EuroSCORE >6 [25] have been associated with better HRQL after cardiac surgery. However, several other studies, including ours, found no association between preoperative clinical factors and change in postoperative HRQL.[17,20] Studies that included preoperative HRQL in their analysis concluded that HRQL prior to surgery was the most promising predictor for postoperative change in HRQL[15,17,20] and that routine preoperative assessment of HRQL should be incorporated in standard care to supplement current risk assessment.[26,27]

Some limitations should be addressed. First, the retrospective design limited the amount of available data. Comparison of responders versus non-responders showed that non-responders were older, more often male and showed a higher prevalence of diabetes mellitus, myocardial infarction, lower LVEF and higher EuroSCORE. These factors can have a negative effect on postoperative HRQL.[15,21–24] With inclusion of these patients likely greater differences in HRQL might have been present and possibly more preoperative predictors would have been identified. A possible reason for non-responding could be the method of approach during the follow up period, where questionnaires were sent by email without a reminder for unanswered questionnaires. Not all patients have email, which is more often the case for elderly. Second, obviously no SF-12 scores were available for deceased patients and these patients were excluded from the analysis. Mortality risk is highest for patients with more comorbidities. It is conceivable that this excluded group of patients had more comorbidities, leading to lower scores for preoperative HRQL and, subsequently different change scores. However, one year mortality was merely 2.6% and it seems unlikely this had a major influence on results. Third, only elective surgery patients were analysed limiting the generalisability and excluding patients with emergency CABG. However, the indication for emergency surgery is focussed on survival, while the main indication for elective CABG is to relieve angina. In elderly patients scheduled for elective surgery risk factors for postoperative HRQL are more essential for the decision making process than in patient presenting for emergency surgery.

Conclusion

In conclusion, one year after CABG surgery the majority of patients experiences equal or improved HRQL when compared to before surgery. Most important preoperative determinant for a change in HRQL is HRQL prior to surgery.

References

1. Pierri MD, Capestro F, Zingaro C, Torracca L. The changing face of cardiac surgery patients: an insight into a Mediterranean region. *Eur J Cardiothorac Surg*. 2010;38(4):407-413.
2. Buth KJ, Gainer RA, Legare J-F, Hirsch GM. The Changing Face of Cardiac Surgery: Practice Patterns and Outcomes 2001-2010. *Can J Cardiol*. 2014;30:224-230. doi:10.1016/j.cjca.2013.10.020
3. Cloin ECW, Noyez L. Changing profile of elderly patients undergoing coronary bypass surgery. *Neth Heart J*. 2005;13(4):132-138.
4. Barsoum EA, Azab B, Patel N, et al. Long-term Outcome after Percutaneous Coronary Intervention Compared with Minimally Invasive Coronary Artery Bypass Surgery in the Elderly. *Open Cardiovasc Med J*. 2016;10:11-18.
5. Nashef SAM, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg*. 1999;16(1):9-13.
6. Parsonnet V, Dean D, Bernstein AD. A method of uniform stratification of risk for evaluating the results of surgery in acquired adult heart disease. *Circulation*. 1989;79(6 Pt 2):I3-12.
7. Bilmoria KY, Liu Y, Paruch JL, et al. Surgical Risk Calculator : A Decision Aide and Informed Consent Tool for Patients and Surgeons. *J Am Coll Surg*. 2014;217(5):833-842.
8. Loponen P, Luther M, Nissinen J, et al. EuroSCORE predicts health-related quality of life after coronary artery bypass grafting. *Interact Cardiovasc Thorac Surg*. 2008;7(4):564-568.
9. Abah U, Dunne M, Cook A, et al. Does quality of life improve in octogenarians following cardiac surgery? A systematic review. *BMJ Open*. 2015;5(4):e006904.
10. Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. *Eur Heart J*. 2010;31:2501-2555.
11. Supervisory Committee for Cardiac Interventions in The Netherlands (Begeleidingscommissie Hartinterventies Nederland, BHN). https://www.bhn-registratie.nl/. Accessed June 2, 2017.
12. Gandek B, Ware JE, Aaronson NK, et al. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: Results from the IQOLA Project. *J Clin Epidemiol*. 1998;51(11):1171-1178.
13. De Smedt D, Clays E, Annemans L, et al. Health related quality of life in coronary patients and its association with their cardiovascular risk profile: Results from the EUROASPIRE III survey. *Int J Cardiol*. 2013;168(2):898-903.
14. Ware J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care*. 1996;34(3):220-233.
15. Welke KF, Stevens JP, Schults WC, Nelson EC, Beggs VL, Nugent WC. Patient characteristics can predict improvement in functional health after elective coronary artery bypass grafting. *Ann Thorac Surg*. 2003;75(6):1849–1855.
16. Jansen Klomp WW, Nierich AP, Peelen LM, et al. Survival and quality of life after surgical aortic valve replacement in octogenarians. *J Cardiothorac Surg*. 2016;11(38).
17. Rumsfeld JS, Magid DJ, O'Brien M, et al. Changes in health-related quality of life following coronary artery bypass graft surgery. *Ann Thorac Surg*. 2001;72(6):2026-2032.
18. Deutsch M-AA, Krane M, Schneider L, et al. Health-related quality of life and functional outcome in cardiac surgical patients aged 80 years and older: A prospective single center study. *J Card Surg*. 2014;29:14-21.
19. Rumsfeld JS, Magid DJ, O'Brien M, et al. Changes in health-related quality of life following coronary artery bypass graft surgery. *Ann Thorac Surg*. 2001;72(6):2026-2032.
20. Grady KL, Lee R, Subačius H, et al. Improvements in Health-Related Quality of Life Before and After Isolated Cardiac Operations. *Ann Thorac Surg*. 2011;91(3):777-783.

21. Kendel F, Dunkel A, Müller-Tasch T, et al. Gender Differences in Health-Related Quality of Life After Coronary Bypass Surgery: Results From a 1-Year Follow-Up in Propensity-Matched Men and Women. *Psychosom Med*. 2011;73(3):280-285.

22. Peric V, Borzanovic M, Stolic R, et al. Predictors of worsening of patients' quality of life six months after coronary artery bypass surgery. *J Card Surg*. 2008;23(6):648-654.

23. Järvinen O, Saarinen T, Julkunen J, Huhtala H, Tarkka MR. Changes in health-related quality of life and functional capacity following coronary artery bypass graft surgery. *Eur J Cardiothorac Surg*. 2003;24(5):750-756.

24. Lindsay GM, Hanlon P, Smith LN, Wheatley DJ. Assessment of changes in general health status using the short-form 36 questionnaire 1 year following coronary artery bypass grafting. *Eur J CARDIO-THORACIC Surg*. 2000;18(5):557-564. doi:10.1016/S1010-7940(00)00542-X

25. Colak Z, Segotic I, Uzun S, Mazar M, Ivancan V, Majeric-Kogler V. Health related quality of life following cardiac surgery — correlation with EuroSCORE. *Eur J Cardio-thoracic Surg*. 2008;33(1):72-76.

26. Rumsfeld JS, Alexander KP, Goff DC, et al. Cardiovascular health: The importance of measuring patient-reported health status a scientific statement from the American heart association. *Circulation*. 2013;127(22):2233-2249.

27. Spertus JA. Evolving applications for patient-centered health status measures. *Circulation*. 2008;118(20):2103-2110.

28. Mols F, Pelle AJ, Kupper N. Normative data of the SF-12 health survey with validation using postmyocardial infarction patients in the Dutch population. *Qual Life Res*. 2009;18(4):403-414. doi:10.1007/s11136-009-9455-5

Supplementary files

Supplementary table 1. Reference scores for SF-12 health related quality of life.[28]

Age group	Physical HRQL	Mental HRQL
Overall	50.6 ± 9.2	50.2 ± 9.2
50 – 59 years	50.5 ± 9.5	50.7 ± 9.0
60 – 69 years	50.5 ± 8.2	51.1 ± 8.7
70 – 79 years	44.4 ± 11.2	49.5 ± 8.5

Supplementary table 2. Baseline characteristics for patients with and without postoperative SF-12

Demographics	With pre- and postoperative SF-12 N=658	With missing SF-12 N=1442	P value
Patient characteristics			
Age (yr)	65.5 ± 9.0	66.3 ± 10.2	0.003
Male gender	542 (82.4%)	1110 (77.0%)	0.005
Body mass index (kg/m2)	26.8 (24.6-29.8)	27.0 (24.6-29.9)	0.736
Hypertension	338 (51.4%)	761 (52.8%)	0.550
Atrial fibrillation	26 (4.0%)	44 (3.1%)	0.287
Diabetes Mellitus	133 (20.2%)	376 (26.1%)	0.004
Stroke	54 (8.2%)	129 (8.9%)	0.577
Pulmonary disease	50 (7.6%)	122 (8.5%)	0.504
Peripheral vascular disease	68 (10.3%)	166 (11.5%)	0.426
Unstable Angina	65 (9.9%)	177 (12.3%)	0.111
Myocardial infarction	75 (11.4%)	222 (15.4%)	0.015
Left ventricular ejection fraction			0.002
Normal (>50%)	546 (83.0%)	1074 (74.5%)	
Moderate .(30-50%)	94 (14.3%)	293 (20.3%)	
Poor (<30%)	18 (2.7%)	53 (3.7%)	
EuroSCORE	3 (1-4)	3 (2-5)	<0.001
Preoperative creatinine (umol/l)	82 (73-95)	84 (73-99)	0.127
Preoperative hemoglobin (mmol/l)	8.8 (8.2-9.3)	8.6 (7.9-9.2)	<0.001
Surgical characteristics			
Duration of surgery (min)	189 (163-226)	193 (161-228)	0.419
Extra corporeal circulation time (min)	83 (68-101)	84 (68-103)	0.783
Mini extra corporeal circulation	485 (73.7%)	990 (68.7%)	0.019
Use of internal mammary artery	626 (95.1%)	1359 (94.2%)	0.404
Packed red blood cell transfusion*	54 (8.2%)	193 (13.4%)	0.001
Blood loss (ml)**	660 (519-850)	700 (530-938)	0.002

Data are presented as mean (±standard deviation), medians (interquartile range) or frequencies (%).

* Intraoperative packed red blood cell transfusion

** Blood loss at 24 hours after surgery

2

Chapter 3

Preoperative frailty and one year functional outcome of elderly cardiac surgery patients. An observational prospective cohort study.

Lisa Verwijmeren
Peter G Noordzij
Edgar J Daeter
Marielle H Emmelot-Vonk
Lisette M Vernooij
Wilton A van Klei
Eric P A van Dongen

Submitted

Abstract

Background: Frailty increases the risk for morbidity and mortality after cardiac surgery. The influence of frailty on functional outcomes is largely unknown. Aim of this article was to study the association of preoperative frailty characteristics on patient reported adverse functional outcomes.

Methods: A prospective two-centre observational cohort study in 555 elective cardiac surgery patients aged ≥70 years. Pre-anaesthesia assessment was supplemented with a geriatric assessment covering the physical, mental, and social domain. Functional outcomes were change in health related quality of life and disability measured at one year.

Results: Frailty characteristics were present in 521 (94%) patients and 120 (22%) patients were considered frail. Adverse functional outcome at one year after surgery occurred in 257 (46%) patients. Seventy-four (29%) patients with adverse functional outcome were frail, compared to 47/298 (16%) patients without adverse functional outcome ($p<0.001$). Worse physical or mental health related quality of life occurred in 134 (24%) and 141 (25%) patients respectively. The most important frailty characteristic associated with worse physical health related quality of life was preoperative physical health related quality of life (β -0.6 per point (95%CI -0.7 to -0.5). Preoperative mental health related quality of life showed the strongest associations for worse mental health related quality of life (β -0.6 per point (95%CI -0.7 to -0.4)). Disability was reported by 120 (22%) patients and associated with preoperative polypharmacy, timed-get-up-and-go test, health related quality of life, living alone or dependent living. Timed-get-up-and-go test had the strongest association with postsurgical disability (β 2.2 per second (95%CI 1.6 to 2.8)).

Conclusions: Preoperative frailty characteristics were common and predictive for adverse functional outcome one year after cardiac surgery. Future research should focus on frailty screening to improve risk stratification and guide surgical decision making in older cardiac surgery patients.

Introduction

The World Health Organization (WHO) defines health as "a state of complete physical, mental and social well-being".[1] As advanced age is associated with multi-morbidity, elderly patients are at increased risk of losing their health. The accumulation of comorbidities can result in a deterioration of functional reserves across multiple organ systems, limiting physical, mental and social functioning. This concept is known as frailty. Frailty in elderly is increasingly recognized as a risk factor for adverse functional outcome after surgery.[2,3] Functional outcomes contribute largely to a patient's general health perspective, and a loss in health related quality of life (HRQL) or disability can result in poorer health in general. Surveys among elderly showed that maintaining HRQL and functioning is valued more than longevity when facing surgery.[4] This underlines the importance to better understand functional recovery after surgery in older patients.[4,5] In addition, information on functional outcomes is essential to determine the cost effectiveness of surgery in the elderly and guide evidence based resource allocation to justify the increasing health care costs.[6]

A growing number of elderly patients is referred for cardiac surgery in an attempt to decrease the burden of the symptoms of chronic cardiac disease.[7] Following cardiac surgery, frail patients are at increased risk for complications, longer length of stay, and mortality.[2,8] Between 15 and 32% of patients report adverse functional outcomes one year after cardiac surgery.[2,3,9–11] Yet, the course of functional recovery in elderly cardiac surgery patients is unclear and preoperative characteristics that affect functional outcome are largely unknown. Prior studies generally assessed the associations between comorbidities or surgical risk scores with adverse functional outcome, but were unable to identify relevant risk factors for clinical practice.[4,9–12]

We hypothesized that frailty assessment offers additional value in predicting risk for adverse functional outcomes after cardiac surgery. The aim of this research was to study the association of preoperative frailty characteristics on adverse functional outcomes and to investigate the trajectory of functional recovery among frail and non-frail elderly patients up to one year after elective cardiac surgery.

Materials and Methods

Design and participants

The Anaesthesia Geriatric Evaluation (AGE) study (NCT02535728) was a prospective two-centre observational cohort study on the association of preoperative frailty and functional outcome in cardiac surgery. Inclusion criteria were patients aged ≥70 years scheduled for elective open cardiac surgery. The local ethics committee gave ethical approval (Medical Ethics Research Committee United, number R15.039) and all patients signed written informed consent.

Details on design and analysis of the AGE study have been previously reported.[13] In short, the AGE study supplemented routine pre-anaesthesia assessment with 11 tests on the physical, mental, and social domain of frailty. The somatic domain, including comorbidities, was part of routine assessment. Tests for physical frailty included: polypharmacy, Mini Nutritional Assessment (MNA), 5-Meter Walk test (5MWT), Timed Get Up and Go test (TGUGT), Nagi's scale, and grip strength. Mental frailty was evaluated by the Short Form-36 (SF36) questionnaire and the Mini Mental State Examination (MMSE). Social frailty included marital status, lower educational level, and dependent living. An elaborate description of frailty characteristics and chosen cut-off values was described previously.[13]

Assessment of covariates and in-hospital complications

Covariates were registered after reviewing electronic medical records and included: comorbidities, EuroSCORE II, echocardiography results, and laboratory results available at time of screening, or on the day before surgery.

Complications were scored according to predefined definitions of the Dutch National Complication Registration of Cardiac Surgery and evaluated by two members of the research team (LV, PGN).[14] Severity of complications was based on the Clavien-Dindo classification.[15] Grading was as follows: a mild complication only required pharmacological treatment and included; deep sternal wound infection, wound infection, pneumonia, urinary tract infection, cardiac arrhythmia, congestive heart failure, and delirium. A moderate complication included myocardial infarction, sepsis, prolonged postoperative ventilator dependency (>24 hours), transient ischemic attack, renal failure, major bleeding, gastro-intestinal complication, and vascular complication or prolonged length of stay. Prolonged length of stay was dependent on type of surgery and set at ≥10, ≥11, ≥14 and ≥17 days for isolated CABG or maze, isolated valve surgery, combined surgery, and aortic surgery, respectively. A severe complication was defined as in-hospital mortality or a life threatening event and included; re-operation, respiratory insufficiency, reintubation, stroke, renal replacement therapy, life threatening bleeding, or re-admittance to the ICU.

Determinant

Consensus on the definition of frailty is lacking and numerous frailty scales exist. Most definitions of frailty rely on the accumulation of deficits in several domains.[16,17] We chose to measure individual frailty characteristics and referred to patients as 'frail' when at least one test in all three domains was affected.

Outcomes

The primary outcome of our study was HRQL at twelve months after surgery. We used the difference in HRQL between baseline and 12 months after surgery to analyse the association between frailty characteristics and the primary outcome. To assess HRQL the SF36 was used, a generic questionnaire with 36 questions on HRQL based on the past four weeks and consisting of eight domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health.[18] Domain scores range from 0 to 100 and are summarized into a physical HRQL and mental HRQL score which is normalized to a score of 50 (standard deviation (SD) ± 10). Higher scores represent better HRQL.[19] Death was scored as the lowest possible score of 0 points. Standardized cut off values for a clinically relevant change in HRQL are not available for the SF36. In line with prior studies we defined worse physical or mental HRQL as a decrease of ≥5 points compared to baseline.[9,10,20] Secondary outcomes were HRQL at three months and disability at three and twelve months. Disability was assessed by the 36-item self-assessment WHO Disability Assessment Schedule 2.0 (WHODAS 2.0).[21] In 36 questions functioning over the past four weeks is assessed. A percentage score is calculated with higher scores indicating more disabilities. Death was scored as maximum disability (100%). A score ≥25% represents disability according to original development and was validated in a surgical cohort[21–23]. To express poor recovery a composite endpoint of adverse functional outcome was computed and defined as worse physical HRQL, worse mental HRQL or disability.

Statistical approach

A data analysis and statistical plan was written and filed with the local ethics committee before data were accessed. To limit bias caused by missing data a multiple imputation analysis with 30 imputation sets was performed and results were pooled using Rubin's Rules.[24,25] Dichotomous and categorical data are presented as frequencies and percentages. Continuous data were checked for normality based on histograms and presented as mean and SD or as median with interquartile range (IQR), as appropriate. Comparisons between groups (complete cases versus patients with missing data and non-frail versus frail patients) were made using Chi square test for dichotomous data and Student-T test or Mann-Whitney-U test for continuous data according to normality. For imputed data a Student-T test was used since a uniform pooling method is not available for non-parametric tests. Comparisons of HRQL scores before and at three and twelve months after surgery were made using dependent samples Student-T test.

Associations between frailty characteristics and mild, moderate or severe complications were analysed by multinomial logistic regression with no complication as reference category. Linear regression analyses were performed to investigate the associations between frailty characteristics and continuous functional outcomes. Dependent variables were change in physical or mental HRQL or disability score at one year after surgery. Effect estimates are presented as β with 95% confidence intervals (CI) with Nagelkerke R^2. To investigate the associations between frailty characteristics and functional outcomes in further detail, logistic regression analyses were performed with worse physical HRQL, worse mental HRQL, and disability as dependent variables. Odds ratio's (OR) are presented with accompanying 95% CI. Area under the Receiver Operating Characteristics curve (AUC) was calculated to express discrimination of each frailty characteristic. To take age, sex, comorbidities and weight of the procedure into account, all associations following from regression analyses were adjusted for EuroSCORE II. A P-value ≤0.05 was considered statistically significant. Analyses were performed using IBM SPSS Statistics version 23 for windows (IBM Corp. Armonk, New York) and figure 2 was created in R version 3.6.1 R Package for Creating Alluvial Diagrams by Bojanowski M and Edwards (2016).

Results

Study population and frailty

The AGE study population consisted of 555 patients (Figure 1). Mean time from screening to surgery was 24 days (range 0-170) and mean time to follow up was 377 days (range 335-468). Preoperative data were complete in 510 (92%) patients. The response rate for HRQL questionnaires at 3 and 12 months after surgery was 90% and 89%, respectively and for disability at 3 and at 12 months 86%. Baseline and frailty characteristics for 163 (29%) patients with missing data were compared to those with complete data. Patients with missing data had more comorbidities and were more frail (Supplementary table 1).

The age of the population ranged from 70 to 87 years and 64 (12%) patients were octogenarians. Physical frailty characteristics were more common (505 (91%) patients) than mental or social frailty characteristics (214 (39%) and 231 (42%) patients respectively). Frailty, defined as at least one affected test in all three domains, was present in 120 (22%) patients. Frail patients were more often female and had a higher EuroSCORE II (Table1).

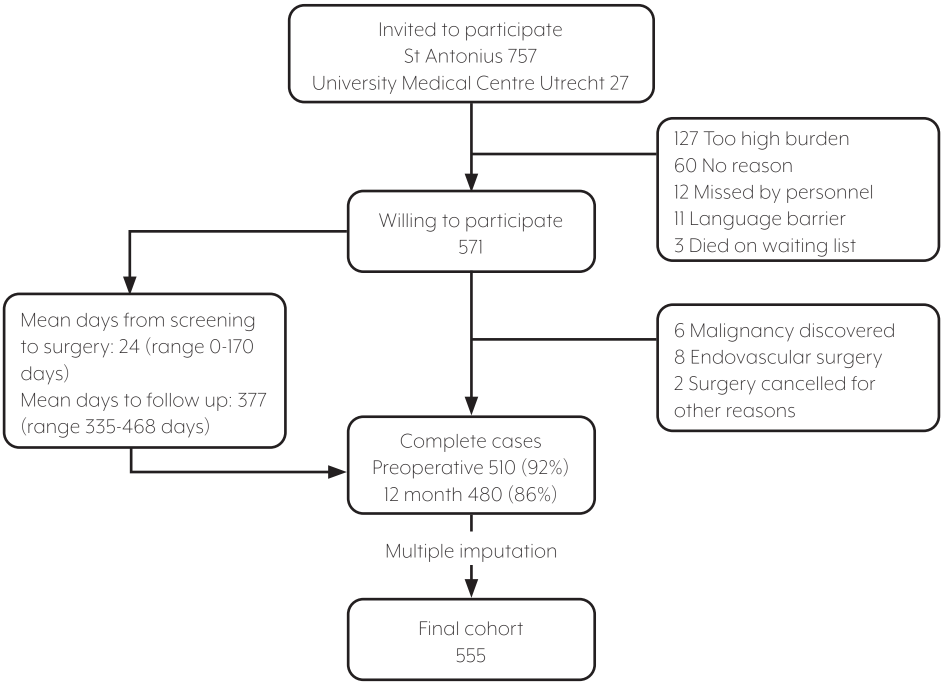


Figure 1. Flowchart of patient inclusion

Table 1. Baseline characteristics for all patients and according to frailty

	All N=555	Non-frail N=435	Frail N=120	P value
Patient characteristics				
Age (years)	75 (72-77)	75 (72 – 77)	75 (72 – 78)	0.569
Female sex	182 (33)	113 (26)	70 (58)	<0.001
Hypertension	462 (83)	361 (83)	101 (84)	1.000
Anginal complaints	209 (38)	167 (38)	42 (35)	0.453
Atrial fibrillation	166 (30)	133 (31)	33 (28)	0.545
Previous MI	85 (15)	66 (15)	19 (16)	1.000
Stroke	77 (14)	63 (14)	14 (12)	0.374
Diabetes Mellitus	114 (21)	85 (19)	29 (24)	0.169
Extra cardiac arteriopathy	68 (12)	50 (12)	18 (15)	0.245
COPD	64 (12)	41 (9)	23 (19)	0.001
Prior cardiac surgery	38 (7)	29 (7)	9 (8)	1.000
LVEF < 50%	118 (21)	80 (18)	38 (32)	0.001
EuroSCORE II	1.8 (1.2-3.3)	1.8 (1.2 – 2.9)	2.4 (1.4– 4.4)	<0.001
NYHA class				<0.001
- 1	81 (15)	74 (17)	7 (6)	
- 2	293 (53)	243 (56)	50 (41)	
- 3	166 (30)	113 (26)	53 (44)	
- 4	15 (3)	4 (1)	11 (9)	
Type of surgery				0.391
- Single CABG/maze	193 (35)	157 (36)	36 (30)	
- Single valve	154 (28)	115 (27)	39 (32)	
- Combined surgery	167 (30)	131 (30)	36 (30)	
- Aortic surgery	41 (7)	31 (7)	10 (8)	
Frailty				
Polypharmacy	6.4 ± 3.4	6 (4 – 8)	8 (5 – 10)	<0.001
MNA (points)	13 (12 – 14)	14 (12 – 14)	12 (10 – 14)	<0.001
Nagi's scale (points)	0 (0 –2)	0 (0 – 1)	2 (1 – 3)	<0.001
5 Meter walk test (sec)	4.7 (4.2 – 5.6)	4.6 (4.1 – 5.2)	5.6 (4.8 – 6.9)	<0.001
Timed get up and go test (sec)	9.9 (8.5 – 11.7)	9.6 (8.4 – 11.1)	12 (9.8 – 12.0	<0.001
Low grip strength	206 (37)	152 (35)	54 (44)	0.034
MMSE (points)	29 (27 - 30)	29 (28 – 30)	27 (25 – 29)	<0.001
Physical HRQL (points)	43 (34 - 51)	45 (37 – 52)	32 (26 – 41)	<0.001
Mental HRQL (points)	51 (41 - 57)	52 (44 – 57)	41 (32 – 54)	<0.001
Living alone	122 (22)	52 (12)	70 (58)	<0.001
Lower education	146 (26)	73 (17)	73 (60)	<0.001
Dependent living	18 (3)	2 (1)	16 (13)	<0.001

Continuous values as mean (± standard deviation) or median (1st to 3rd quartile), categorical values as frequency (%). MI: myocardial infarction, COPD: chronic obstructive pulmonary disease, LVEF: left ventricular ejection fraction, EuroSCORE: European System for Cardiac Operative Risk Evaluation, NYHA: New York Heart Association, CABG: Coronary Artery Bypass Graft, MNA: Mini Nutritional Assessment, MMSE: Mini Mental State Examination, HRQL: health related quality of life

One year trajectory of functional recovery

Adverse functional outcome at one year after surgery was present in 257 (46%) patients (Figure 2). The one year postoperative trajectory of frail and non-frail patients is shown in Figure 3. Of the 120 patients identified as frail before surgery, 74 (62%) had adverse functional outcome, compared to 183 (42%) of the 435 non-frail patients ($p<0.001$). Any complication occurred in 328 (59%) patients. Prevalence of frailty differed between patients with or without a complication (no complication 40 (18%); mild complication 18 (18%); moderate complication 37 (31%); and severe complication 25 (24%) patients respectively, $p<0.014$). EuroSCORE II was associated with increased risk for moderate (OR 1.2 (95% CI 1.1 – 1.3)) and severe complications (OR 1.3 (95% CI 1.2 – 1.4)). Associations of individual frailty characteristics and complications are shown in Table 2.

Frailty and adverse functional outcomes

Physical health related quality of life

After three months and one year, median physical HRQL was similar to preoperative scores (45 (IQR 36-52), p=0.327 and 46 (IQR 36-54), p=0.245 respectively). Analysis of physical HRQL domains showed improvements in physical functioning and role physical (Supplementary table 2). EuroSCORE II (β -0.8 (95%CI -1.3 – -0.3), R^2 2%) and preoperative physical and mental HRQL were associated with change in physical HRQL at one year (Table 3). Compared to baseline, 134 (24%) patients experienced worse physical HRQL at one year after surgery. Risk factors for worse physical HRQL were EuroSCORE II (OR 1.1 (95% CI 1.0 – 1.2) AUC 0.58) and preoperative physical and mental HRQL (Supplementary table 3).

Mental health related quality of life

At three months and one year, median mental HRQL was 52 (IQR 41-57) and 52 (IQR 41-57) points and not different from preoperative scores (p=0.095 and p=0.053 respectively). Analysis of HRQL domains showed equal scores for three months and one year (Supplementary table 2). Polypharmacy, MNA, TGUGT, preoperative mental HRQL, and living alone were associated with change in mental HRQL at one year (Table 3). Worse mental HRQL at one year was reported by 141 (25%) patients. Frailty characteristics that were associated with worse mental HRQL at one year were TGUGT, preoperative physical HRQL and mental HRQL, living alone, and dependent living (Supplementary table 3).

Table 2. Association of individual frailty characteristics and in-hospital complications adjusted for EuroSCORE II using multinomial logistic regression

Frailty characteristic	Mild complication (n=103)			Moderate complication (n=121)			Severe complication (n=104)		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Polypharmacy	1.0	1.0 – 1.1	0.234	1.1	1.1 – 1.2	<0.001	1.1	1.0 – 1.2	0.088
MNA†	0.9	0.8 – 1.1	0.323	0.9	0.8 – 1.0	0.108	1.0	0.8 – 1.1	0.609
Nagi's scale	1.1	0.8 – 1.3	0.604	1.4	1.2 – 1.7	<0.001	1.2	1.0 – 1.5	0.103
5 Meter walk test	1.0	0.9 – 1.2	0.645	1.2	1.0 – 1.3	0.049	1.1	0.9 – 1.3	0.213
TGUGT	1.0	1.0 – 1.1	0.402	1.1	1.0 – 1.2	0.009	1.1	1.0 – 1.2	0.013
Low grip strength	0.9	0.7 – 1.2	0.766	1.3	0.8 – 2.1	0.264	1.4	0.9 – 2.3	0.181
MMSE†	1.0	0.9 – 1.2	0.731	1.0	0.9 – 1.1	0.805	0.9	0.8 – 1.1	0.311
Physical HRQL	1.0	1.0 – 1.0	0.103	1.0	0.9 – 1.0	0.001	1.0	1.0 – 1.0	0.781
Mental HRQL	1.0	1.0 – 1.0	0.346	1.0	1.0 – 1.0	0.159	1.0	1.0 – 1.0	0.636
Living alone	0.8	0.4 – 1.4	0.387	1.1	0.7 – 1.9	0.683	0.8	0.5 – 1.5	0.543
Lower education	1.0	0.6 – 1.8	0.873	1.3	0.8 – 2.1	0.343	1.3	0.7 – 2.2	0.373
Dependent living	3.2	0.5 – 20.0	0.207	5.2	1.0 – 26.5	0.047	7.0	1.4 – 34.8	0.018

No complication (n=227) was used as the reference category.
† Indicates a questionnaire where a high score represents a lower risk.
OR: odds ratio, CI: confidence interval, EuroSCORE: European System for Cardiac Operative Risk Evaluation MNA: Mini Nutritional Assessment, TGUGT: Timed Get Up and Go Test, MMSE: Mini Mental State Examination, HRQL: health related quality of life

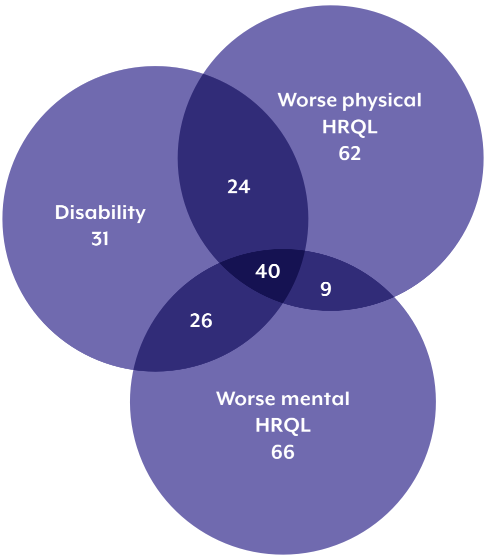


Figure 2. Venn diagram showing the number of patients with adverse functional outcome at 12 months after cardiac surgery and overlap of different functional outcomes. 257 patients experienced adverse functional outcome at one year. Due to rounding off after imputational analysis totals in this graph adds up to 258 patients.

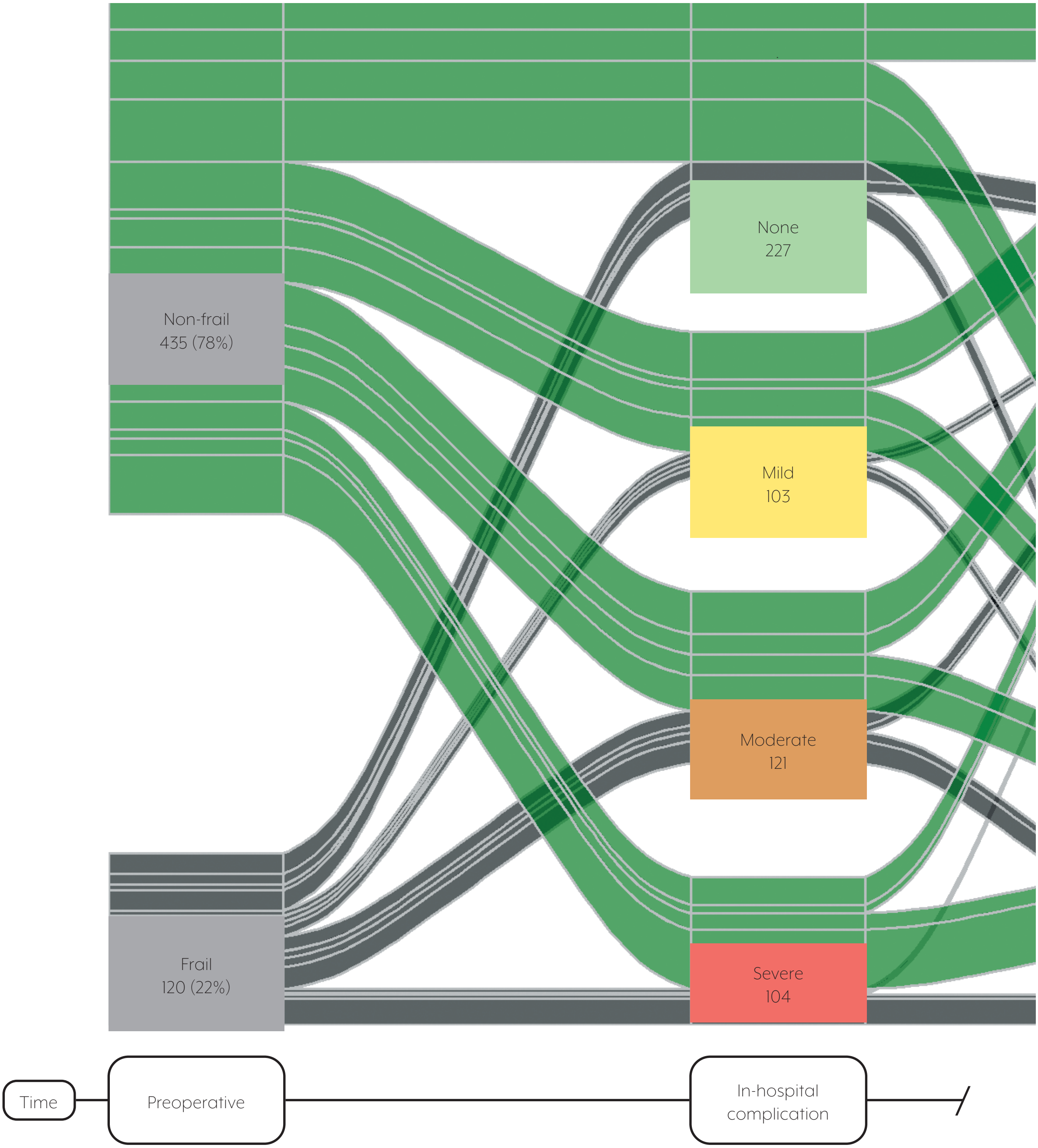
Table 3. Associations of individual frailty characteristics adjusted for EuroSCORE II with change in health related quality of life at one year and disability at one year

Frailty characteristic	Change in physical HRQL			Change in mental HRQL			Disability score		
	β	95% CI	ΔR² (%)	β	95% CI	ΔR²	β	95% CI	ΔR²
Polypharmacy	- 0.1	- 0.5 – 0.3		- 0.4	- 0.8 – 0.0	1	**1.4**	**0.8** – 2.0	**4**
MNA†	- 0.2	- 0.9 – 0.5		- 1.5	- 2.2 – - 0.8	3	- 0.6	- 1.7 – 0.5	
Nagi's Scale	1.0	- 0.1 – 2.1		0.4	- 0.7 – 1.5		**4.4**	**2.8** – 6.1	5
5 Meter walk test	- 0.5	- 1.3 – 0.2		- 0.4	- 1.2 – 0.5		**3.3**	**2.1** – 4.5	**5**
TGUGT	- 0.3	- 0.7 – 0.1		- 0.4	- 0.8 – 0.0	1	**2.2**	**1.6** – 2.8	**9**
Low grip strength	- 1.3	- 3.8 – 1.2		- 0.3	- 3.0 – 2.4		**4.9**	**1.0** – 8.9	**1**
MMSE†	0.1	- 0.6 – 0.7		- 0.1	- 0.8 – 0.6		- 1.0	- 2.0 – 0.1	
Physical HRQL	- 0.6	- 0.7 – - 0.5	16	0.1	- 0.0 – 0.2		**- 0.4**	**- 0.6** – - 0.2	3
Mental HRQL	0.2	0.0 – 0.3	1	- 0.6	- 0.7 – - 0.4	15	**- 0.3**	**- 0.5** – - 0.1	**2**
Living alone	- 1.4	- 4.4 – 1.5		- 3.4	- 6.5 – - 0.7	1	**7.8**	**3.3** – 12.4	**2**
Lower education	- 0.6	- 3.4 – 2.2		2.3	- 0.7 – 5.3		3.8	- 0.6 – 8.2	
Dependent living	- 4.8	- 11.8 – 2.2		- 5.3	- 12.8 – 2.1		28.5	**17.7** – 39.2	**5**

Bold font indicates p value <0.050
† A higher score on the test indicates resilience and a lower score frailty.
CI: Confidence Interval, EuroSCORE: European System for Cardiac Operative Risk Evaluation, MNA: Mini Nutritional Assessment, TGUGT: Timed Get Up and Go Test, MMSE: Mini Mental State Examination, HRQL: health related quality of life

Disability

Mean disability score was 11 (IQR 4-22) at three months and 10 (IQR 4-22) at one year ($p=0.038$). EuroSCORE II was associated with more disability (β 2.2 (95% CI 1.3 – 3.0), R^2 5%) Frailty characteristics associated with disability scores at one year were polypharmacy, Nagi's scale, 5MWT, TGUGT, grip strength, preoperative physical and mental HRQL, living alone, and dependent living (Table 3). Disability at one year was reported by 120 (22%) patients. Out of all patients with disability, 31 (26%) had limitations in physical functioning on Nagi's scale before surgery. EuroSCORE II (OR 1.2 (95%CI 1.1 – 1.3) AUC 0.67), polypharmacy, Nagi's scale, 5MWT, TGUGT, preoperative mental and physical HRQL, living alone, and dependent living were associated with disability at one year (Supplementary table 3).



Non-frail
435 (78%)
Frail
120 (22%)
None
227
Mild
103
Moderate
121
Severe
104
Time
Preoperative
In-hospital
complication

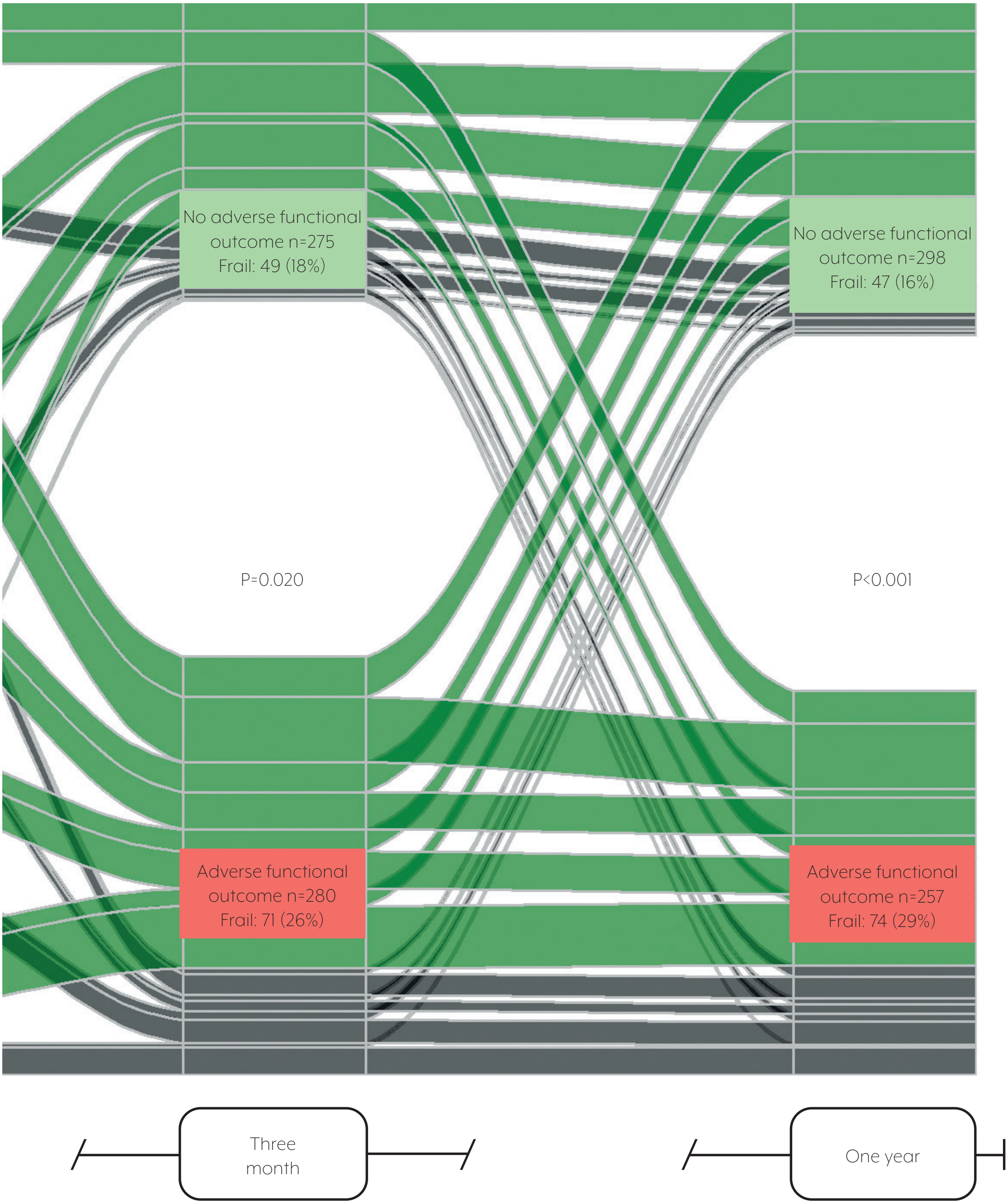


Figure 3. Alluvial chart showing postoperative complications and functional recovery according to frailty. The waves show the postoperative recovery trajectory for all patients up to one year after surgery. The width of the waves corresponds to the number of patients following that trajectory. Grey waves represent frail patients and green waves non-frail patients. A patient was considered frail when at least one frailty characteristic in all three domains was affected. Adverse functional outcome was a composite of worse physical or mental HRQL or postoperative disability.

Discussion

The AGE study analysed eleven frailty characteristics to better understand the association between preoperative frailty and functional recovery of elderly patients after elective cardiac surgery. We found that the first year of recovery after cardiac surgery is complex and older patients report a myriad of recovery trajectories. A vast majority of older cardiac surgery patients had one or more frailty characteristics and over half of all patients had frailty characteristics in multiple domains. Preoperative frailty was associated with adverse functional outcome, but individual frailty characteristics were more closely related with postsurgical disability than worse HRQL. One out of four older patients reported worse HRQL one year after cardiac surgery, and one out of five patients reported disability.

The results of our study confirm that a considerate proportion of cardiac surgery patients report worse HRQL after surgery.[2,3,9–12] Especially in the elderly, a majority of cardiac surgery procedures is aimed at improving HRQL by reducing complaints of chronic cardiac disease. To increase the number of older patients that will truly benefit from surgery it is important to identify risk factors for adverse functional outcome. However, studies that investigated routine care data to identify predictors of worse HRQL after cardiac surgery showed conflicting results with limited clinical applicability.[9–12] In our study, we sought to identify preoperative frailty characteristics that influenced HRQL after one year, but found mainly poor predictors. The most important predictor of postsurgical HRQL was preoperative HRQL. Preoperative HRQL explained 16% and 15% of variation in physical and mental HRQL respectively. Patients with poor preoperative HRQL were more likely to improve, while patients with satisfactory preoperative HRQL were at risk for worse HRQL. This finding has previously been reported by others.[6,10,26] Subsequently, preoperative decision making in older surgical patients with satisfactory HRQL should carefully weigh the expected improvement in survival and disease burden versus the risk of deterioration in HRQL.[6,27]

One out of five patients in our study cohort experienced disability at one year after cardiac surgery. Disability questionnaires were assessed after surgery, and not compared to preoperative measures. Therefore, postsurgical disability could represent patients with new or worsened disability, and patients with persistent disability, that did not fully benefit from surgery. Although, the reported incidence of disability in our study is similar to prior reports, assessment methods differed across reports and direct comparisons cannot be made.[2–4,28] Most preoperative frailty characteristics were associated with postsurgical disability. The TGUGT test was the most robust predictor for disability in our cohort. Associations between frailty and disability were seen in other studies as well.[2,3,28] In line with our results, overall frailty, gait speed, grip strength, dependent living, and ADL functioning were identified as individual frailty characteristics that predicted disability.[2,3,28] Yet, carefulness is warranted when comparing cardiac surgery studies on functional outcome. Many tools are available to measure postoperative disability and questionnaires vary between studies. In our study, the WHODAS 2.0 questionnaire was used as was recently recommended by the Standardised Endpoints in Perioperative Medicine initiative.[29] Also, the definition and prevalence of frailty may vary between cardiac populations.[2,3]

The AGE study illustrates the complexity of one year functional recovery in older cardiac surgery patients (Figure 3). Approximately half of the patients reported no adverse functional outcome. Most of these patients were already recovered after three months. Depending on type of surgery, it seems plausible that some patients need more time to recover, which could explain the patients that improved in functional outcome between three and twelve months. This supports the recommendation to routinely measure patient reported outcomes after one year.[29] Nevertheless, reasons that are not related to surgery may affect functional outcome during a year of follow up. This may have been the case for the patients who reported no adverse functional outcome at three months, but deteriorated in the period between three months and one year. In elderly patients comorbidities are more prevalent, and might worsen over time. Also, changes in social environment (e.g. loss of a partner, or family member) can negatively influence HRQL. One might argue that this is more eminent in frail patients who are often less resilient. Lastly, patient reported outcomes are susceptible to subjectivity, which is especially the case for HRQL. For example, patients with good coping strategies are less likely to experience worse HRQL in case of a setback, such as postsurgical disability. This is known as the disability paradox and illustrated by 31 patients with disabilities and preserved HRQL (Figure 3).[30] Furthermore, over time patients change their internal standards, values and conceptualization of HRQL.[31] Patients with mild disabilities may have experienced an initial worse HRQL, but adapted over time, resulting in a preserved HRQL after one year.

Strengths of the current study include the thorough screening for preoperative frailty and one year follow up of HRQL and disability. Because associations of individual characteristics on functional outcomes were presented, our results can be used by anaesthesiologists and surgeons to implement a routine preoperative frailty screening in older cardiac surgery patients. Disability does not always affect HRQL.[30,31] Including both measures of functional outcome offers a complete insight in a patient's functional recovery. Finally, our sample size is one of the largest in studies that assessed frailty and functional outcomes after cardiac surgery.

Several limitations should be discussed. First, our study sample consisted of patients undergoing various types of surgery that included low and high risk procedures. Although surgical risk can affect functional outcome, our cohort is representative of a real world cardiac surgery population. To reduce bias we included EuroSCORE II in our analysis. Second, the cut-off point for worse HRQL is not predefined by the SF36. We defined worse HRQL as a decrease ≥ 5 points, which is in line with other studies.[9,10,32] Whether or not this represents a clinically significant change in HRQL has not been validated. Third, 29% of all eligible patients were not included in our study. In 16% because of a high study burden. Although inclusion rates are comparable to other studies, this may have introduced some bias.[3,26,33] It is conceivable that frail patients are more inclined to deny consent compared to non-frail patients meaning a possible underrepresentation of frailty in our cohort. Fourth, 14% loss to follow up occurred. A comparison between complete cases and patients with missing values showed that sex, pulmonary disease, NYHA class, and subsequently, EuroSCORE II differed between groups. Also, patients with missing data had more frailty characteristics. As some of these values are associated with adverse functional outcome a complete case analysis might have underestimated effect sizes of preoperative frailty on adverse outcome. Multiple imputation was performed to achieve unbiased estimates of associations.

Frailty has become an established risk factor for postsurgical morbidity and mortality.[8] In elderly patients preserved HRQL and daily functioning are often of greater importance than longevity.[4] Despite the challenges that accompany the assessment and prediction of functional recovery, it is essential for full informed consent.[6,13,27] Future research should focus on preoperative interventions to improve functional outcome in high risk surgical patients. Preoperative multidisciplinary team care is emerging as a standard of care in complex surgical patients. Recent trials in hip-fracture and vascular surgery showed that a geriatric assessment and patient specific interventions executed by a multidisciplinary team can reduce complications and discharge to a higher level of dependency and, more importantly, improve HRQL.[34,35] In cardiac surgery similar trials are ongoing.[36,37]

In conclusion, preoperative frailty characteristics were common and associated with adverse functional outcome one year after cardiac surgery. Frailty characteristics were primarily related to postsurgical disability while postsurgical HRQL was mainly associated with preoperative HRQL. The results of our study advocate for the routine assessment of preoperative frailty and HRQL among older cardiac surgery patients to improve risk stratification.

References

1 World Health Organization. Constitution of the World Health Organization. April 7. 1948. https://www.who.int/about/who-we-are/constitution (accessed Dec 20, 2019).

2 Hosler QP, Maltagliati AJ, Shi SM, et al. A Practical Two-Stage Frailty Assessment for Older Adults Undergoing Aortic Valve Replacement. J Am Geriatr Soc 2019; 67: 2031–7.

3 Afilalo J, Lauck S, Kim DH, et al. Frailty in Older Adults Undergoing Aortic Valve Replacement. The FRAILTY-AVR Study. J Am Coll Cardiol 2017; 70: 689–700.

4 Sun LY, Tu J V., Lee DS, et al. Disability-free survival after coronary artery bypass grafting in women and men with heart failure. Open Hear 2018; 5: 1–12.

5 Rumsfeld JS, Alexander KP, Goff DC, et al. Cardiovascular health: The importance of measuring patient-reported health status a scientific statement from the American heart association. Circulation 2013; 127: 2233–49.

6 de Heer F, Gökalp AL, Kluin J, Takkenberg JJM. Measuring what matters to the patient: health related quality of life after aortic valve and thoracic aortic surgery. *Gen Thorac Cardiovasc Surg* 2019; 67: 37–43.

7 Pierri MD, Capestro F, Zingaro C, Torracca L. The changing face of cardiac surgery patients: an insight into a Mediterranean region. Eur J Cardiothorac Surg 2010; 38: 407–13.

8 Lee DH, Buth KJ, Martin BJ, Yip AM, Hirsch GM. Frail patients are at increased risk for mortality and prolonged institutional care after cardiac surgery. Circulation 2010; 121: 973–8.

9 Blokzijl F, Houterman S, van Straten BHM, et al. Quality of life after coronary bypass: a multicentre study of routinely collected health data in the Netherlands†. Eur J Cardio-Thoracic Surg 2019; 56: 526–33.

10 Verwijmeren L, Noordzij PG, Daeter EJ, van Zaane B, Peelen LM, van Dongen EPA. Preoperative determinants of quality of life a year after coronary artery bypass grafting: A historical cohort study. J Cardiothorac Surg 2018; 13: 1–8.

11 Abah U, Dunne M, Cook A, et al. Does quality of life improve in octogenarians following cardiac surgery? A systematic review. BMJ Open 2015; 5: e006904.

12 Charles EJ, Mehaffey JH, Hawkins RB, et al. Meaningful Patient-centered Outcomes 1 Year Following Cardiac Surgery. Ann Surg 2019; may 2: [Epub ahead of print].

13 Verwijmeren L, Peelen LM, van Klei WA, et al. Anaesthesia geriatric evaluation to guide patient selection for preoperative multidisciplinary team care in cardiac surgery. Br J Anaesth 2020; 124: 377–85.

14 Afdeling Klinische Informatiekunde AA. Handboek BHN Registratieproject v4.0.1. 2015; : 1–189.

15 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240: 205–13.

16 Hall DE, Arya S, Schmid KK, et al. Development and initial validation of the Risk Analysis Index for measuring frailty in surgical populations. JAMA Surg 2017; 152: 175–82.

17 Mitnitski A, Collerton J, Martin-Ruiz C, et al. Age-related frailty and its association with biological markers of ageing. BMC Med 2015; 13: 1–9.

18 Ware J jr, Sherbourne C. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992; jun: 473–83.

19 Zee KI Van Der, Sanderman R. Het meten van de algemene gezondheidstoestand met de Rand-36: Een handleiding, 2nd edn. Groningen: Research institute SHARE UMCG / Rijksuniversiteit Groningen, 2012.

20 Joskowiak D, Meusel D, Kamla C, Hagl C, Juchem G. Impact of Preoperative Functional Status on Quality of Life after Cardiac Surgery. *Thorac Cardiovasc Surg* 2019. DOI:10.1055/s-0039-1696953.

21 Ustün TB, Chatterji S, Kostanjsek N, et al. Developing the World Health Organization Disability Assessment Schedule 2.0. Bull World Health Organ 2010; 88: 815–23.

22 International Classification of Functioning, Disability and Health (ICF) Practical Manual V.0.9. 2013. https://www.who.int/classifications/icf/en/ (accessed Sept 11, 2019).

23 Shulman MA, Myles PS, Chan MT V., McIlroy DR, Wallace S, Ponsford J. Measurement of Disability-free Survival after Surgery. Anesthesiology 2015; 122: 524–36.

24 Marshall A, Altman DG, Holder RL, Royston P. Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines. BMC Med Res Methodol 2009; 9: 57.

25 Groenwold RHH, Donders ART, Roes KCB, Harrell FE, Moons KGM. Dealing With Missing Outcome Data in Randomized Trials and Observational Studies. Am J Epidemiol 2012; 175: 210–7.

26 Kurfirst V, Mokráček A, Krupauerová M, et al. Health-related quality of life after cardiac surgery - the effects of age, preoperative conditions and postoperative complications. J Cardiothorac Surg 2014; 9: 1–8.

27 Whiteman AR, Dhesi JK, Walker D. The high-risk surgical patient: A role for a multi-disciplinary team approach? Br J Anaesth 2016; 116: 311–4.

28 Hoogerduijn JG, de Rooij SE, Grobbee DE, Schuurmans MJ. Predicting functional decline in older patients undergoing cardiac surgery. Age Ageing 2014; 43: 218–21.

29 Moonesinghe SR, Jackson AIR, Boney O, et al. Systematic review and consensus definitions for the Standardised Endpoints in Perioperative Medicine initiative: patient-centred outcomes. Br J Anaesth 2019; 123: 664–70.

30 Huber M, Knottnerus JA, Green L, et al. How should we define health? BMJ 2011; 343: d4163.

31 Sprangers MA., Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. Soc Sci Med 1999; 48: 1507–15.

32 Joskowiak D, Meusel D, Kamla C, Hagl C, Juchem G. Impact of Preoperative Functional Status on Quality of Life after Cardiac Surgery. Thorac Cardiovasc Surg 2019; sep 9.

33 Hoogerduijn JG, Buurman BM, Korevaar JC, Grobbee DE, De rooij SE, Schuurmans MJ. The prediction of functional decline in older hospitalised patients. Age Ageing 2012; 41: 381–7.

34 Prestmo A, Hagen G, Sletvold O, et al. Comprehensive geriatric care for patients with hip fractures: A prospective, randomised, controlled trial. Lancet 2015; 385: 1623–33.

35 Partridge JSL, Harari D, Martin FC, et al. Randomized clinical trial of comprehensive geriatric assessment and optimization in vascular surgery. Br J Surg 2017; 104: 679–87.

36 Yau DKW, Wong MKH, Wong WT, et al. PREhabilitation for improving QUality of recovery after ELective cardiac surgery (PREQUEL) study: Protocol of a randomised controlled trial. BMJ Open 2019; 9: 1–9.

37 Stammers AN, Kehler DS, Afilalo J, et al. Protocol for the PREHAB study-Pre-operative Rehabilitation for reduction of Hospitalization After coronary Bypass and valvular surgery: a randomised controlled trial. BMJ Open 2015; 5: e007250.

Supplementary files

Supplementary Table 1. Baseline characteristics according to complete cases or cases with missing data

Patient characteristics	Complete cases N=392	Cases with missing data N=163	P-value	Cases with missing (%)
Age (years)	74 (72 - 77)	75 (72 - 78)	0.840	0
Male sex	279 (71)	94 (58)	0.002	0
Hypertension	331 (84)	131 (80)	0.242	0
Anginal complaints	145 (37)	64 (39)	0.615	0
Atrial fibrillation	115 (29)	51 (31)	0.647	0
Previous MI	58 (15)	27 (17)	0.598	0
Stroke	53 (14)	24 (15)	0.709	0
Diabetes Mellitus	77 (20)	37 (23)	0.417	0
Extra cardiac arteriopathy	42 (11)	26 (16)	0.087	0
COPD	38 (10)	26 (16)	0.036	0
Prior cardiac surgery	30 (8)	8 (5)	0.244	0
LVEF < 50%	79 (20)	39 (24)	0.305	1 (0)
EuroSCORE II	1.7 (1.2 – 2.8)	2.3 (1.4 - 4.5)	<0.001	0
NYHA class			<0.001	0
- 1	66 (17)	15 (9)		
- 2	211 (55)	82 (50)		
- 3	110 (28)	56 (34)		
- 4	5 (1)	10 (6)		
Type of surgery			0.074	0
- Single CABG/maze	145 (37)	48 (29)		
- Single valve	107 (27)	47 (29)		
- Combined surgery	114 (29)	53 (33)		
- Aortic surgery	26 (7)	15 (9)		
Frailty				
Polypharmacy	6.2 (±3.1)	7.1 (±3.9)	0.011	4 (1)
MNA (points)	13 (12 – 14)	13 (12 – 14)	0.056	0
Nagi's scale (points)	0 (0 – 1)	1 (0 – 2)	0.009	2 (0)
5 Meter walk test (sec)	4.6 (4.1 – 5.3)	5.1 (4.3 – 5.9)	0.001	7 (1)
TGUGT (sec)	9.7 (8.4 – 11.3)	10.5 (8.8 – 13.0)	0.004	8 (1)
Low grip strength	137 (35)	68 (42)	0.119	1 (0)
MMSE (points)	29 (28 – 30)	28 (27 - 29)	0.003	6 (1)
Physical HRQL (points)	44 (35 – 52)	41 (32 – 50)	0.108	7 (1)
Mental HRQL (points)	52 (43 – 57)	49 (37 – 56)	0.018	7 (1)
Living alone	70 (18)	52 (32)	<0.001	0
Lower education	87 (22)	54 (36)	0.001	12 (2)
Dependent living	6 (2)	12 (7)	<0.001	0

Continuous values as mean (± standard deviation) or median (1st to 3rd quartile), categorical values as frequency (%).
MI: myocardial infarction, COPD: chronic obstructive pulmonary disease, LVEF: left ventricular ejection fraction, EuroSCORE: European System for Cardiac Operative Risk Evaluation, NYHA: New York Heart Association, CABG: Coronary Artery Bypass Graft, MNA: Mini Nutritional Assessment, TGUGT: Timed Get Up and Go Test, MMSE: Mini Mental State Examination, HRQL: health related quality of life

Supplementary Table 2. Change in HRQL at 3 and 12 months compared to baseline

		Preoperative Median (IQR)		At 3 months Median (IQR)		P value*	At 1 year Median (IQR)		P value*
Physical HRQL	Physical functioning	65	40-82	71	50-90	<0.001	75	50-90	<0.001
	Role physical	25	0-100	34	0-100	0.021	51	0-100	<0.001
	Bodily pain	78	57-100	78	57-100	0.102	80	57-100	0.367
	General health	58	45-70	61	45-75	0.016	60	45-75	0.642
Mental HRQL	Vitality	60	45-75	60	45-75	0.535	65	47-80	0.405
	Social functioning	75	63-100	75	63-100	0.170	88	63-100	0.609
	Role emotional	100	33-100	100	33-100	0.792	100	33-100	0.106
	Mental health	76	64-88	80	64-92	0.736	80	62-92	0.406

* P-value for difference compared to preoperative values
HRQL: Health Related Quality of Life

Supplementary Table 3. Logistic regression of individual frailty characteristics adjusted for EuroSCORE II on adverse functional outcome at one year

Frailty characteristics	Worse physical HRQL		Worse Mental HRQL		Disability	
	OR (95% CI)	**AUC**	**OR**	**AUC**	**OR**	**AUC**
Polypharmacy	1.0 (0.96–1.1)	0.58	1.1 (1.0 – 1.1)	0.56	**1.1 (1.1 – 1.2)**	**0.68**
MNA†	1.0 (0.9 – 1.1)	0.58	1.1 (1.0 – 1.2)	0.56	0.9 (0.8 – 1.0)	0.67
Nagi's scale	1.0 (0.8 – 1.2)	0.58	1.1 (1.0 – 1.3)	0.55	**1.6 (1.3 – 1.9)**	**0.71**
5 Meter walk test	1.1 (1.0 – 1.2)	0.60	1.1 (1.0 – 1.2)	0.56	**1.4 (1.2 – 1.6)**	**0.72**
TGUGT	1.1 (1.0 – 1.1)	0.59	**1.1 (1.0 – 1.2)**	**0.55**	**1.3 (1.2 – 1.4)**	**0.74**
Low grip strength	1.1 (0.7 – 1.7)	0.59	1.0 (0.7 – 1.5)	0.55	1.4 (0.9 – 2.2)	0.66
MMSE†	0.9 (0.9 – 1.0)	0.59	1.0 (0.9 – 1.1)	0.55	0.9 (0.8 – 1.0)	0.68
Physical HRQL	**1.1 (1.0 – 1.1)**	**0.67**	**1.0 (1.0 – 1.0)**	**0.59**	**1.0 (0.9 – 1.0)**	**0.69**
Mental HRQL	**1.0 (1.0 – 1.0)**	**0.64**	**1.1 (1.0 – 1.1)**	**0.65**	**1.0 (1.0 – 1.0)**	**0.67**
Living alone	1.3 (0.8 – 2.1)	0.59	**1.7 (1.1 – 2.7)**	**0.57**	**1.9 (1.2 – 3.1)**	**0.68**
Lower education	1.1 (0.7 – 1.8)	0.58	1.0 (0.7 – 1.6)	0.53	1.4 (0.9 – 2.3)	0.68
Dependent living	1.5 (0.5 – 4.1)	0.58	**3.2 (1.1 – 9.2)**	**0.55**	**9.4 (2.9 – 30.6)**	**0.70**

Bold font indicates p value <0.050
† A higher score on the test indicates resilience and a lower score frailty.
EuroSCORE: European System for Cardiac Operative Risk Evaluation, MNA: Mini Nutritional Assessment, TGUGT: Timed Get Up and Go Test, MMSE: Mini Mental State Examination, HRQL: health related quality of life

Chapter 4

Anaesthesia Geriatric Evaluation (AGE) to guide patient selection for preoperative multi-disciplinary team care in cardiac surgery

Lisa Verwijmeren
Linda M Peelen
Wilton A van Klei
Edgar J Daeter
Eric P A van Dongen
Peter G Noordzij

BJA 2020; 124 (4) p377-385

Abstract

Background. A multi-disciplinary approach to improve postoperative outcomes in frail elderly patients is gaining interest. Multi-disciplinary team care should be targeted at complex patients at high risk for adverse postoperative outcome to limit the strain on available resources and prevent an unnecessary increase in patient burden. This study aimed to improve patient selection for multi-disciplinary care by identifying risk factors for disability after cardiac surgery in elderly patients.

Methods. Two-centre prospective cohort study in 537 patients aged ≥70 years undergoing elective cardiac surgery. Before surgery 11 frailty characteristics were investigated. Outcome was disability at three months defined as World Health Organisation Disability Assessment Schedule 2.0 ≥25%. Multivariable modelling using logistic regression, concordance statistic (c-statistic), and net reclassification index were used to identify factors contributing patient selection.

Results. Disability occurred in 91 (17%) patients. Ten out of 11 frailty characteristics were associated with disability. A multivariable model including EuroSCORE II and preoperative haemoglobin yielded a c-statistic of 0.71 (95% CI 0.66 – 0.77). After adding prespecified frailty characteristics (polypharmacy, gait speed, physical disability, preoperative health related quality of life, and living alone) to this model the c-statistic improved to 0.78 (95% CI 0.73 – 0.83). Net reclassification index was 0.32 ($p<0.001$) showing improved discrimination for patients at risk for disability at three months.

Conclusions. Using preoperative frailty characteristics improves discrimination between elderly patients with and without disability at three months after cardiac surgery and can be used to guide patient selection for preoperative multi-disciplinary team care.

4

Introduction

Normal ageing and enhanced medical management of chronic cardiac disease results in a growing number of elderly patients being referred for cardiac surgery.[1] Improvements in surgical techniques and perioperative care have made cardiac surgery feasible for elderly patients, but higher age remains associated with an increased risk for adverse outcome.[2] Higher complication rates in elderly patients can be attributed to a relatively small group of patients that is often characterized by advanced age, multi-morbidity and frailty.[3,4] Similar to other medical specialties, a collaborative approach of multiple specialties in a multi-disciplinary team (MDT) has been suggested in these complex patients.[5,6]

A MDT meeting can be useful to weigh the risks and benefits of surgery, improve frailty assessment and discuss options for prehabilitation in order to optimize preoperative shared decision making and improve postoperative outcomes. However, support for preoperative MDT care is not universal as evidence for cost effectiveness is lacking and inappropriate referral is likely to delay surgical treatment in many healthy patients in whom MDT involvement can be considered redundant.[7] To limit the strain on available resources and prevent an unnecessary increase in patient burden, MDT care should be targeted at complex patients at high risk for adverse outcome.[5]

The selection of patients who may benefit from preoperative MDT care cannot be merely based on age due to the increasing number of elderly patients. In addition, it may not benefit in fit elderly surgery patients who can safely proceed with cardiac surgery. Commonly used risk models in cardiac surgery can be used to identify high risk patients, however these models focus on postoperative mortality.[8–10] Especially for elderly patients with vulnerable health or frailty, functional outcomes are important, as a small reduction in functional status can lead to a higher level of dependency for activities of daily living. This study therefore aimed to improve patient selection for preoperative MDT care by identifying risk factors for postoperative disability in elderly cardiac surgery patients.

Methods

Design

The Anaesthesia Geriatric Evaluation (AGE) study was a prospective observational cohort study carried out in two tertiary referral centres for cardiac surgery in The Netherlands (St. Antonius Hospital Nieuwegein and University Medical Centre Utrecht). Inclusion took place from July 2015 until August 2017. Ethical approval was given by the local ethics committee (Medical Ethics Research Committee United, number R15.039). The study was registered at clinicaltrials.gov (NCT02535728) and performed in accordance with the declaration of Helsinki. All subjects gave written informed consent.

Population

All consecutive patients undergoing elective cardiac surgery were screened for recruitment. Inclusion criteria were: age ≥70 years, elective open cardiac surgery (including coronary artery bypass grafting (CABG), surgery for atrial fibrillation (i.e. minimal invasive surgical ablation (mini-Maze) or Cox-Maze (CM) IV procedure), heart valve repair or replacement (i.e. surgical aortic valve replacement, mitral valve replacement or repair via sternotomy or port access), thoracic aortic surgery (i.e. ascending aortic repair, thoracic aortic aneurysm repair), or any combination of these procedures. Exclusion criteria were home care or living in an assisted living facility prior to surgery because in these patients a MDT meeting was deemed necessary regardless of the presence of additional risk factors.

Clinical characteristics and data collection

Preoperative anaesthesia assessment was performed in all patients and consisted of a medical history, physical examination, laboratory tests and routinely performed transthoracic cardiac echocardiography. Comorbidities were collected from referral letters and electronic medical files. Medication history was available from hospital pharmacy services. To assess the overall burden of comorbidities the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) was calculated for each patient[8]. Data were managed using REDCap web application tools.

Anaesthesia Geriatric Evaluation

Indication for surgery was set by the cardiologist and cardiothoracic surgeon. Study patients were identified by consulting scheduled cardiac surgeries. Eligible patients were informed by mail and telephone prior to their visit to the anaesthesia preoperative clinic. An anaesthesia geriatric evaluation was performed at the clinic by the first author (LV) immediately after routine preoperative assessment. The results of AGE were not available for treating physicians. Physical, mental and social frailty were assessed. Analysis of physical frailty included nutritional status, gait speed, polypharmacy, daily functioning and grip strength. Screening for mental frailty included an assessment of cognition and health related quality of life (HRQL). To assess social frailty we evaluated a patient's living situation and educational status. Table 1 explains used tests for all frailty characteristics with corresponding cut-off values. Patients received routine perioperative care and surgical procedures were performed according to standard clinical practice. About a third of patients were transferred to the referral hospital for postoperative care several days after surgery. Discharge letters were obtained to receive data on postoperative complications and date of discharge.

Outcomes

Primary outcome was disability or death at three months after surgery. Disability was measured with the 36-item Self-assessment World Health Organisation Disability Assessment Schedule 2.0 (WHODAS 2.0), which was send to each surviving patient by mail.[11] In case of incomplete or missing questionnaires patients were contacted by phone by a member of the study team to collect missing data and when necessary questionnaires were sent a second time. The WHODAS 2.0 covers limitations over the past 30-days in six domains (i.e. cognition, mobility, self-care, getting along with people, life activities and participation in society, and self-care). Summary scores were calculated following instructions from the WHODAS 2.0 manual.[11] Summary scores range from 0% to 100% with 0% representing no disability and 100% representing complete dependency. Death was scored as maximum disability (100%). In this study disability was defined as a score ≥25%, and a score <25% was considered as disability free survival.[11–13] Assessment of outcome was not blinded but since questionnaires were self-assessed by patients the risk of bias was negligible.

Missing data

Removing patients with missing data from the analysis (a complete case analysis) can lead to bias since data is often not missing at random but associated with patient characteristics. To limit bias, missing data were replaced by multiple imputation.[14,15] Pre- and postoperative data, including missing WHODAS 2.0 summary scores, were imputed in twenty imputation sets and results were pooled using Rubin's Rule.[16]

Table 1. Description of frailty tests in the anaesthesia geriatric evaluation

Frailty characteristic	Test	Method of assessment	Cut off value
Physical domain			
Nutritional status	Mini Nutritional Assessment	Six item questionnaire on weight loss, eating, BMI, and psychological status	A score ≤11 out of 14 identified patients at risk for malnutrition[36]
Gait speed	5-Meter walk test	Patients were instructed to walk at their normal pace with walking aids if needed for five meters. Time between first footfall after the starting line and first footfall after the five meter line was recorded	Impaired gait speed was defined as ≥6 seconds or inability to perform the test[18,37]
	Timed get up and go test	Time was recorded between standing up from a seated position in a chair, walk for three meters with walking aids if needed and return to a seated position.	Impaired gait speed was defined as ≥10 seconds or inability to perform the test[38,39]
Polypharmacy	Number of prescriptions	Assessment by hospital pharmacy services	≥5 Prescribed medications[40]
Daily functioning	Nagi's scale of physical disability	Seven item questionnaire on lifting heavy objects, kneeling, raising arms above the head, walking one flight of stairs, and walking 1,5 kilometres	A score ≥3 implied impairments[41]
Handgrip strength	Hydraulic handheld dynamometer	Best result of three consecutive tests to squeeze dynamometer with lower arm unsupported and in a 90⁰ angle	According to age and sex[42]
Mental domain			
Cognition	Mini Mental State Examination	Eleven item questionnaire on orientation in time and place, short term memory, attention, and following verbal and written commands.	A score of ≤25 out of 30 was considered as mildly impaired cognition[43]
Health related quality of life	Medical Outcomes Study Short Form 36	36 item self-assessed questionnaire on physical and mental well-being generating two scores representing mental and physical health related quality of life	A deviation of >1 standard deviation from the population mean was considered impaired[44,45]
Social domain			
Living situation	Interview		Impaired when a patients was living without a partner or family
Educational status	Interview		Impaired when no education beyond secondary education was followed

Statistical analysis

Data are presented as frequencies and percentages for categorical data and as median with first and third quartile (1^{st}-3^{rd}Q) for continuous data. Differences between patients with and without disability at three months after surgery were tested with Chi square test for dichotomous or categorical variables and Student T test for continuous variables.

To investigate the incremental value of AGE in patient referral for a MDT meeting two models were developed using multivariable logistic regression analysis: a basic model included variables that were readily available without additional testing (EuroSCORE II and preoperative haemoglobin (Hb)), and an AGE model in which frailty characteristics were added to the basic model. Variables included in the AGE model were based on previous literature on frailty as risk factor for adverse outcome in cardiac surgery and clinical feasibility and included: medication use[17]; 5MWT[18]; Nagi's scale[19]; preoperative HRQL[20] and living alone.[21] Clinical feasibility was based on three main concepts: implementation in routine preoperative care, options for prehabilitation, and limited patient burden.

A net reclassification index (NRI) was calculated to compare the discriminative abilities of the basic model and the AGE model to classify patients into low, intermediate or high risk groups of disability. The NRI is a sensitive measure for comparing the discriminatory values of risk models. In our study, it compares the estimated probabilities for disability and disability-free survival. The NRI improved when the AGE model showed higher estimated probabilities for disability in disabled patients, compared to the basic model. Similarly, the NRI improved when the estimated probabilities for disability-free survival were lower in patients without disability, compared to the basic model. The NRI was calculated using the proportions of patients that were classified to a different risk level (low, moderate, high) after using the AGE model.[22,23] Risk groups were low, intermediate and high and defined as <10%, 10% to 20%, or ≥20% predicted risk respectively.[20,24–27]

Pearson's correlation coefficient was used to test for multicollinearity. Of variables with a correlation > 0.7 one was chosen to stay in the model. Possible non-linearity of the continuous variables in the model was assessed by comparing the log likelihood of different models with the variable added continuously or after transformation (square root transformation or log transformation). Values of $P < 0.05$ were considered statistically significant. Data analysis were performed using IBM SPSS Statistics version 23 for Windows (IBM Corp. Armonk, New York).

Sample Size Analysis

When designing the AGE study sample size was based on a rule of thumb that for each predictor variable in a multivariable model ten patients are needed with the outcome variable. As described above we included seven variables in our model. This would result in at least 70 patients. In absence of available evidence on postoperative disability after cardiac surgery at the time of developing this study, worse HRQL was chosen as a surrogate end point, which has been reported in up to 16% of patients after open cardiac surgery.[25–27] In order to develop the model at least 70/0.16 = 438 patients would be needed giving the current sample size sufficient power.

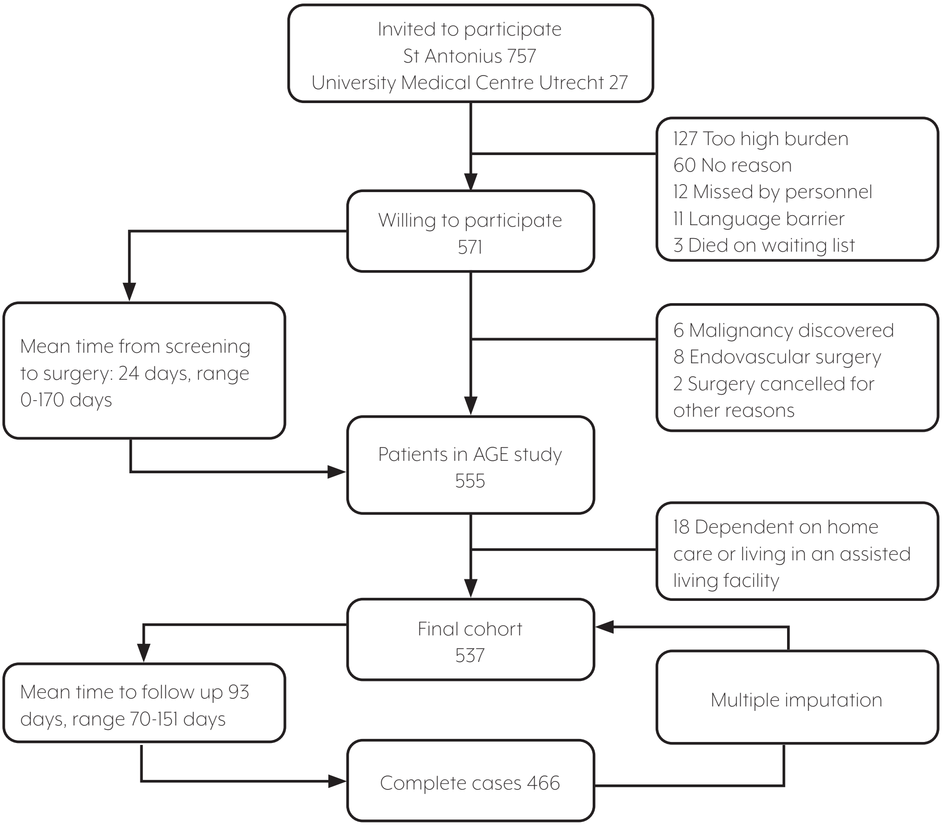


Figure 1. Flowchart of patient inclusion

Results

Study population and outcome

A total of 784 patients were eligible for inclusion during the study period, 571 (73%) patients signed informed consent and underwent AGE. Thirty four patients were excluded from the analysis for the following reasons: in 16 patients surgery was cancelled and 18 patients were dependent on home care or living in an assisted living facility prior to surgery (Figure 1). The final cohort consisted of 537 patients, of whom 435 (81%) had complete data. WHODAS 2.0 was complete in 463 (86%) patients. Characteristics of patients with and without missing data are given in supplemental tables 1 and 2. Median age was 75 years (1^{st}-3^{rd}Q 72 - 77) and 63 (12%) patients were octogenarian. Two-thirds of patients were male and median EuroSCORE II was 1.8 (1^{st}-3^{rd}Q 1.2 - 3.2). Coronary artery surgery and isolated aortic valve replacement were most commonly performed in 190 (35%) and 146 (27%) patients, respectively. Thirty percent of patients (n=163) underwent combined procedures. Disability-free survival was present in 446 (83%) patients. Disability occurred in 91 (17%) patients, of whom 17 (3%) patients were deceased. Baseline characteristics according to postoperative disability are presented in Table 2.

Anaesthesia Geriatric Evaluation

Slow gait speed, decreased grip strength and risk for malnutrition were most common and occurred in 253 (47%), 191 (36%) and 110 (21%) of the 537 patients respectively (Table 3). Median number of prescriptions was 6 (1^{st}-3^{rd}Q 4-8) and 357 (67%) patients had ≥5 prescribed medications. Polypharmacy was associated with postoperative disability (OR 1.16 and 95% CI 1.08 – 1.25 for each additional prescription). Preoperative physical impairment was present in 86 (16%) patients and increased the odds for postoperative disability (OR 1.73 (95% CI 1.41 – 2.11 per point increase on the Nagi scale and OR 1.39 (95% CI 1.19 – 1.62) per second increase on 5MWT). Physical disability prior to surgery was reported in 57/537 (11%) patients. 23 (40%) of these patients had disabilities at three months (of whom 4 patients (7%) were deceased). Physical or mental HRQL was below the population mean in 106 (20%) and 93 (17%) patients respectively. Higher HRQL led to lower odds for disability after surgery (OR 0.95 (95% CI 0.92 – 0.97) and OR 0.97 (95% CI 0.95 – 0.99) per unit increase for physical and mental HRQL respectively). 115 (21%) patients were living alone. Patients who lived alone had increased odds for postoperative disability (OR 2.14 (95% CI 1.24-3.68)). All unadjusted odds ratios are presented in supplemental table 3. 87 (16%) patients were non-frail, one or more frailty characteristics were present in 450 (84%) patients and 252 (47%) patients were frail in two or more domains (Figure 2).

Table 2. Baseline table according to patients with or without disabilities at three months

	Disability free survival (n=446)	Disability (n=91)	P-value
Patient characteristics			
Age (years)	74 (72-77)	75 (73-79)	0.019
Male sex	308 (69.1)	54 (59.3)	0.079
Medical history			
Hypertension	367 (82.2)	79 (86.8)	0.183
Anginal complaints	170 (38.1)	36 (39.6)	>0.999
- Unstable angina	25 (5.6)	8 (8.8)	0.255
Atrial fibrillation	130 (29.1)	29 (31.9)	0.684
Previous MI	63 (14.1)	16 (17.6)	0.490
- Recent MI	15 (3.3)	1 (1.1)	0.317
Stroke	58 (12.6)	17 (18.7)	0.125
Diabetes Mellitus	77 (17.3)	31 (34.1)	0.001
- Insulin dependent	20 (4.5)	8 (8.8)	0.105
Extra cardiac arteriopathy	44 (9.9)	22 (24.2)	<0.001
COPD	44 (9.9)	15 (16.5)	0.089
Prior cardiac surgery	27 (6.1)	9 (9.9)	0.203
LVEF < 50%	90 (20.2)	22 (24.2)	0.409
NYHA class*			<0.001
- 1	71 (15.9)	8 (8.8)	
- 2	247 (55.4)	44 (48.4)	
- 3	121 (27.1)	33 (36.3)	
- 4	7 (1.6)	7 (7.7)	
EuroSCORE II	1.7 (1.2-2.7)	3.4 (2.0-5.0)	<0.001
Laboratory values			
Haemoglobin (mmol L^{-1})	8.8 (8.2-9.4)	8.3 (7.5-8.9)	<0.001
Creatinine (umol L^{-1})	88 (75-102)	90 (76-115)	0.036
Type of surgery*			0.001
- Single CABG/MAZE	165 (37.0)	25 (27.5)	
- Single valve	129 (28.9)	17 (18.7)	
- Combined surgery	128 (28.7)	36 (39.6)	
- Aortic surgery	24 (5.4)	14 (15.4)	

MI myocardial infarction; COPD chronic obstructive pulmonary disease; LVEF left ventricular ejection fraction; NYHA New York heart association; CABG coronary artery bypass graft

Continuous values as median (1^{st} – 3^{rd} quartile), categorical as frequency (%)

* Due to imputation percentages add up to > 100%.

Table 3. Frailty characteristics in patients with or without disabilities at three months

	Disability free survival (n=446)	Disability (n=91)	P-value
Physical domain			
Nutritional status (points)	13 (12-14)	13 (11-14)	0.048
Gait speed (5-MWT, seconds)	4.6 (4.1-5.3)	5.3 (4.7-6.2)	<0.001
Gait speed (TGUGT, seconds)	9.6 (8.4-11.1)	11.6 (9.8-13.7)	<0.001
Polypharmacy (prescriptions)	6 (4-8)	7 (5-10)	<0.001
Daily functioning (points)	0 (0-1)	1 (0-2)	<0.001
Low grip strength	153 (34.3)	38 (41.8)	0.130
Mental domain			
Cognition (points)	29 (28-30)	28 (27-29)	<0.004
Health related quality of life			
Physical (points)	45 (36-52)	36 (30-46)	<0.001
Mental (points)	52 (53-57)	47 (37-54)	<0.003
Social domain			
Living alone	85 (19.1)	30 (33.0)	0.004
Lower education level	100 (22.4)	37 (40.7)	0.001

Continuous values as median (1^{st}– 3^{rd} quartile), categorical as frequency (%)
5-MWT: 5 meter walk test, TGUGT: time get up and go test

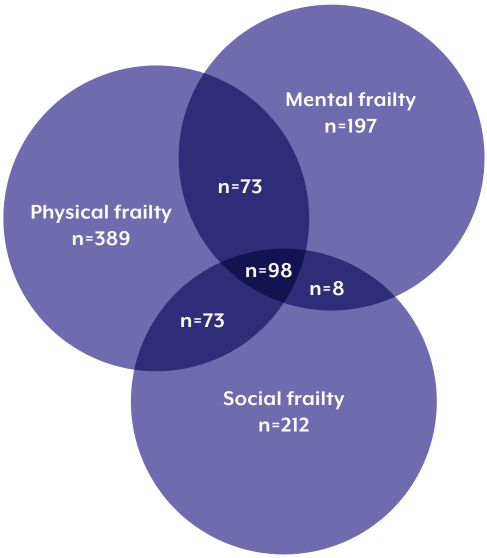


Figure 2. Venn diagram showing overlapping frailty domains

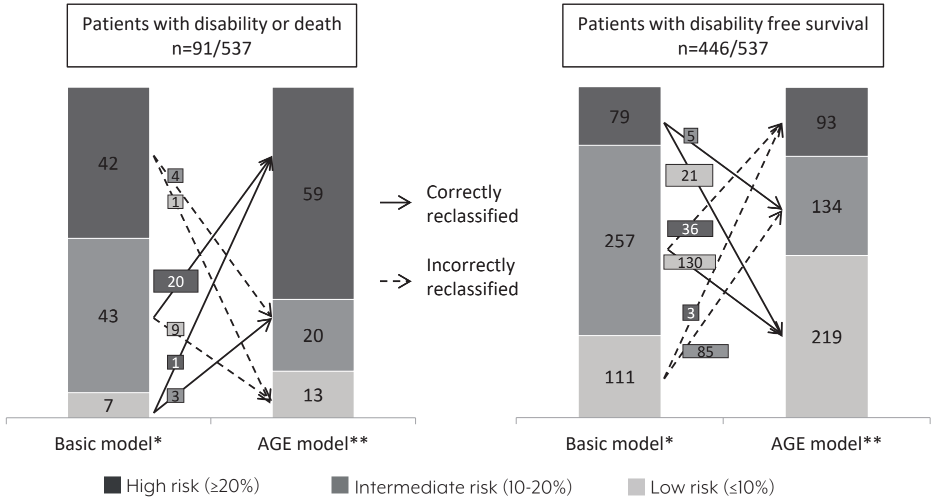


Figure 3. Net Reclassification Index
Not all numbers add up due to rounding off following imputation analysis.
* Basic model includes EuroSCORE II and preoperative haemoglobin.
** AGE model includes polypharmacy, gait speed measured by 5-meter walk test, daily functioning, physical and mental health related quality of life, and living alone

Patient selection for MDT care

In multivariable logistic regression analysis a risk stratification model including EuroSCORE II and preoperative Hb had moderate to good discriminative ability for postoperative disability (basic model c-statistic 0.71 and 95% CI 0.66 – 0.77). Discrimination improved after adding frailty characteristics to the model (AGE model c-statistic 0.78 and 95% CI 0.73 – 0.83). Figure 3 shows the reclassification of patients with and without postoperative disability for both models. For patients with disability, the basic model classified 42/91 patients as high risk and 43/91 patients as intermediate risk. When using the AGE model, reclassification occurred primarily from patients in the intermediate risk group to the high risk group: 23 patients were correctly classified as having a higher risk while 13 patients were incorrectly classified as having a lower risk. For patients without disability, 111/446 patients were classified as low risk for disability according to the basic model compared to 219/446 patients for the AGE model. Reclassification occurred mainly from intermediate risk to low risk when using the AGE model: 156/446 patients were correctly reclassified as low risk for disability while 124/446 were incorrectly reclassified as higher risk. Overall NRI was 0.32 ($p<0.001$).

Discussion

The AGE study aimed to identify preoperative risk factors for poor functional outcome in older cardiac surgery patients to improve patient selection for preoperative MDT care. In our population-based cohort of elderly patients undergoing a wide range of cardiac surgery procedures, we found that frailty was commonly present and was associated with disability at three months after surgery. Adding frailty characteristics to a risk model based on commonly available characteristics for operative mortality only, improved risk stratification for disability after surgery by 32%. Therefore, frailty can be used to identify older high risk cardiac surgery patients who may benefit from preoperative shared decision making and a personalized perioperative treatment plan.

Preoperative risk management of adverse functional outcome is of major concern for elderly cardiac surgery patients and their health care providers. Especially in frail patients information on expected changes in daily functioning and quality of life after surgery is more likely to influence preoperative decision making than survival rates. This was illustrated in a recent survey amongst heart failure patients in the year following CABG. In a cohort of 40,083 patients, the incidence of self-reported disability after one year was 5%, compared to a mortality rate of 4%.[28] Sex and comorbidity were important disability risk factors but preoperative frailty was not taken into account. The same authors performed another survey in 1,015 patients and reported that four out of five respondents were willing to sacrifice longevity for an improvement in HRQL.[28] Our results add to recent evidence on disability risk factors in cardiac surgery and confirm that postoperative disability is a more frequent complication than death and frailty assessment improved discriminative value for disability.[28–30] In a study of patients undergoing AVR, death or worsening disability after one year was present in 14% and 20% of patients, respectively. Frailty was identified as an important disability risk factor and risk prediction improved by adding frailty to an operative risk model.[30]

The number of elderly patients in cardiac surgery population is steadily growing and more frail patients are being referred for surgery. In our cohort the majority of patients had at least one frailty characteristic and more than half of patients were frail in two out of three domains (figure 2). Understanding the complexity of geriatric patients undergoing surgery is essential in order to make the right treatment decisions. In this setting an MDT approach can be beneficial.[5] However, inappropriate referral to a MDT can lead to a treatment delay, unnecessary patient burden, and higher costs. Moreover, a significant effort is requested from team members and hospital resources. Especially for anaesthesiologists with demanding time schedules in the operating theatre it can be challenging to attend MDT meetings. Therefore, accurate selection of high risk complex cases is essential. If our suggested AGE model would have been applied, 152 patients (28%) at high risk for disability (figure 3) would have been referred for MDT care during the study period, and together with 18 patients with home care or living in an assisted living facility prior to surgery who were excluded from the analyses this would result in an average of two patients being discussed on a weekly basis. To further reduce the burden on patients and physicians, less frailty tests could be performed. Although, many tests for frailty are available, our model showed good predictive abilities with a selection of tests covering multiple domains of frailty. Additionally, for some tests shorter self-administered questionnaires are available showing closely correlated results compared to the longer versions.[31]

The following study limitations should be considered. First, WHODAS 2.0 was only administered during follow up and a comparison with preoperative results was not possible. Disability at three months could be a reflection of preoperative disability. Although the results of the Nagi scale showed that preoperative disability was present in 25% of the patients with disability at three months after surgery, suggesting that disability at three months after surgery often concerned new disability, we have to emphasize that comparing the preoperative Nagi scale with the WHODAS 2.0 score at three months is not possible. Second, the AGE study cohort included patients undergoing a broad range of cardiac surgery procedures. Patients undergoing a complex surgical procedure are likely to be at higher risk for postoperative disability compared to patients with lower risk surgery. This limitation was taken into account by including EuroSCORE II in the regression analysis. Third, as in many studies with follow up questionnaires a loss to follow up occurred. In our study patients with missing data were characterized by female sex, higher EuroSCORE II and NYHA class, and more frailty characteristics. To limit bias due to missing data we performed a multiple imputation analysis where missing values were replaced by estimates drawn from the distribution of the variable in the population. Applying this method results in unbiased estimates of associations.[14,15] Last, selected frailty characteristics were tested as opposed to frailty scales. Although frailty scales are more common in research, using individual frailty characteristics facilitates targeted prehabilitation and allows for a selection of tests with the highest predictive value.

In addition to predicting adverse functional outcome, efforts should be made to attenuate the risk of postoperative disability in older cardiac surgery patients. Randomized trials in elderly patients undergoing non-cardiac surgery (i.e. hip-fracture surgery and vascular surgery) have shown that a preoperative comprehensive geriatric assessment (CGA) can be effective in reducing complications and discharge to a higher level of dependency and improve HRQL.[32,33] Currently, trials on prehabilitation are being performed in cardiac surgery patients but the results have to be awaited.[34,35]

Elderly patients presenting for cardiac surgery often appear fit as cardiologists are unlikely to refer patients with apparent frailty. Yet, in a majority of our study patients frailty characteristics were present. In these pre-frail patients, targeted prehabilitation, ideally initiated when being referred for surgery, and an MDT approach to optimize perioperative care may improve postoperative outcomes. For a small group of older patients with complex multi-morbidity, cognitive disorders or geriatric syndromes a full CGA by a geriatrician should be performed to improve multidisciplinary decision making.

In conclusion, a preoperative MDT is emerging as a standard of care for complex surgical patients. To limit the strain on resources and prevent an unnecessary increase in patient burden, only a selection of high risk patients could be discussed. Adding frailty characteristics to commonly available characteristics for operative mortality improved risk stratification and therefore may aid patient selection for MDT.

References

1. Pierri MD, Capestro F, Zingaro C, Torracca L. The changing face of cardiac surgery patients: An insight into a Mediterranean region. *Eur J Cardio-thoracic Surg*. 2010;38(4):407-413.
2. Lee DH, Buth KJ, Martin BJ, Yip AM, Hirsch GM. Frail patients are at increased risk for mortality and prolonged institutional care after cardiac surgery. *Circulation*. 2010;121(8):973-978.
3. Kim D, Kim C, Placide S, Lipsitz L, Marcantonio E. Preoperative Frailty Assessment and Outcomes at 6 Months or Later in Older Adults Undergoing Cardiac Surgical Procedures: A Systematic Review. *Ann Intern Med*. 2016;165(9):650-660.
4. Furukawa H, Tanemoto K. Frailty in cardiothoracic surgery: systematic review of the literature. *Gen Thorac Cardiovasc Surg*. 2015.
5. Whiteman AR, Dhesi JK, Walker D. The high-risk surgical patient: A role for a multi-disciplinary team approach? *Br J Anaesth*. 2016;116(3):311-314.
6. Kesson EM, Allardice GM, George WD, Burns HJG, Morrison DS. Effects of multidisciplinary team working on breast cancer survival: retrospective, comparative, interventional cohort study of 13 722 women. *BMJ*. 2012;344:e2718.
7. Rittman T, Corns R, Kumar A, Bhangoo R, Ashkan K. Is referral to the neuro-oncology MDT safe? *Br J Neurosurg*. 2012;26(3):321-324.
8. Nashef SAM, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg*. 1999;16(1):9-13.
9. Parsonnet V, Dean D, Bernstein AD. A method of uniform stratification of risk for evaluating the results of surgery in acquired adult heart disease. *Circulation*. 1989;79(6 Pt 2):I3-12.
10. Bilimoria KY, Liu Y, Paruch JL, et al. Development and evaluation of the universal ACS NSQIP surgical risk calculator: A decision aid and informed consent tool for patients and surgeons. *J Am Coll Surg*. 2013;217(5):833-842.
11. Ustün TB, Chatterji S, Kostanjsek N, et al. Developing the World Health Organization Disability Assessment Schedule 2.0. *Bull World Health Organ*. 2010;88(11):815-823.
12. Shulman MA, Myles PS, Chan MT V., McIlroy DR, Wallace S, Ponsford J. Measurement of Disability-free Survival after Surgery. *Anesthesiology*. 2015;122(3):524-536.
13. International Classification of Functioning, Disability and Health (ICF) Practical Manual V.0.9. https://www.who.int/classifications/icf/en/. Published 2013. Accessed September 11, 2019.
14. Groenwold RHH, Donders ART, Roes KCB, Harrell FE, Moons KGM. Dealing With Missing Outcome Data in Randomized Trials and Observational Studies. *Am J Epidemiol*. 2012;175(3):210-217.
15. Donders ART, van der Heijden GJMG, Stijnen T, Moons KGM. Review: a gentle introduction to imputation of missing values. *J Clin Epidemiol*. 2006;59(10):1087-1091.
16. Marshall A, Altman DG, Holder RL, Royston P. Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines. *BMC Med Res Methodol*. 2009;9(1):57.
17. Badgwell B, Stanley J, Chang GJ, et al. Comprehensive geriatric assessment of risk factors associated with adverse outcomes and resource utilization in cancer patients undergoing abdominal surgery. *J Surg Oncol*. 2013;108(3):182-186.
18. Afilalo J, Eisenberg MJ, Morin J-F, et al. Gait speed as an incremental predictor of mortality and major morbidity in elderly patients undergoing cardiac surgery. *J Am Coll Cardiol*. 2010;56(20):1668-1676.
19. Afilalo J, Mottillo S, Eisenberg MJ, et al. Addition of frailty and disability to cardiac surgery risk scores identifies elderly patients at high risk of mortality or major morbidity. *Circ Cardiovasc Qual Outcomes*. 2012;5(2):222-228.

20. Verwijmeren L, Noordzij PG, Daeter EJ, van Zaane B, Peelen LM, van Dongen EPA. Preoperative determinants of quality of life a year after coronary artery bypass grafting: A historical cohort study. *J Cardiothorac Surg*. 2018;13(1):1-8.

21. Bjørnnes AK, Parry M, Falk R, Watt-Watson J, Lie I, Leegaard M. Impact of marital status and comorbid disorders on health-related quality of life after cardiac surgery. *Qual Life Res*. 2017;26(9):2421-2434.

22. Pencina MJ, D'Agostino, Ralph B S, D'Agostino, Ralph B J, Ramachandran S V. Evaluating the added predictive ability of a new marker: From area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27:157-172.

23. Pencina MJ, D'Agostino RB, Pencina KM, Janssens ACJW, Greenland P. Interpreting incremental value of markers added to risk prediction models. *Am J Epidemiol*. 2012;176(6):473-481.

24. Kim DH, Afilalo J, Shi SM, et al. Evaluation of Changes in Functional Status in the Year After Aortic Valve Replacement. *JAMA Intern Med*. 2019;02120:1-9.

25. Rumsfeld JS, Magid DJ, O'Brien M, et al. Changes in health-related quality of life following coronary artery bypass graft surgery. *Ann Thorac Surg*. 2001;72(6):2026-2032.

26. Peric V, Borzanovic M, Stolic R, et al. Predictors of worsening of patients' quality of life six months after coronary artery bypass surgery. *J Card Surg*. 2008;23(6):648-654.

27. Welke KF, Stevens JP, Schults WC, Nelson EC, Beggs VL, Nugent WC. Patient characteristics can predict improvement in functional health after elective coronary artery bypass grafting. *Ann Thorac Surg*. 2003;75(6):1849–1855.

28. Sun LY, Tu J V., Lee DS, et al. Disability-free survival after coronary artery bypass grafting in women and men with heart failure. *Open Hear*. 2018;5(2):1-12.

29. Lytwyn J, Stammers AN, Kehler DS, et al. The impact of frailty on functional survival in patients 1 year after cardiac surgery. *J Thorac Cardiovasc Surg*. 2017;154(6):1990-1999.

30. Afilalo J, Lauck S, Kim DH, et al. Frailty in Older Adults Undergoing Aortic Valve Replacement. The FRAILTY-AVR Study. *J Am Coll Cardiol*. 2017;70(6):689-700.

31. De Smedt D, Clays E, Annemans L, et al. Health related quality of life in coronary patients and its association with their cardiovascular risk profile: Results from the EUROASPIRE III survey. *Int J Cardiol*. 2013;168(2):898-903.

32. Prestmo A, Hagen G, Sletvold O, et al. Comprehensive geriatric care for patients with hip fractures: A prospective, randomised, controlled trial. *Lancet*. 2015;385(9978):1623-1633.

33. Partridge JSL, Harari D, Martin FC, et al. Randomized clinical trial of comprehensive geriatric assessment and optimization in vascular surgery. *Br J Surg*. 2017;104(6):679-687.

34. Yau DKW, Wong MKH, Wong WT, et al. PREhabilitation for improving QUality of recovery after ELective cardiac surgery (PREQUEL) study: Protocol of a randomised controlled trial. *BMJ Open*. 2019;9(5):1-9.

35. Stammers AN, Kehler DS, Afilalo J, et al. Protocol for the PREHAB study-Pre-operative Rehabilitation for reduction of Hospitalization After coronary Bypass and valvular surgery: a randomised controlled trial. *BMJ Open*. 2015;5(3):e007250.

36. Rubenstein LZ, Harker JO, Salvà A, Guigoz Y, Vellas B. Screening for Undernutrition in Geriatric Practice: Developing the Short-Form Mini-Nutritional Assessment (MNA-SF). *J Gerontol Med Sci*. 2001;56a(6):366-372.

37. Wilson CM, Kostsuca SR, Boura JA. Utilization of a 5-Meter Walk Test in Evaluating Self-selected Gait Speed during Preoperative Screening of Patients Scheduled for Cardiac Surgery. *Cardiopulm Phys Ther J*. 2013;24(3):36-43.

38. Podsiadlo D, Richardson S. The timed Up & Go: a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc*. 1991;39(2):142-148.

39. Robinson TN, Wu DS, Sauaia A, et al. Slower walking speed forecasts increased postoperative morbidity and 1-year mortality across surgical specialties. *Ann Surg*. 2013;258(4):582-590.

40. Schwartz JB, Schmader KE, Hanlon JT, et al. Pharmacotherapy in Older Adults with Cardiovascular Disease: Report from an American College of Cardiology, American Geriatrics Society, and National Institute on Aging Workshop. *J Am Geriatr Soc*. 2018;67(2).

41. Nagi SZ. An epidemiology of disability among adults in the United States. *Milbank Mem Fund Q Health Soc*. 1976;54(4):439-467.

42. Webb AR, Newman LA, Taylor M, Keogh JB. Hand grip dynamometry as a predictor of postoperative complications reappraisal using age standardized grip strengths. *JPEN J Parenter Enteral Nutr*. 1989;13(1):30-33.

43. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198.

44. Ware JE. *SF-36 Physical and Mental Health Summary Scales: A User's Manual*. Boston: Health institute, New England Medical Center; 1994.

45. Mols F, Pelle AJ, Kupper N. Normative data of the SF-12 health survey with validation using postmyocardial infarction patients in the Dutch population. *Qual Life Res*. 2009;18(4):403-414.

Supplemental Table 1. Baseline table according to patients with or without missing data

	Complete cases (n=435, 81%)	Cases with missings (n=102, 19%)	P-value	Number of missings
Patient characteristics				
Age (years)	74 (72-77)	75 (72-78)	0.791	0
Male sex	303 (69.7)	59 (57.8)	0.022	0
Medical history				
Hypertension	362 (83.2)	84 (82.4)	0.834	0
Anginal complaints	169 (38.9)	37 (36.3)	0.360	0
- Unstable angina	30 (6.9)	2 (2.0)	0.058	0
Atrial fibrillation	122 (28.0)	37 (36.7)	0.101	0
Previous MI	61 (14.0)	18 (17.6)	0.352	0
- Recent MI	15 (3.4)	1 (1.0)	0.191	1
Stroke	55 (12.6)	20 (19.6)	0.068	0
Diabetes Mellitus	83 (19.1)	24 (23.5)	0.311	0
- On insulin	21 (4.8)	7 (6.9)	0.405	0
Extra cardiac arteriopathy	49 (11.3)	17 (16.7)	0.135	0
COPD	43 (9.9)	16 (15.7)	0.092	0
Prior cardiac surgery	30 (6.9)	6 (5.9)	0.712	0
LVEF < 50%	85 (19.5)	27 (26.5)	0.121	0
NYHA class			0.001	0
- 1	72 (16.6	7 (6.9)		
- 2	240 (55.2)	51 (50.0)		
- 3	116 (26.7)	37 (36.3)		
- 4	7 (1.6)	7 (6.9)		
EuroSCORE II	1.8 (1.2-3.0)	2.2 (1.4-4.4)	0.020	0
Laboratory values				
Haemoglobin (mmol L^{-1})	8.8 (8.2-9.3)	8.5 (7.6-9.3)	0.168	0
Creatinine (umol L^{-1})	88 (75-104)	57 (74-113)	0.498	0
Type of surgery			0.674	0
- Single CABG/MAZE	159 (36.6)	31 (30.4)		
- Single valve	115 (26.4)	31 (30.4)		
- Combined surgery	130 (29.9)	33 (32.4)		
- Aortic surgery	31 (7.1)	7 (6.9)		

MI myocardial infarction; COPD chronic obstructive pulmonary disease; LVEF left ventricular ejection fraction; NYHA New York heart association; CABG coronary artery bypass graft
Continuous values as median (1^{st} quartile – 3^{rd} quartile), categorical as frequency (%)

Supplemental Table 2. Anaesthesia Geriatric Evaluation results according to patients with or without missing data

	Complete cases (n=435, 81%)	Cases with missings (n=102, 19%)	P-value	Number of missings
Physical domain				
Nutritional status (points)	13 (12-14)	13 (12-14)	0.145	0
Gait speed (5-MWT, seconds)	4.6 (4.1-5.3)	5.1 (4.3-5.9)	0.008	3
Gait speed (TGUGT, seconds)	9.7 (8.5-11.3)	10.5 (8.8-12.8)	0.032	4
Polypharmacy (prescriptions)	6 (4-8)	6 (4-9)	0.683	4
Daily functioning (points)	0 (0-1)	1 (0-2)	0.041	2
Low grip strength	150 (34.5)	41 (40.6)	0.248	1
Mental domain				
Cognition (points)	29 (28-30)	28 (27-29)	0.022	6
Quality of life				
Physical (points)	44 (35-52)	41 (32-50)	0.174	7
Mental (points)	52 (44-57)	48 (35-55)	0.013	7
Social domain				
Living alone	81 (18.6)	34 (33.3)	0.001	0
Lower education level	100 (23.0)	33 (36.7)	0.007	12

5 MWT five meter walk test; MMSE: mini mental state examination; TGUGT: time get up and go test.
Continuous values as median (1st quartile – 3rd quartile), categorical as frequency (%)

Supplemental Table 3. Univariable Odds ratio's for all frailty characteristics and variables in the models (n = 537)

	Univariable Odds ratio (95% Confidence interval)
EuroSCORE	1.26 (1.15-1.38)**
Haemoglobin	0.59 (0.45-0.78)**
Nutritional status (points)	0.55 (0.77-0.99)*
Gait speed (5-MWT, seconds)	1.39 (1.19-1.62)**
Gait speed (TGUGT, seconds)	1.19 (1.10-1.28)**
Polypharmacy (prescriptions)	1.16 (1.08-1.25)**
Daily functioning (points)	1.73 (1.41-2.11)**
Low grip strength	1.40 (0.85-2.29)
Cognition (points)	0.82 (0.73-0.93)*
Physical health related quality of life	0.95 (0.92-0.97)**
Mental health related quality of life	0.97 (0.95-0.99)*
Living alone	2.14 (1.24-3.68)*
Lower education level	2.33 (1.39-3.90)*

5-MWT: 5 meter walk test; TGUGT: time get up and go test
* p value <0.05, **p value < 0.005

Chapter 5

Associations between preoperative biomarker and cardiac surgery associated acute kidney injury in elderly patients

Lisa Verwijmeren
Madeleen Bosma
Lisette M Vernooij
Esther M van der Linde
Ineke M Dijkstra
Edgar J Daeter
Eric P A Van Dongen
Wilton A Van Klei
Peter G Noordzij

Submitted

Abstract

Background: Cardiac surgery associated acute kidney injury (CSA-AKI) is common and associated with mortality. To improve risk stratification, we studied the predictive value of a panel of preoperative biomarkers associated with preoperative renal injury in older cardiac surgery patients.

Methods: This was a secondary analysis of the Anaesthesia Geriatric Evaluation study. Twelve biomarkers were analysed preoperatively in 539 older cardiac surgery patients. Primary outcome was CSA-AKI. The association between preoperative biomarker values and CSA-AKI was investigated using multivariable regression analysis and a panel of biomarkers with the highest discrimination for CSA-AKI was identified. Secondary outcomes were one-year mortality and patient-reported disability.

Results: CSA-AKI occurred in 80 (15%) patients. Preoperative biomarker concentrations differed significantly between patients with and without CSA-AKI. A model with all biomarkers and EuroSCORE II improved discrimination for CSA-AKI versus EuroSCORE II alone (area under the curve 0.79 (95% CI 0.74 – 0.84) versus 0.70 (95% CI 0.64 – 0.75)). A reduced model including N-terminal pro b-type natriuretic peptide, high sensitivity C-reactive protein, haemoglobin, glucose, and magnesium yielded an area under the curve of 0.77 (95% CI 0.71 – 0.82). CSA-AKI increased the relative risk for mortality 5.74 fold (95% CI 2.92 – 11.27) and for disability 1.62 fold (95% CI 1.01 – 2.59).

Conclusions: CSA-AKI is an important postoperative complication after cardiac surgery in elderly patients and associated with one-year mortality and disability. Preoperative biomarker concentrations can be used to improve risk stratification.

Introduction

Cardiac surgery associated acute kidney injury (CSA-AKI) occurs in up to 30% of patients.[1,2] Postoperative renal injury is a risk factor for chronic kidney disease and reduces short and long term survival after cardiac surgery.[2,3] Even when renal function returns to baseline at the time of hospital discharge, long term mortality risk remains increased.[3,4] One year after cardiac surgery, patients who experienced CSA-AKI report a lower health related quality of life than patients without renal injury.[5] In addition, loss of renal function increases hospital costs.[6] Age is an important risk factor for CSA-AKI.[1,7,8] Depending on type of surgery, the odds for long term mortality are three-fold higher for patients aged >70 years compared to younger patients.[3]

5

The pathophysiology of CSA-AKI is complex. Multiple perioperative determinants, such as cardiopulmonary bypass, systemic inflammation, hypotension, and blood loss contribute to a compromised glomerular blood flow and renal hypoxemia.[9,10] Accurate preoperative risk stratification is important to initiate preventive measures. However, prediction models that comprise solely of clinical risk factors (i.e. comorbidity, age and gender) have moderate levels of accuracy.[11] Chronic disease, low grade inflammation and endothelial dysfunction are key pathways in the pathogenesis of renal injury in cardiac patients prior to surgery (Figure 1).[12] Biomarkers that represent these pathways may improve preoperative risk stratification for CSA-AKI.[13,14] In this study, we aimed to evaluate the associations of preoperative biomarkers that reflect cardiac dysfunction, inflammation, renal dysfunction and metabolic disorders with CSA-AKI. In addition, we investigated the relation of CSA-AKI with one-year mortality and self-reported disability in older cardiac surgery patients.

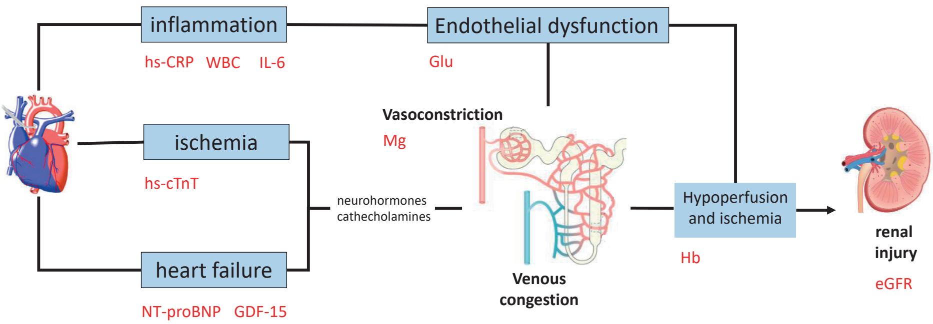


Figure 1. Potential pathways in the pathogenesis of preoperative renal injury in cardiac patients Legend: hs-cTnT: high sensitivity cardiac troponin T, NT-proBNP: N-terminal pro b-type natriuretic peptide, GDF-15: growth differentiation factor-15, hs-CRP: high sensitivity C reactive protein, IL-6: interleukin-6, WBC: white blood cell count, Hb: haemoglobin, eGFR: estimated glomerular filtration rate, Glu: glucose, Mg: magnesium

Methods

Design and participants

This is a prospectively designed sub-study of the Anaesthesia Geriatric Evaluation (AGE) study (clinicaltrials.gov no NCT02535728). The AGE study was a two-centre observational cohort study on the association of frailty with one-year functional outcome after cardiac surgery in elderly patients. Eligible patients were aged ≥70 years and scheduled for elective open cardiac surgery. An elaborate description of the design and analysis of the AGE study was previously reported.[15] In short, standard pre-anaesthesia assessment was supplemented with a comprehensive geriatric assessment. Further perioperative care was performed according to local standardized operating procedures. The local Research Ethics Committee approved the study protocol and all patients provided written informed consent (Medical Ethics Research Committee United, number R15.039). Preoperative data were extracted from electronic medical records and included comorbidities, medication use, EuroSCORE II, and echocardiography results, which were available at time of preoperative screening, or on the day before surgery.

Biomarkers

Twelve biomarkers were analysed and stratified in four categories (cardiac, inflammatory, renal, and metabolic). Cardiac biomarkers consisted of high-sensitive (hs) cardiac troponin (cTn) T, N-terminal pro b-type natriuretic peptide (NT-proBNP), and growth differentiation factor-15 (GDF-15). Inflammatory biomarkers included hs-C reactive protein (CRP), interleukin-6 (IL-6), and white blood cell count (WBC). Renal biomarkers were haemoglobin (Hb) and estimated glomerular filtration rate (eGFR) calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).[16] Metabolic biomarkers included glucose, albumin, phosphate and magnesium. Blood samples for Hb, WBC and creatinine/eGFR were collected at the outpatient clinic as part of routine care and directly analysed on a Sysmex 9000 system (Sysmex, Kobe, Japan) or a Sapphire system (Abbott Laboratories, Lake Forest, IL, USA) (for WBC and Hb), and a cobas® platform (Roche Diagnostics, Mannheim, Germany) or an Atellica system (Siemens Healthcare, Erlangen, Germany) for creatinine. For the remaining markers, blood samples were collected in the operating theatre from the arterial catheter, after induction of anaesthesia and before surgical incision. Plasma was stored in cryogenic tubes at -80°C until batch analysis was performed. The plasma biomarkers were analysed on an automated cobas® 8000 platform (Roche Diagnostics, Mannheim, Germany) by the following assays: Elecsys® cTnT hs assay (fifth generation assay), Elecsys® IL-6, Elecsys® GDF-15, Elecsys® proBNP II, CRPL3 (3rd generation CRP assay), ALBT2 (Tina-quant albumin 2nd generation assay), GLUC3 (glucose HK assay), MG2 (magnesium 2nd generation assay), PHOS2 (inorganic phosphate assay version 2) (Roche Diagnostics, Mannheim, Germany). Cut-off values for all biomarkers were set according to the manufacturer's manual (Roche Diagnostics, Mannheim, Germany), were locally determined (WBC), or according to international guidelines (Hb and eGFR) and represented the 95th percentile (and 99th percentile in the case of hs-cTnT): hs-cTnT ≥0.014 μg/mL; NT-proBNP ≥486 for females and ≥470 pg/mL for males; GDF-15 ≥2199 pg/mL; CRP ≥5 mg/L; IL-6: ≥7 pg/mL; WBC ≥10.8 for females and ≥10.6 10^9/L for males; glucose ≥6.38 mmol/L; albumin ≤35 g/L; phosphate ≥1.45 mmol/L and magnesium ≤0.66 mmol/L. The cut off values for Hb were ≤7.45 mmol/L for females and ≤8.07 mmol/L for males.[17] Cut off value for eGFR was ≤60 ml/min/1.73m2.[18] All analyses were performed using standardized diagnostic methods.

Outcomes

The primary outcome was CSA-AKI, defined as an absolute increase of serum creatinine ≥26.5 μmol/L or 1.5 times the baseline value, within 48 hours after surgery.[18] Postoperative serum creatinine values were routinely determined on the first and second day after surgery on an automated cobas® 8000 platform (Roche Diagnostics, Mannheim, Germany) or an Atellica system (Siemens Healthcare, Erlangen, Germany). Secondary outcomes were mortality and self-reported disability one year after surgery. Vital status, including date of death in case of mortality, was assessed by consulting the national personal records database. Disability was measured according to the self-assessment 36-item World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0), and reported as a percentage score of limitations in functioning over the past four weeks. Scores ranged from 0% (no disability) to 100% (fully disabled). In our study, disability was defined as a score ≥25%.[15] Deceased patients were excluded from the analysis regarding postsurgical disability.

Missing data

Multiple imputation was used to handle missing data. This reduces bias by creating multiple datasets of which the missing values are estimated using information from the same source population. These multiple imputed datasets are pooled afterwards.[19] Pre- and postoperative missing values, including disability data were imputed in 30 datasets and pooled using Rubin's Rules.[20] Biomarker assays were performed after imputation analyses. Because only a small amount of biomarker values was missing (16/555 patients, 2.9%), and missing values were completely at random, we excluded these patients from the analyses.

Statistical analysis

Biomarkers with right skewed distributions were natural log transformed. Differences between patients with or without CSA-AKI were presented as frequencies with percentages for dichotomous and categorical data and median with interquartile range (IQR) for continuous data. Significance was tested with a Chi square test or Mann Whitney U test, as appropriate. Unadjusted relative risks (RR) with 95% confidence interval (CI) were calculated for the association between CSA-AKI and one-year mortality and self-reported disability. Mortality was further analysed by Kaplan Meier curves and log-rank tests. Differences in biomarker concentrations were tested with Student T tests. Correlations between biomarkers were analysed by Pearson's correlations coefficient. Associations of preoperative biomarkers with CSA-AKI were assessed with logistic regression analyses. In univariable analyses biomarkers were tested as continuous variables and according to aforementioned predefined cut-off points. To improve the readability of our results, we refer to biomarker values above or below the cut-off value as 'elevated' or 'decreased' as appropriate. To determine which biomarker had the strongest association with CSA-AKI we used multivariable logistic regression analysis.

First, a full model was created including all biomarkers and EuroSCORE II. Second, backwards selection was applied based on a likelihood ratio test with EuroSCORE II as a fixed variable. Biomarker values were included as a continuous variable and standardised to enable direct comparison. Standardisation was performed by subtracting the mean from the patient specific value and dividing it by the standard deviation of that particular variable. Therefore, the highest standardised OR implied the strongest association in the multivariable model. Biomarkers with a negative association (i.e. Hb, eGFR, albumin, and magnesium) were added as an inverse value. For each model the area under the curve (AUC) was calculated to express the discriminative ability for CSA-AKI. Differences between models were compared with the log likelihood ratio test. A $p<0.05$ was considered statistically significant. Data were analysed using SPSS v24 for Windows (IBM Corp. Armonk, New York).

Results

Patient population

The AGE study cohort consisted of 555 patients. Preoperative blood samples were missing in 16 (2.9%) patients, the remaining 539 patients were included in the analysis. Median age was 75 years (IQR 72-77) and 181 (33.6%) patients were female. Eighty patients (14.8%) had CSA-AKI. Patients with CSA-AKI more often had hypertension, diabetes mellitus, chronic renal failure, a higher NYHA class, and higher EuroSCORE II (Table 1). The overall mortality rate was 2.8% (n=15) during hospital stay and 5.6% (n=30) after one year. Patients with CSA-AKI had approximately a six-fold increased risk for one-year mortality (RR 5.74 (95% CI 2.92 – 11.27)). Survival for patients with and without CSA-AKI is presented in Figure 2. Of the 509 surviving patients, 116 (22.8%) reported disabilities at one year after surgery. Patients with CSA-AKI were at increased risk for disability (RR 1.62 (95% CI 1.01 – 2.59)).

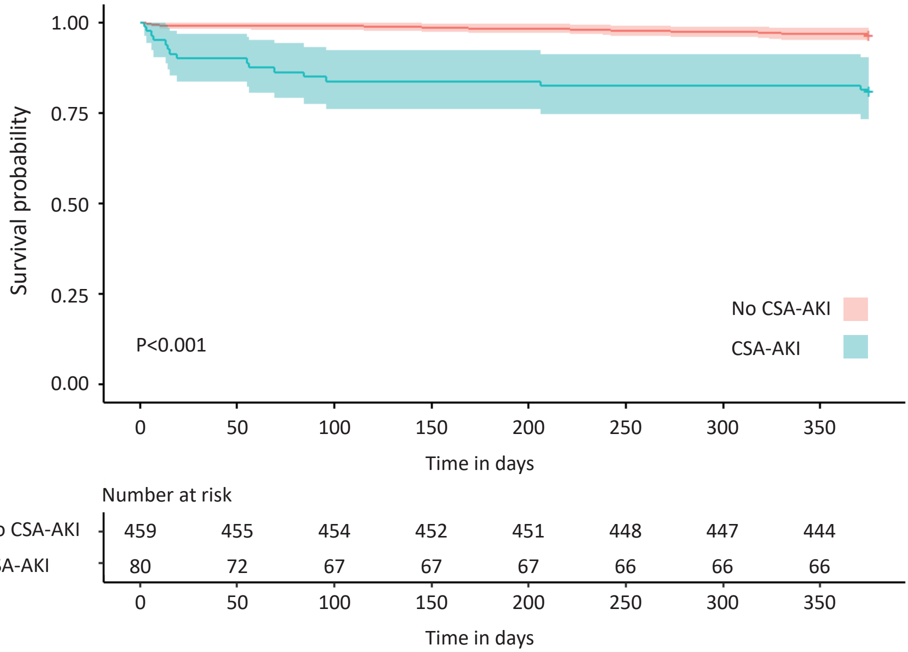


Figure 2. Kaplan Meier curve for mortality according to cardiac surgery associated acute kidney injury
CSA-AKI: cardiac surgery associated acute kidney injury

5

Table 1. Baseline characteristics

	No CSA-AKI 459 (85%)	CSA-AKI 80 (15%)	P
Age (median [IQR])	74 [72 - 77]	75 [73 - 78]	0.176
Female sex, n (%)	153 (33.3)	28 (35.0)	0.871
Current smoker, n (%)	34 (7.4)	7 (8.8)	0.850
Smoking history, n (%)	263 (57.3)	52 (65.0)	0.243
Hypertension, n (%)	374 (81.5)	74 (92.5)	0.023
Hypercholesterolemia, n (%)	285 (62.1)	56 (70.0)	0.219
Angina, n (%)	173 (37.7)	28 (35.0)	0.738
NYHA class, n (%)			0.012
1	73 (15.9)	6 (7.5)	
2	241 (52.5)	42 (52.5)	
3	136 (29.6)	26 (32.5)	
4	9 (2.0)	6 (7.5)	
Left ventricular ejection fraction, n (%)			0.843
≤ 50%	87 (19.0)	17 (21.2)	
≤ 30%	9 (2.0)	2 (2.5)	
Diabetes, n (%)	85 (18.5)	25 (31.2)	0.014
Chronic renal failure, n (%)	54 (11.8)	19 (23.8)	0.007
Peripheral vascular disease, n (%)	50 (10.9)	15 (18.8)	0.071
Stroke/TIA, n (%)	61 (13.3)	13 (16.2)	0.593
Atrium fibrillation, n (%)	133 (29.0)	30 (37.5)	0.162
EuroSCORE II (median [IQR])	1.69 [1.20 - 3.00]	2.70 [2.06 - 4.56]	<0.001
Frailty, n (%)	98 (21.4)	19 (24.0)	0.664
Type of surgery, n (%)			0.001
Single CABG or maze	166 (36.1)	16 (20.0)	
Single valve	134 (29.2)	18 (22.5)	
Combined surgery	128 (27.9)	36 (45.0)	
Aortic surgery	31 (6.8)	10 (12.5)	

NYHA: New York Heart Association, TIA: Transient ischaemic accident, EuroSCORE II: European System for Cardiac Operative Risk Evaluation II, CABG: Coronary artery bypass graft

Table 2. Biomarker concentrations at baseline

	No CSA-AKI 459 (85%)	CSA-AKI 80 (15%)	P
Cardiac biomarkers			
hs-cTnT (μg/mL)	0.014 [0.010 - 0.021]	0.017 [0.012 - 0.026]	0.003
NT-proBNP (pg/mL)	420 [190 - 1011]	795 [376 - 1662]	<0.001
GDF-15 (pg/mL)	1330 [1010 - 1868]	1790 [1273 - 2633]	<0.001
Inflammatory biomarkers			
hs-CRP (mg/L)	1.2 [1.0 - 2.6]	2.2 [1.0 - 5.2]	<0.001
IL-6 (pg/mL)	3.1 [2.1 - 4.5]	4.3 [2.8 - 7.8]	<0.001
WBC (10^9/L)	7.3 [6.3 - 8.6]	7.3 [6.4 - 8.6]	0.625
Renal biomarkers			
Hb (mmol/L)	8.8 [8.2 - 9.4]	8.2 [7.5 - 8.9]	<0.001
eGFR (ml/min/1.73m^2)	69 [58 – 82]	61 [48 – 72]	<0.001
Metabolic biomarkers			
Glucose (mmol/L)	5.9 [5.4 - 6.6]	6.2 [5.6 - 7.2]	0.020
Albumin (g/L)	39 [36 - 41]	38 [36 - 41]	0.779
Phosphate (mmol/L)	0.98 [0.87 - 1.10]	1.02 [0.91 - 1.12]	0.037
Magnesium (mmol/L)	0.78 [0.73 - 0.83]	0.76 [0.68 - 0.81]	0.012

All values are median concentrations with interquartile range.
hs-cTnT: high sensitivity cardiac troponin T, NT-proBNP: N-terminal pro b-type natriuretic peptide, GDF-15: growth differentiation factor-15, high sensitivity C reactive protein, IL-6: interleukin-6, WBC: white blood cell count, Hb: haemoglobin, eGFR: estimated glomerular filtration rate

Cardiac biomarkers

Preoperative cardiac biomarker concentrations were higher in patients with CSA-AKI (Table 2). Correlation coefficients between cardiac biomarker concentrations are presented in Supplementary Figure 1. The strongest relationship was found between hs-cTnT and GDF-15 (r=0.50). Hs-cTnT, NT-proBNP and GDF-15 concentrations before surgery were elevated in 307 (57.0%), 262 (48.6%) and 109 (20.2%) patients respectively, and were all univariably associated with CSA-AKI (Figure 3).

Inflammatory biomarkers

Patients with CSA-AKI had significantly higher preoperative concentrations of CRP and IL-6 on average (Table 2). The correlation between CRP and IL-6 concentrations was strong (r=0.67). Preoperative inflammation was correlated with GDF-15 concentrations (r=0.44 for IL-6 and r=0.26 for CRP, supplementary Figure 1). Elevated CRP and IL-6 concentrations were present in 68 (12.6%) and 83 (15.4%) patients respectively, and were both associated with CSA-AKI (Figure 3).

Renal biomarkers

Preoperative concentrations of renal biomarkers were lower in patients with CSA-AKI (Table 2). There was a weak correlation between renal function and preoperative Hb concentrations (r=0.20). Lower eGFR prior to surgery was related to higher cardiac biomarker concentrations (Supplementary Figure 1). Preoperative anaemia was present in 85 (15.8%) patients and associated with CSA-AKI (Figure 3). Preoperative renal insufficiency (based on eGFR) was present in 176 (32.7%) patients and was associated with CSA-AKI (Figure 3).

Metabolic biomarkers

In patients with CSA-AKI, preoperative glucose and phosphate concentrations were significantly higher and magnesium concentrations were significantly lower, compared with patients without CSA-AKI (Table 2). Impaired fasting glucose and hypomagnesemia occurred in 167 (31.0%) and 46 (8.5%) patients, respectively, and were both associated with CSA-AKI. Per point increase in preoperative glucose concentration, the odds for CSA-AKI increased by 1.2 (95% CI 1.0 - 1.4, Figure 3). No association was found between low albumin concentrations (which was present in 85 (15.8%) patients) and CSA-AKI and none of the patients had an elevated phosphate concentration before surgery.

Multivariable analysis

Figure 4 presents standardised effect estimates of a multivariable model including all biomarkers and EuroSCORE II. EuroSCORE II, NT-proBNP, hs-CRP, Hb, and magnesium were significantly associated with CSA-AKI. The C-index of this full model was more discriminative (AUC 0.79 (95% CI 0.74 – 0.84) compared to a model including only EuroSCORE II (AUC 0.70 (95% CI 0.64 – 0.75)), and model fit improved significantly ($p<0.001$). After backward selection, the final model included five biomarkers associated with CSA-AKI in addition to EuroSCORE II: NT-proNBP (standardized OR 1.4 (95% CI 1.1 - 1.9)), hs-CRP (standardized OR 1.3 (95% CI 1.1 – 1.7)), Hb (standardized OR 1.5 (95% CI 1.1 – 1.9), glucose (standardized OR 1.3 (95% CI 1.0 – 1.6), magnesium (standardized OR 1.4 (95% CI 1.0 – 2.0), and EuroSCORE II (standardized OR 1.4 (95% CI 1.1 – 1.9)). Discrimination of this model was AUC 0.77 (95% CI 0.71 – 0.82). Model fit was not significantly different from the model including the complete biomarker panel ($p=0.411$).

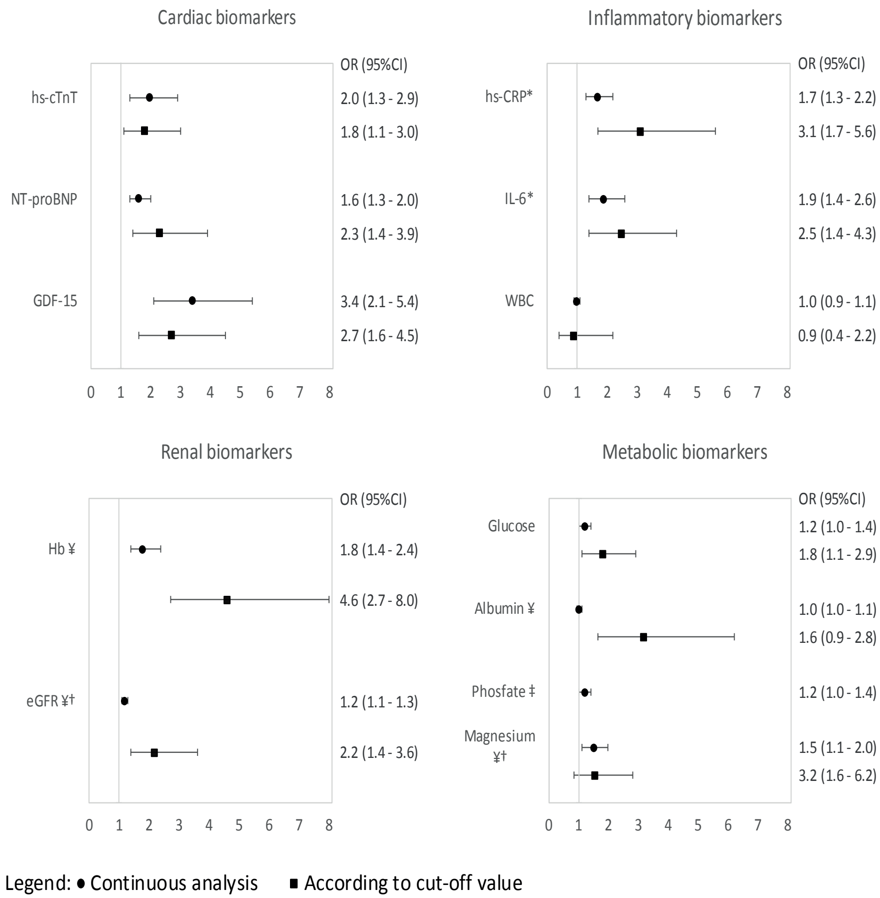


Figure 3. Crude associations between preoperative biomarkers concentrations and CSA-AKI

All odds ratios are unadjusted, several transformations were applied: * natural logarithmic transformation, ¥ inverse transformation, † odds ratio per 5-point difference, ‡ odds ratio per 0.10-point difference. hs-cTnT: high sensitivity cardiac troponin T, NT-proBNP: N-terminal pro b-type natriuretic peptide, GDF-15: growth differentiation factor-15, high sensitivity C reactive protein, IL-6: interleukin-6, WBC: white blood cell count, Hb: haemoglobin, eGFR: estimated glomerular filtration rate

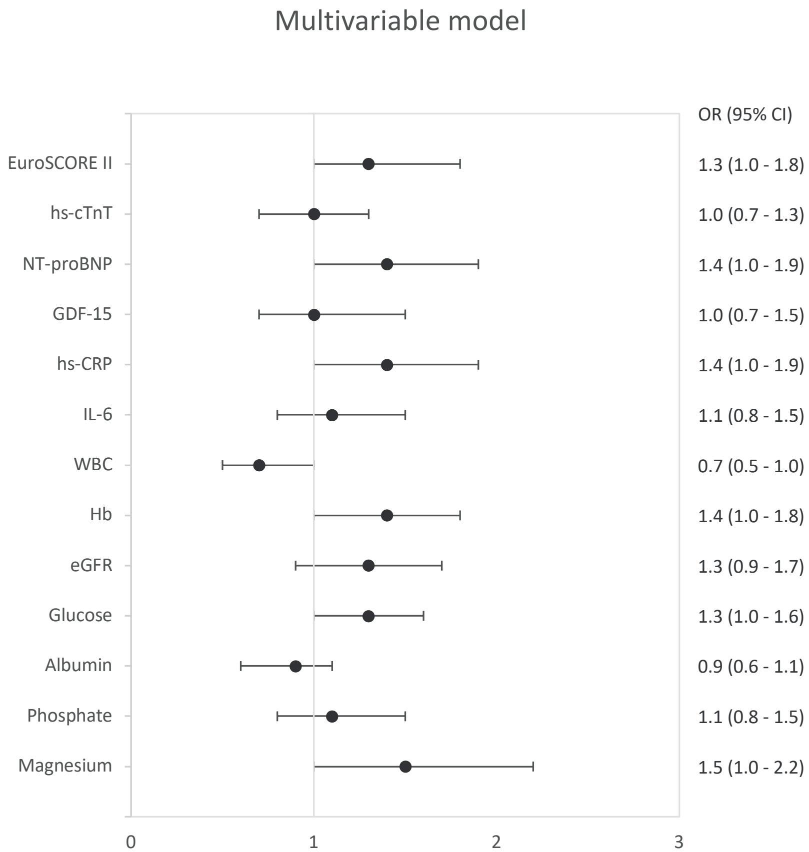


Figure 4. Multivariable analysis for the association of a preoperative biomarker panel and CSA-AKI
Legend: Odds ratio's represent standardised ORs meaning a higher ratio indicates a stronger association. hs-cTnT: high sensitivity cardiac troponin T, NT-proBNP: N-terminal pro b-type natriuretic peptide, GDF-15: growth differentiation factor-15, high sensitivity C reactive protein, IL-6: interleukin-6, WBC: white blood cell count, Hb: haemoglobin, eGFR: estimated glomerular filtration rate

Discussion

In elderly patients undergoing cardiac surgery CSA-AKI occurred in 15% of patients and was associated with one-year mortality and disability. Preoperative biomarkers that reflect cardiac dysfunction, inflammation, renal dysfunction and metabolic disorders were independently associated with CSA-AKI. A multivariable model that included a biomarker panel improved preoperative risk stratification for CSA-AKI compared to a clinical model alone, or a clinical model that included a single biomarker.

5

Our results confirmed that preoperative cardiac, inflammatory, renal and metabolic biomarkers are associated with the occurrence of CSA-AKI.[13,14,21–24] A biomarker panel that was selected based on the multifactorial pathogenesis of renal injury in cardiac patients improved discriminative performance of our model (AUC 0.79, 95% CI 0.74 – 0.84), compared to a single biomarker. Another study that associated multiple preoperative biomarkers with CSA-AKI focussed on inflammation, compromised renal blood flow and ischemia-reperfusion injury.[14] Preoperative inflammatory biomarkers (soluble tumour necrosis factor receptor 1 and 2) had the highest discrimination for CSA-AKI (AUC 0.75, CI 0.68-0.81).[14] Both biomarkers have been associated with progression of renal disease, illustrating that existing renal failure is an important risk factor for CSA-AKI.[25,26] In addition, our results showed that chronic cardiac disease contributes to the development of CSA-AKI and can be used to improve risk stratification. Heart failure is an important prognosticator in cardiac disease and is associated with chronic kidney disease.[27] EuroSCORE II contains detailed clinical information on preoperative heart failure, i.e. left ventricular function and New York Heart Association functional classification, to accurately predict postoperative mortality. In addition to preoperative echocardiography results and clinical symptoms, NT-proBNP added information to preoperative risk assessment for CSA-AKI in our study. NT-proBNP remained associated with CSA-AKI in our full model, that included EuroSCORE II and 11 other biomarkers.

The results of our study suggest that different pathophysiological processes are involved in the pathogenesis of renal injury in cardiac disease. Preoperative concentrations of NT-proBNP, hs-CRP, glucose, magnesium and haemoglobin had the strongest association with CSA-AKI. Chronic cardiac disease is characterized by episodes of myocardial ischemia, heart failure, and a systemic hormonal and inflammatory response.[1,9] Depending on disease severity, these processes impair renal oxygenation by cardiac and endothelial dysfunction (Figure 1). High levels of circulating neurohormones induce renal sodium and water retention, which reduce glomerular blood flow (venous congestion) and impair renal microcirculation.[27]

Local oedema and inflammation lead to areas with impaired renal oxygenation and trigger systemic inflammation.[24] Renal hypoxemia is enhanced by co-existing anaemia. Furthermore, endogenous cathecholamines increase vascular tone and reduce glomerular perfusion. Homeostasis of the renal microcirculation is dependent on endothelium derived nitric oxide mediated vasodilation. Magnesium naturally counteracts vasoconstriction and potentiates the action of endogenous vasodilators.[28] Hypomagnesemia may lead to renal vasoconstriction and impair glomerular blood flow. High glucose levels have been associated with changes in the function of the glomerular endothelial glycocalyx, reducing its function as a protein restrictive layer and aggravating endothelial dysfunction.[29]

Preoperative biomarkers can be used to diagnose new diseases and assess the progress of previously diagnosed comorbidity. Targeted preoperative interventions based on biomarker results to improve outcome after cardiac surgery are scarce.[30] Future research that aims to reduce the incidence of CSA-AKI should consider a preoperative biomarker panel to identify patient specific risks that are suitable for targeted preoperative interventions.

This study has several limitations. Firstly, preoperative blood samples were missing in 16 patients. Because missing blood samples were not related to patient characteristics or outcome, the risk of bias was low. In 73 patients disability questionnaires were missing. We performed multiple imputation in an attempt to limit bias.[19] However, this could have influenced the association between CSA-AKI and disability at one year. Secondly, the definition of AKI includes a seven day measurement of eGFR urine volume. In our study eGFR was available during the first two days after surgery, and urine volume was not collected. Hence, patients that developed CSA-AKI at a later time point were not counted. Incidence of CSA-AKI might be an underrepresentation. A major strength of our study was the use of 12 preoperative biomarkers which represented the multifactorial pathogenesis of renal injury in cardiac patients. We realize that there are many other biomarkers that are potentially associated with CSA-AKI. For practical reasons, we chose a biomarker panel that can be routinely assessed in clinical care. Although GDF-15 and IL-6 are less common, they are available from Roche, Abbott, Siemens, and Beckman for IL-6, and from Roche and Abbott for GDF-15. Because these systems are widely used this allows for reproducibility and comparison of our results by others and facilitates clinical implementation. Other strengths of this study include the thorough preoperative screening of all patients and data availability.

Conclusion

Cardiac surgery associated acute kidney injury is common in elderly patients and is associated with higher risk for one-year mortality or disability. A preoperative biomarker panel based on cardiac dysfunction, inflammation, renal dysfunction and metabolic disorders improved preoperative risk stratification for CSA-AKI.

References

1. O'Neal JB, Shaw AD, Billings FT. Acute kidney injury following cardiac surgery: Current understanding and future directions. *Crit Care*. 2016;20(1):1-9.
2. Rosner MH, Okusa MD. Acute kidney injury associated with cardiac surgery. *Clin J Am Soc Nephrol*. 2006;1(1):19-32.
3. Hobson CE, Yavas S, Segal MS, et al. Acute Kidney Injury Is Associated With Increased Long-Term Mortality After Cardiothoracic Surgery. *Circulation*. 2009;119(18):2444-2453.
4. Loef BG, Epema AH, Smilde TD, et al. Immediate postoperative renal function deterioration in cardiac surgical patients predicts in-hospital mortality and long-term survival. *J Am Soc Nephrol*. 2005;16(1):195-200.
5. Mishra P, Luckraz H, Nandi J, et al. Long-term Quality of Life Postacute Kidney Injury in Cardiac Surgery Patients. *Ann Card Anaesth*. 2018;21:41-45.
6. Lau D, Pannu N, James MT, et al. Costs and consequences of acute kidney injury after cardiac surgery: A cohort study. *J Thorac Cardiovasc Surg*. 2020;March.
7. Lopez-Delgado JC, Esteve F, Torrado H, et al. Influence of acute kidney injury on short- and long-term outcomes in patients undergoing cardiac surgery: Risk factors and prognostic value of a modified RIFLE classification. *Crit Care*. 2013;17(6):R293.
8. Mårtensson J, Bellomo R. Perioperative renal failure in elderly patients. *Curr Opin Anaesthesiol*. 2015;28(2):123-130. http://www.ncbi.nlm.nih.gov/pubmed/25674985.
9. Ostermann M, Liu K. Pathophysiology of AKI. *Best Pract Res Clin Anaesthesiol*. 2017;31(3):305-314.
10. Fuhrman DY, Kellum JA. Epidemiology and pathophysiology of cardiac surgery-associated acute kidney injury. *Curr Opin Anaesthesiol*. 2016;30(1):60-65.
11. Kiers HD, Van Den Boogaard M, Schoenmakers MCJ, et al. Comparison and clinical suitability of eight prediction models for cardiac surgery-related acute kidney injury. *Nephrol Dial Transplant*. 2013;28(2):345-351.
12. Berl T, Henrich W. Kidney-Heart Interactions: Epidemiology, Pathogenesis, and Treatment. *Clin J Am Soc Nephrol*. 2006;1(1):8-18.
13. Patel UD, Garg AX, Krumholz HM, et al. Preoperative Serum Brain Natriuretic Peptide and Risk of Acute Kidney Injury After Cardiac Surgery. *Circulation*. 2012;125(11):1347-1355.
14. McBride WT, Kurth MJ, McLean G, et al. Stratifying risk of acute kidney injury in pre and post cardiac surgery patients using a novel biomarker-based algorithm and clinical risk score. *Sci Rep*. 2019;9(1):16963.
15. Verwijmeren L, Peelen LM, van Klei WA, et al. Anaesthesia geriatric evaluation to guide patient selection for preoperative multidisciplinary team care in cardiac surgery. *Br J Anaesth*. 2020;124(4):377-385.
16. Levey AS, Stevens LA, Schmid CH, et al. A New Equation to Estimate Glomerular Filtration Rate Andrew. *Ann Intern Med*. 2009;150(9):604-612.
17. WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and Mineral Nutrition Information System. Geneva, World Health Organization, 2011 (WHO/NMH/NHD/MNM/11.1). http://www.who.int/vmnis/indicators/haemoglobin. pdf. Published 2011. Accessed June 9, 2020.
18. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group . KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Inter Suppl. https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf. Published 2013. Accessed June 9, 2020.
19. Donders ART, van der Heijden GJMG, Stijnen T, Moons KGM. Review: a gentle introduction to imputation of missing values. *J Clin Epidemiol*. 2006;59(10):1087-1091.
20. Marshall A, Altman DG, Holder RL, Royston P. Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines. *BMC Med Res Methodol*. 2009;9(1):57.

21. Enger TB, Pleym H, Stenseth R, Greiff G, Wahba A, Videm V. A Preoperative Multimarker Approach to Evaluate Acute Kidney Injury After Cardiac Surgery. *J Cardiothorac Vasc Anesth*. 2017;31(3):837-846.
22. Guenancia C, Kahli A, Laurent G, et al. Pre-operative growth differentiation factor 15 as a novel biomarker of acute kidney injury after cardiac bypass surgery. *Int J Cardiol*. 2015;197(2015):66-71.
23. Heringlake M, Charitos EI, Gatz N, et al. Growth differentiation factor 15: A novel risk marker adjunct to the EuroSCORE for risk stratification in cardiac surgery patients. *J Am Coll Cardiol*. 2013;61(6):672-681.
24. Zelt J, Mielniczuk L, Liu P, et al. Utility of Novel Cardiorenal Biomarkers in the Prediction and Early Detection of Congestive Kidney Injury Following Cardiac Surgery. *J Clin Med*. 2018;7(12):540.
25. Barr ELM, Barzi F, Hughes JT, et al. High baseline levels of tumor necrosis factor receptor 1 are associated with progression of kidney disease in indigenous australians with diabetes: The eGFR follow-up study. *Diabetes Care*. 2018;41(4):739-747.
26. Parodis I, Ding H, Zickert A, et al. Serum soluble tumour necrosis factor receptor-2 (sTNFR2) as a biomarker of kidney tissue damage and long-term renal outcome in lupus nephritis. *Scand J Rheumatol*. 2017;46(4):263-272.
27. Rangaswami J, Bhalla V, Blair JEA, et al. Cardiorenal Syndrome: Classification, Pathophysiology, Diagnosis, and Treatment Strategies: A Scientific Statement From the American Heart Association. *Circulation*. 2019;139(16).
28. Barbosa EB, Tomasi CD, de Castro Damasio D, et al. Effects of magnesium supplementation on the incidence of acute kidney injury in critically ill patients presenting with hypomagnesemia. *Intensive Care Med*. 2016;42(6):1084-1085.
29. Singh A, Fridén V, Dasgupta I, et al. High glucose causes dysfunction of the human glomerular endothelial glycocalyx. *Am J Physiol Physiol*. 2011;300(1):F40-F48.
30. Spahn DR, Schoenrath F, Spahn GH, et al. Effect of ultra-short-term treatment of patients with iron deficiency or anaemia undergoing cardiac surgery: a prospective randomised trial. *Lancet*. 2019;393(10187):2201-2212.

	hs-cTnT	NT-proBNP	GDF-15	hs-CRP	IL-6	WBC	Hb	eGFR	Glucose	Fosfaat	Magnesium
NT-proBNP	0.38										
GDF-15	0.50	0.33									
hs-CRP	0.14	0.17	0.26								
IL-6	0.29	0.23	0.44	0.67							
WBC	0.09	0.13	0.16	0.18	0.22						
Hb	-0.06	-0.08	-0.25	-0.20	-0.20	0.03					
eGFR	-0.45	-0.32	-0.51	-0.12	-0.26	-0.15	0.20				
Glucose	0.16	-0.02	0.27	0.01	0.02	0.09	-0.01	-0.05			
Phosphate	-0.03	0.08	0.05	0.11	0.08	0.00	-0.26	-0.04	-0.01		
Magnesium	-0.04	-0.03	-0.09	0.00	-0.04	-0.02	0.06	0.02	-0.16	0.04	
Albumin	-0.06	-0.14	-0.06	-0.14	-0.17	-0.03	0.10	0.06	0.15	0.02	0.06

Legend	
0.0-0.2	Weak
0.2-0.4	Mild
0.4-0.6	Moderate
0.6-0.8	Strong

Supplementary Figure. Correlations between preoperative biomarker concentrations
Legend: hs-cTnT: high sensitivity cardiac troponin T, NT-proBNP: N-terminal pro b-type natriuretic peptide, GDF-15: growth differentiation factor-15, high sensitivity C reactive protein, IL-6: interleukin-6, WBC: white blood cell count, Hb: haemoglobin, eGFR: estimated glomerular filtration rate

5

Chapter 6

Predictive value of frailty characteristics for postoperative delirium and the impact on one year health related quality of life after cardiac surgery in elderly patients.

Lisa Verwijmeren
Peter G Noordzij
Lisette M Vernooij
Edgar J Daeter
Marielle Emmelot-Vonk
Wilton A van Klei
Eric P A van Dongen

Manuscript in preparation

Abstract

Background: Postoperative delirium is a common complication in elderly patients undergoing cardiac surgery. Frailty scales predict postoperative delirium, but focus mainly on physical frailty overlooking mental and social frailty. We investigated whether a frailty assessment including physical, mental, and social characteristics improved risk prediction for postoperative delirium.

Methods: This was a sub-study of the Anaesthesia Geriatric Evaluation (AGE) study. Frailty screening was performed before cardiac surgery in all patients. Primary outcome was the occurrence of a delirium during hospitalisation and secondary outcome was health related quality of life at three and twelve months. Associations were investigated by logistic regression, area under the curve, and net reclassification indices. A restricted maximum likelihood estimation investigated health related quality of life for patients with and without a delirium.

Results: Postoperative delirium occurred in 95/537 patients. Three frailty characteristics in the physical domain, three in the mental domain and two in the social domain were associated with a delirium. A multivariable model with characteristics of each domain and adjusted for clinical factors had a discrimination of 0.684 (95% CI 0.622 - 0.746). Discrimination of clinical factors alone was 0.614 (95% CI 0.552 - 0.676). Net reclassification index showed that the frailty model correctly identified patients at high risk 8% better, and patients at low risk 17% better than clinical factors alone. Overall reclassification improved 25% ($p<0.001$). A delirium negatively impacted physical and mental health over the course of one year follow up.

Conclusions: Postoperative delirium occurs frequently after cardiac surgery and is associated with reduced health related quality of life after one year. Frailty screening in multiple domains improves preoperative risk stratification. These data might be used to allocate preventive strategies to patients at high risk.

Introduction

Delirium is an acute confusional state with a fluctuating course that is characterized by an alteration of consciousness with a reduced ability to focus, sustain, or shift attention. Postoperative delirium is a frequent complication of cardiac surgery.[1,2] Short term effects of delirium include longer length of hospital stay, and higher susceptibility to severe postoperative complications or mortality. Long term complications include persistent functional decline, long term cognitive impairment, increased health care costs and institutionalism.[3,4]

Age is an important predisposing factor for postoperative delirium.[2] Since the population referred for cardiac surgery grows increasingly older, it is likely that the incidence of delirium will increase concurrently.[5,6] Besides age, preoperative risk factors for delirium include a prior delirium, history of stroke, peripheral vascular disease, diabetes mellitus, cognitive impairment, depression, and use of psychotropic drugs.[2,7] Additionally, frailty is increasingly recognized as a risk factor for adverse outcomes after cardiac surgery in elderly patients and has been described by some studies as a risk factor for postoperative delirium.[3,8–13] Overall, preoperative frailty increased the risk for postoperative delirium three to eight-fold.[13] However, these studies mainly focussed on physical frailty, and overlooked mental or social frailty. Characteristics from these domains might improve risk stratification for postoperative delirium, which is important to initiate preventive measures in high-risk patients.[14] We hypothesised that a frailty assessment including multiple domains improved preoperative risk assessment for delirium.

The aim of this study was to investigate the predictive value of preoperative frailty characteristics on postoperative delirium in an elderly population undergoing elective cardiac surgery and to assess the impact of postoperative delirium on health related quality of life up to one year after cardiac surgery.

Methods

Study design and patient selection

This study was a sub-study of the prospective observational cohort study “Anaesthesia Geriatric Evaluation and Quality of Life After Cardiac Surgery (AGE) study”, which was registered at clinicaltrials.gov under NCT02535728. In short, the aim of the AGE study was to investigate the association between preoperative frailty characteristics and health related quality of life one year after cardiac surgery. Patients aged ≥70 years and scheduled for elective open cardiac surgery (coronary, valve, rhythm, aortic, or combined surgery) were included between July 2015 until August 2017. All patients participating in the AGE study gave written informed consent and the study was performed in accordance with the declaration of Helsinki. In depth details on design and analyses of the AGE study were reported previously.[15]

Frailty screening and covariate assessment

Frailty was assessed on the physical, mental, and social domain directly after routine preoperative anaesthesia screening, which evaluated the somatic domain. Frailty characteristics included nutritional status, gait speed, polypharmacy, daily functioning, grip strength, cognition, HRQL, living situation, educational status, and dependency on others for activities in daily living. For this study we included depression as a frailty characteristic, since it is a known risk factor for delirium.[2] Depression was defined as a prescription of antidepressants (selective serotonin reuptake inhibitor, tricyclic antidepressant (TCA), or non-TCA). Additional pre- and postoperative characteristics were prospectively collected from electronic medical records. Preoperative data included: patient characteristics, comorbidities, EuroSCORE II, echocardiography, and laboratory results available at time of screening, or on the day before surgery. Postoperative data included complications defined according to the Dutch National Complication Registration of Cardiac Surgery[16], in-hospital mortality, and intensive care unit (ICU) and hospital length of stay.

Outcomes

Primary outcome was the occurrence of a delirium during postoperative hospitalisation. Patients were routinely screened for postoperative delirium by nursing personnel. The Intensive Care Delirium Screening Checklist (ICDSC) and the Delirium Observation Screening (DOS) were used to diagnose postoperative delirium in the ICU and on the ward respectively. Both methods were based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders and have been widely validated.[17–19] Delirium was defined as a score ≥4 on the ICDSC, and ≥3 on the DOS.[18,20] The checklists are routinely assessed every eight hours during ICU stay and on indication at the ward. Approximately one third of patients was referred to another hospital for further recovery, in that case discharge letters were requested and screened for postoperative delirium.

Our secondary outcome was health related quality of life according to the Medical Outcomes Study questionnaire Short Form 36 (SF-36). This is a questionnaire with 36 items on overall HRQL.[21] Reponses are summarised in a physical HRQL and a mental HRQL score. Scores have been normalised to a mean of 50 and standard deviation (SD) of ± 10 points with higher scores representing better HRQL.[22] A score of 0 was given in case of death during follow up. HRQL was measured before, and at three and twelve months after surgery.

Statistical analysis

To prevent bias due to missing data we performed multiple imputation analysis. Missing preoperative data and SF-36 domain scores were imputed in 30 sets. Analyses were performed in each set and results were pooled using Rubin's Rules.[23] Comparisons of patients with or without missing data was described previously.[24] Baseline characteristics were compared between patients with or without delirium by Chi square test, Mann Whitney U test, or Student T test depending on type of data and normality. Histograms were inspected to determine normality.

Associations between frailty characteristics and delirium were analysed using logistic regression analysis. First, univariable analysis was performed to analyse the association between frailty characteristics and postoperative delirium. Second, a multivariable model was created. Frailty characteristics included in the model were chosen based on prior literature and clinical feasibility i.e. gait speed, polypharmacy, daily functioning, preoperative HRQL, depression, living alone and dependent living).[15] Frailty characteristics were adjusted for EuroSCORE II. To assess the added value of this frailty model it was compared to a clinical model including EuroSCORE II and preoperative haemoglobin. Differences in model fit were assessed by the likelihood ratio test and model discrimination was assessed using C-statistic. Additionally, a net reclassification index (NRI) was calculated. The NRI evaluated the improvement in predictive performance of the frailty model versus the clinical model. Reclassification of the frailty model is improved when the predicted probability for delirium is higher in patients with the outcome, and lower in patients without the outcome compared to the predicted probabilities by the clinical model. The cut off points to define risks were set at <10% predicted probability as low risk, ≥10 and <20% for intermediate risk and ≥20% as high risk.

To investigate the effect of postoperative delirium on HRQL over the course of one year we conducted generalized linear mixed modelling for physical and mental HRQL. Time and delirium were added as fixed parts and 'patient' as random part. As HRQL trajectories were not linear over time, a quadratic polynomial was added for time to improve model fit. An interaction term between delirium and time was used to assess if HRQL scores differed over time between patients with or without delirium. Unbiased variance estimates for the final models were generated by restricted maximum likelihood estimation (REML). Estimates are expressed as linear regression coefficients (β) with 95% confidence intervals (95% CI). Analysis were performed in IBM SPSS Statistics version 23 for Windows (IBM Corp., Armonk, NY, USA) and R statistics (Version 3.5.1– © 2018-07-02, R, Inc., for Windows). A p of <0.05 was considered statistically significant.

Results

Patient population

The AGE study consisted of 555 patients. Preoperative serum albumin analyses were performed after imputation, and 16 (2.9%) patients with missing albumin data were excluded from the analysis. The final cohort consisted of 539 patients. Median age was 75 (IQR 72 – 77) years and 181 (33.6%) patients were female. Single CABG or maze surgery was most often performed (182 patients, 33.8%), followed by combined surgery (164 patients, 30.4%), single valve surgery (152 patients, 28.2%), and aortic surgery (41 patients, 7.6%). Hypertension was the most common cardiovascular comorbidity and was present in 448 (83.1%) patients. Non-cardiac comorbidities were common, 180 (33.4%) patients had preoperative renal failure, 110 (20.4%) diabetes mellitus, and 74 (13.7%) a history of stroke. Preoperative cognitive dysfunction was rare (4 (0.7%) patients), and 17 (3.2%) patients were dependent on others in activities of daily living.

Preoperative risk factors for delirium

Postoperative delirium was diagnosed in 95 (17.6%) patients. Patients with a delirium were characterised by older age, extra cardiac arteriopathy, lower albumin, more complex surgery, and consequently, a higher EuroSCORE II (Table 1). Eight out of thirteen frailty characteristics were associated with a postoperative delirium (Table 2, supplementary Table 1). Patients with a delirium had a worse nutritional status, slower walking speed and mobility. Scores for cognition and mental HRQL were lower, and more patients had medication for depressive disorders. Patients with delirium had a low educational level and were more often dependent on other in activities of daily living, compared to patients without a delirium.

A clinical model including EuroSCORE II and haemoglobin for the prediction of postoperative delirium yielded a C statistic of 0.614 (95% CI 0.552 - 0.676). Discrimination improved by adding frailty characteristics to the model (C-statistic 0.684 (95% CI 0.622 - 0.746)). Table 3 presents adjusted odds ratios for the predictors in the model. According to the NRI frailty improved risk stratification. In patients with a delirium the frailty model reclassified 8% of patients to the high risk category. And, for patients without a delirium the frailty model reclassified 17% of patients to a lower risk category. The overall NRI was 25% ($p<0.001$) meaning one in four patients was correctly assigned to a different risk category based on frailty characteristics.

Table 1. Baseline

	No delirium 444	Delirium 95	p-value
Age	74 (72 – 77)	76 (73 – 78)	0.001
Gender	148 (33.3)	33 (34.7)	0.793
Alcohol abuse	54 (12.2)	9 (9.5)	0.459
Comorbidities			
Hypertension	373 (84)	75 (78.9)	0.232
Dyslipidaemia	275 (61.9)	66 (69.5)	0.167
Paroxysmal atrial fibrillation	139 (31.3)	24 (25.3)	0.244
Previous cardiac surgery	29 (6.5)	8 (8.4)	0.509
Diabetes mellitus	85 (19.1)	25 (26.3)	0.115
Stroke	57 (12.8)	17 (17.9)	0.194
Renal failure	145 (32.7)	35 (36.8)	0.433
Extracardiac arteriopathy	46 (10.4)	19 (20.0)	0.009
Chronic obstructive pulmonary disease	44 (9.9)	14 (14.7)	0.168
Cognitive dysfunction	3 (0.7)	1 (1.1)	0.698
Left ventricular ejection fraction	95 (21.4)	20 (21.1)	0.933
Laboratory			
Haemoglobin (continuous)	8.7 ±0.9	8.5 ±0.9	0.069
eGFR (continuous)	67 ±16	64 ±17	0.098
Albumin	39 ±3	38 ±3	0.021
Surgical			
EuroSCORE II	1.8 (1.2 – 3.1)	2.5 (1.6 – 4.2)	<0.001
Type of surgery			<0.001
Single CABG or Maze	165 (37.2)	17 (17.9)	
Single valve	130 (29.3)	22 (23.2)	
Combined	124 (27.9)	40 (42.1)	
Aortic	25 (5.6)	16 (16.8)	

Numbers are n (%), means ± standard deviation, or medians (inter quartile range)
CABG: coronary artery bypass graft, eGFR: estimated glomerular filtration rate

Table 2. Frailty characteristics

	No delirium 444	Delirium 95	p-value
Physical domain			
Nutritional status (points) †	13 (12 – 14)	12 (11 – 14)	0.015
Gait speed (5MWT, s)	4.7 (4.1 – 5.5)	5.0 (4.4 – 6.0)	0.001
Mobility (TGUGT, s)	9.7 (8.4 – 11.5)	11.0 (9.4 – 12.5)	<0.001
Polypharmacy (prescriptions)	6 (4 – 8)	6 (4 – 9)	0.361
Daily functioning (points)	0 (0 – 1)	1 (0 – 2)	0.070
Low grip strength	158 (35.7)	40 (42.1)	0.170
Mental domain			
Cognition (points) †	29 (28 – 30)	28 (27 – 29)	<0.001
Depression	19 (4.3)	12 (12.6)	0.002
Health-related quality of life			
Physical (points) †	44 (34 – 51)	40 (32 – 49)	0.055
Mental (points) †	52 (42 – 57)	48 (36 – 54)	0.004
Social domain			
Living alone	94 (21.2)	26 (27.4)	0.188
Lower education level	110 (24.7)	32 (33.8)	0.041
Dependent living	8 (1.8)	9 (9.5)	<0.001

Values are medians (interquartile range) or n (%). 5MWT: 5-Meter Walk test, TGUGT: Timed Get Up and Go test
† Indicates a questionnaire or test where a high score represents a lower risk.

Table 3. Multivariable model for postoperative delirium

	OR	95% CI
EuroSCORE II (points)	**1.15**	**(1.06 - 1.26)**
Haemoglobin †	0.95	(0.74 - 1.22)
Gait speed (5MWT, s)	1.15	(0.99 - 1.33)
Polypharmacy (prescriptions)	0.95	(0.88 - 1.03)
Daily functioning (points)	0.79	(0.6 - 1.04)
Depression	**2.59**	**(1.08 - 6.21)**
Physical HRQL (points) †	0.98	(0.96 - 1.01)
Mental HRQL (points) †	**0.97**	**(0.95 – 1.00)**
Living alone	1.17	(0.68 - 2.03)
Dependent living	**4.26**	**(1.4 - 12.96)**

EuroSCORE II: European System for Cardiac Operative Risk Evaluation II, 5MWT: 5 meter walk test, HRQL: health related quality of life
† Indicates a questionnaire or test where a high score represents a lower risk.

Figure 1.a

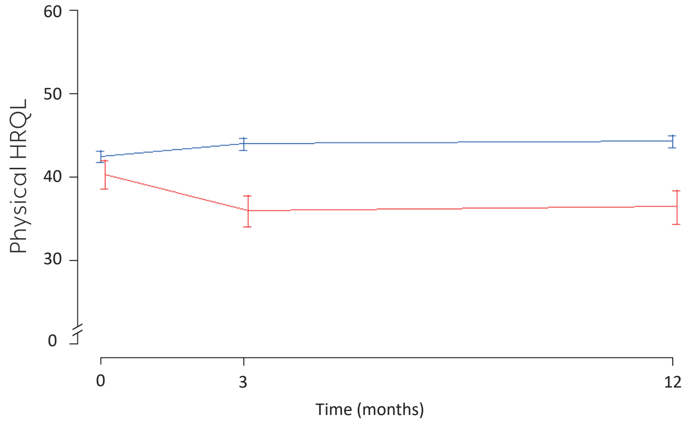


Figure 1.b

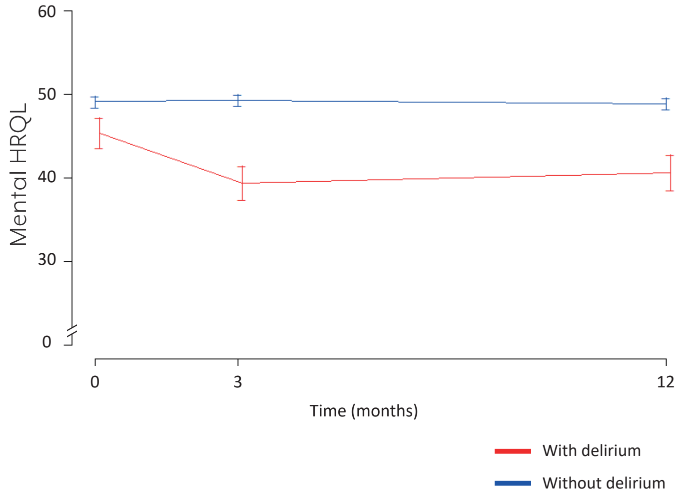


Figure 1. Physical (a) and mental (b) health related quality of life according to patients with or without delirium. HRQL: health related quality of life

Associations of delirium on long term outcomes

Baseline physical HRQL was 44 points and was lower for patients with a delirium (mean difference -5.4, $p<0.001$) compared to patients without a delirium. Over time physical HRQL changed significantly ($p=0.032$). However, when taking delirium into account HRQL changed only for patients with a delirium ($p=0.030$, Figure 1a). Mental HRQL at baseline for the overall cohort was 49 points and remained stable over time ($p=0.642$). Patients with a delirium had 6.4 points lower mental HRQL at baseline ($p<0.001$). Over time, mental HRQL decreased for patients with a delirium ($p=0.024$, Figure 1b).

Discussion

In elderly patients undergoing cardiac surgery 18% of patients experienced a postoperative delirium. Preoperative frailty characteristics were independently associated with postoperative delirium. A model including frailty characteristics improved preoperative risk stratification compared to a clinical model alone. Patients with a postoperative delirium reported a lower health related quality of life during one year recovery.

Our results confirm that preoperative frailty is moderately predictive for postoperative delirium. [3,10–13] Adding frailty characteristics improved model performance (C-statistic 0.684 (95% CI 0.622 - 0.746)), compared to clinical factors. Another study in a similar cardiac population found that both the Modified Fried Criteria and the short physical performance battery improved discrimination for a postoperative delirium (C-statistics 0.695 (95% CI 0.580-0.810) and 0.699 (95% CI 0.581-0.816) respectively).[13] Both frailty scores rely on measures of physical frailty solely. In our study frailty characteristics were measured on three domains (physical, mental and social). Besides gait speed, polypharmacy, and daily functioning, cognitive functioning, mental HRQL, depression, and living dependent were associated with delirium (supplementary table 1). This implies that the addition of frailty characteristics of more domains leads to better identification of the high risk patient. This is in line with a study in 89 patients undergoing various types of elective cardiac surgeries and focussing on the combination of frailty and mild cognitive impairment.[11] Frailty was assessed by the Japanese version of the Cardiovascular Health Study which are based on the Fried criteria. Patients with a combination of frailty and cognitive impairment had the highest odds for a postoperative delirium. Frailty or cognitive impairment alone was not significantly associated with delirium.[11]

Prevention of postoperative delirium has focussed on pharmacological prophylaxis. However, a positive effect has not been found.[14,25] Non-pharmacological interventions are effective in reducing delirium, but are often applied after surgery.[26] Due to the multifactorial causes of delirium, a multicomponent non-pharmacological approach has been recommended for delirium prevention.[14] Preoperative frailty screening has the ability to identify areas of impairment and could guide multicomponent prevention. Optimisation could be implemented during the waiting period for elective cardiac surgery. In patients undergoing elective abdominal surgery for colorectal carcinoma or an abdominal aortic aneurysm a multimodal prehabilitation program with interventions on physical health, nutritional status, factors of frailty and preoperative anaemia was compared to a control group. Delirium incidence was significantly reduced from 11.7 to 8.2% (OR 0.56; 95% CI 0.32–0.98; p = 0.043). A suggestion for future research could be to investigate a frailty led prehabilitation program for the prevention of a delirium after cardiac surgery.

Our results should be interpreted in light of several limitations. First, delirium was assessed by reviewing patient charts. Although validated delirium checklists were used, there are some drawbacks to this method.[20,27] One of these drawbacks is that a delirium is often underdiagnosed, most often the hypoactive delirium.[28] Real incidence of delirium could exceed the 18% that was observed in this study. Second, the duration and severity of a delirium was not recorded. A more severe delirium has been associated with a higher occurrence of poor functional recovery.[3] Possibly, the effect on delirium on HRQL seen in this study was caused by patients with a severe delirium, and is less pronounced for patients with a mild delirium. Third, there could be an interaction between other complications and delirium. On the one hand, a delirium can be caused by an earlier complication, i.e. infection. On the other hand, a confused patient is less likely to mobilise or follow instructions increasing the risk for a new complication. The results presented in this study could be influenced by the relation between complications and HRQL. Fourth, the occurrence of a prior delirium in a patients' medical history was unknown. However, it is an important risk factor for a new delirium. When using our results in future studies or clinical care this should be included as a preoperative risk factor. Last, depression was defined as the use of antidepressants. When interpreting our results it should be taken into account that use of antidepressants is not the same as a current depression, and the use of an antidepressant can be for a different indication. Among the strengths of this study was the extensive screening of frailty characteristics before surgery. Additionally, patients that were referred to a second hospital for postoperative care were assessed for delirium by checking referral letters. Also, loss to follow up was low for HRQL questionnaires and bias was further reduced by performing multiple imputation.

To summarise, a postoperative delirium occurs frequently after cardiac surgery and is associated with reduced HRQL after one year. Frailty characteristics in physical, mental and social domain, are associated with a postoperative delirium. A predictive model including frailty improves risk stratification. Clinicians can allocate preventive strategies for delirium to high risk patients based on frailty assessment.

References

1. Gosselt ANC, Slooter AJC, Boere PRQ, Zaal IJ. Risk factors for delirium after on-pump cardiac surgery: A systematic review. *Crit Care*. 2015;19(1):1-8.
2. Lin Y, Chen J, Wang Z. Meta-analysis of factors which influence delirium following cardiac surgery. *J Card Surg*. 2012;27(4):481-492.
3. Shi SM, Sung M, Afilalo J, et al. Delirium Incidence and Functional Outcomes After Transcatheter and Surgical Aortic Valve Replacement. *J Am Geriatr Soc*. 2019;67(7):1393-1401.
4. Loponen P, Luther M, Wistbacka JO, et al. Postoperative delirium and health related quality of life after coronary artery bypass grafting. *Scand Cardiovasc J*. 2008;42(5):337-344.
5. Statline. Prognose bevolking; geslacht en leeftijd, 2020-2060. 17-12-2019. https://opendata.cbs.nl/statline/#/CBS/nl/dataset/84646NED/table?ts=1591866408680. Published 2019. Accessed June 11, 2020.
6. Buth KJ, Gainer RA, Legare J-F, Hirsch GM. The Changing Face of Cardiac Surgery: Practice Patterns and Outcomes 2001-2010. *Can J Cardiol*. 2014;30:224-230.
7. Rudolph JL, Jones RN, Levkoff SE, et al. Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. *Circulation*. 2009.
8. Lee DH, Buth KJ, Martin BJ, Yip AM, Hirsch GM. Frail patients are at increased risk for mortality and prolonged institutional care after cardiac surgery. *Circulation*. 2010;121(8):973-978.
9. Sündermann S, Dademasch A, Praetorius J, et al. Comprehensive assessment of frailty for elderly high-risk patients undergoing cardiac surgery. *Eur J Cardiothorac Surg*. 2011;39(1):33-37.
10. Nomura Y, Nakano M, Bush B, et al. Observational Study Examining the Association of Baseline Frailty and Postcardiac Surgery Delirium and Cognitive Change. *Anesth Analg*. 2019;129(2):507-514.
11. Itagaki A, Sakurada K, Matsuhama M, Yajima J, Yamashita T, Kohzuki M. Impact of frailty and mild cognitive impairment on delirium after cardiac surgery in older patients. *J Cardiol*. 2020;(2019).
12. Brown CH, Max L, Laflam A, et al. The Association between Preoperative Frailty and Postoperative Delirium after Cardiac Surgery. *Anesth Analg*. 2016;123(2):430-435.
13. Jung P, Pereira MA, Hiebert B, et al. The impact of frailty on postoperative delirium in cardiac surgery patients. *J Thorac Cardiovasc Surg*. 2015;149(3):869-875.
14. Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. *Lancet*. 2014;383:911-922.
15. Verwijmeren L, Peelen LM, van Klei WA, et al. Anaesthesia geriatric evaluation to guide patient selection for preoperative multidisciplinary team care in cardiac surgery. *Br J Anaesth*. 2020;124(4):377-385.
16. Afdeling Klinische Informatiekunde AA. Handboek BHN Registratieproject v4.0.1. https://nederlandsehartregistratie.nl. Published 2015.
17. Devlin JW, Skrobik Y, Gélinas C, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. *Crit Care Med*. 2018;46(9):e825-e873.
18. Koster S, Hensens AG, Oosterveld FGJ, Wijma A, van der Palen J. The delirium observation screening scale recognizes delirium early after cardiac surgery. *Eur J Cardiovasc Nurs*. 2009;8(4):309-314.
19. Schuurmans MJ, Shortridge-Baggett LM, Duursma SA. The Delirium Observation Screening Scale: a screening instrument for delirium. *Res Theory Nurs Pr*. 2003;17(1):31-50.
20. Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive care delirium screening checklist: Evaluation of a new screening tool. *Intensive Care Med*. 2001;27(5):859-864.
21. Ware J jr, Sherbourne C. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;jun(30(6)):473-483.

22. Zee KI Van Der, Sanderman R. *Het Meten van de Algemene Gezondheidstoestand Met de Rand-36: Een Handleiding*. 2nd ed. Groningen: Research institute SHARE UMCG / Rijksuniversiteit Groningen; 2012.

23. Marshall A, Altman DG, Holder RL, Royston P. Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines. *BMC Med Res Methodol*. 2009;9(1):57.

24. Verwijmeren L, Noordzij PG, Daeter EJ, et al. Preoperative frailty and one year functional outcome of elderly cardiac surgery patients. An observational prospective cohort study. *Unpublished*. 2020.

25. Mu JL, Lee A, Joynt GM. Pharmacologic agents for the prevention and treatment of delirium in patients undergoing cardiac surgery: Systematic review and metaanalysis. *Crit Care Med*. 2015;43(1):194-204.

26. Pieri M, De Simone A, Rose S, et al. Trials Focusing on Prevention and Treatment of Delirium After Cardiac Surgery: A systematic Review of Randomized Evidence. *J Cardiothorac Vasc Anesth*. 2020;34(6):1641-1654.

27. Koster S, Oosterveld FGJ, Hensens AG, Wijma A, van der Palen J. Delirium After Cardiac Surgery and Predictive Validity of a Risk Checklist. *Ann Thorac Surg*. 2008.

28. Katznelson R, Djaiani G, Tait G, et al. Hospital administrative database underestimates delirium rate after cardiac surgery. *Can J Anesth*. 2010;57(10):898-902.

Supplementary files

Supplementary Table 1. Univariable associations of frailty characteristics with delirium

	OR	95% CI
Physical domain		
Nutritional status (points)	0.87	(0.78 – 0.97)
Gait speed (5MWT, s)	1.20	(1.06 – 1.34)
Gait speed (TGUGT, s)	1.11	(1.05 – 1.19)
Polypharmacy (prescriptions)	1.05	(0.99 – 1.12)
Daily functioning (points)	1.16	(0.97 – 1.39)
Low grip strength	1.30	(0.84 – 2.06)
Mental domain		
Cognition (points)	0.85	(0.77 – 0.74)
Depression	3.23	(1.51 – 6.92)
Health-related quality of life		
Physical (points)	0.98	(0.96 – 1.00)
Mental (points)	0.97	(0.95 – 0.99)
Social domain		
Living alone	1.40	(0.85 – 2.33)
Lower education level	1.56	(0.97 – 2.52)
Dependent living	5.70	(2.14 – 15.20)

OR: odds ratio, CI: confidence interval, EuroSCORE II: European System for Cardiac Operative Risk Evaluation, 5MWT: 5 meter walk test, TGUGT: time get up and go test

Chapter 7

General discussion

Ageing of the general population together with advancements in medical management of chronic cardiac disease will lead to an increase in the number of older patients being referred for cardiac surgery. In general, cardiac surgery is considered safe in elderly patients. However, postoperative morbidity and mortality are more prevalent in elderly patients characterised by multi-morbidity and frailty. Frailty is an established risk factor for complications or death after cardiac surgery, but its potential association with patient reported outcomes such as health related quality of life (HRQL) or disability is less clear.

Aim

The aim of this thesis was to assess the associations of frailty characteristics and functional outcomes after cardiac surgery in elderly patients. More specifically, we aimed to identify which frailty characteristics were associated with worse HRQL or disability at one year after surgery. Additionally, the preoperative determinants of common postoperative complications, i.e. acute kidney injury and delirium, and their impact on functional outcome after cardiac surgery were investigated.

In this discussion we will reflect on our findings and place them in a broader context. Throughout the discussion we will refer to two clinical cases presented in Box 1.

Findings

Frailty

In addition to routine preoperative anaesthesia assessment we evaluated 11 frailty characteristics in geriatric cardiac surgery patients (**Chapter 3, 4, and 6**). In our cohort some frailty characteristics were prevalent, i.e. polypharmacy, impaired gait speed, or decreased grip strength, whereas others were uncommon, i.e. cognitive impairment or dependency in activities of daily living. Obviously, limitations in physical functioning are likely to be present in patients presenting for cardiac surgery due to their chronic cardiac disease, which will reflect in tests on physical frailty. This explains the higher prevalence of physical frailty characteristics. However, more severe frailty was less common. Cardiac surgery is considered high risk surgery and patients with more severe comorbidity or frailty are often referred for alternative treatments by their cardiologist.

Box 1. Clinical scenarios

Patient A This patient was discussed in the introduction. A 78 year old man referred for combined CABG and AVR surgery, with diabetes mellitus and a LVEF of 25%. He uses six different prescriptions. Additional screening of frailty revealed slight mobility impairments with a slower gait speed on the timed get up and go test. And he experienced a lower preoperative physical HRQL compared to the general population. His surgery and postoperative hospital stay were uncomplicated. He reported moderate disabilities at three and twelve months. His physical HRQL was decreased compared to baseline at three months, but improved afterwards and was comparable to the population mean at one year follow up. His mental HRQL was equivalent to baseline at both three and twelve months.

Patient B is a 75 year old woman also referred for combined CABG and AVR surgery. Her comorbidities included hypertension, dyslipidaemia and a transient ischaemic attack four years ago. She used seven different prescribed drugs. Frailty screening revealed a risk for malnutrition based on recent weight loss, impaired mobility with slow walking speed on the timed get up and go test and five meter walk test. Her preoperative physical and mental HRQL were lower compared to the population mean. Her surgery is uncomplicated, after one night on the intensive care unit she is transferred to the ward. On day five she experiences respiratory distress and she is readmitted to the ICU. After treatment with diuretics and non-invasive ventilation she recovers and is transferred to the ward after three days. Total hospital stay is 16 days after which she is discharged home, with home care. Her physical self-reported HRQL was decreased at three months compared to baseline, but mental HRQL was improved. She reported important disabilities in physical functioning. After one year her disabilities were still present, her physical HRQL improved slightly but did not recover to baseline. Mental HRQL remained better compared to baseline and was similar to the population mean.

Frailty is a prevalent condition in cardiac surgery patients and increases the risk for postoperative complications.[1–3] This thesis showed that frailty is associated with patient reported outcomes and our findings support the recommendation of several international guidelines that frailty should be assessed during preoperative assessment.[4–7] However, frailty assessment occurs rarely in routine preoperative care.

Among barriers for implementation is the lack of consensus on the best instrument to diagnose frailty. Also, frailty tests are time consuming and can be a burden for cardiac patients and health care personnel. Evidence showing that frailty screening improves outcomes, such as survival or complications, is not yet available.[8] Frailty assessment as described in this thesis consisted of 11 tests and was based on a comprehensive geriatric assessment (Figure 1, Chapter 1).[5] From our experience we learned that a full screening added approximately 20 minutes to routine pre-anaesthesia assessment. To cover this loss in time trained personnel dedicated to geriatric assessment might be required. Alternatively, a selection of frailty tests can be used. We showed that a model consisting of 5 out of 11 frailty characteristics (**Chapter 4**) improved the predicting of postsurgical disability at three months. The use of patient-assessed questionnaires facilitated quick assessment. A suggestion from literature for a more efficient screening is a frailty scale. The most common scales are the clinical frailty scale, the Fried Frailty Scale or Edmonton Frail Scale.[8] A disadvantage of frailty scales is that a more elaborate geriatric assessment is still needed to facilitate prehabilitation. Notwithstanding the drawbacks of frailty screening, we advocate for its implementation in routine clinical practice to improve risk assessment for both complications and patient reported outcomes, and to facilitate targeted prehabilitation.

Health related quality of life

The WHO definition of health is *"a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"* and is complemented by the more recent concept of "*health as the ability to adapt and self-manage, in light of the physical, emotional and social challenges of life*".[9,10] Both definitions include mental and social wellbeing. This emphasizes the importance of patient reported outcome measures after surgery besides classical endpoints on physical wellbeing, i.e. complications and mortality. Studies on change in postoperative HRQL show that most patients benefit from surgery, but up to one in five patients experience worse HRQL after a procedure.

In this thesis we aimed to identify preoperative determinants of postoperative HRQL and to investigate the impact of a postoperative delirium on HRQL. Our findings confirmed that a considerable proportion (16-25%) of patients suffer a loss in HRQL after CABG (**Chapter 2 and 3**). Preoperative clinical characteristics, represented by EuroSCORE II, were moderately associated with worse physical HRQL. Polypharmacy, nutritional status, mobility (timed get up and go test), preoperative mental HRQL, and living alone were associated with worse mental HRQL after one year. However, these associations were modest. The most important preoperative determinant for a loss in HRQL was preoperative HRQL.

A patient with poor preoperative HRQL is more likely to improve in HRQL after surgery, while a patient with satisfactory preoperative HRQL is at risk to worsen. These findings confirm the results of others and can be explained as follows.[11–13] Patients with a satisfactory preoperative HRQL often have good physical functioning, and when this worsens after surgery a patient has to adapt its lifestyle. One of many examples could be that mobility is impaired and a patients is unable to travel independently to relatives. These impairments can have a (temporarily) negative impact on HRQL. In other words, a patient with a good HRQL before surgery has much to lose. From the perspective of a patient with poor preoperative HRQL, it is the other way around. When surgery is successful in relieving physical or mental symptoms, these patients often experience a relevant improvement in their HRQL. For example, patient A in our clinical example had moderate disabilities at three and twelve months after his surgery. His physical HRQL was worse compared to baseline at three months but improved over time and was better than baseline at twelve months. This could be an example of a patient that adapts to the new situation and evaluates his physical HRQL to be better over the course of time, despite new disabilities. Patient B has persistent disabilities at three and twelve months and a worse physical HRQL compared to baseline. Her mental HRQL however improves after surgery. Cardiac comorbidities and the prospect of surgery can trigger anxiety or sadness and lead to a lower preoperative mental HRQL. Successful surgery might reduce anxiety leading to an improved mental HRQL.

A second important finding is that most preoperative predictors, including frailty, were poorly associated with change in HRQL (**chapter 2 and 3)**. The causes of a change in HRQL after surgery are multifactorial and can vary over time. This makes predicting a change in HRQL after surgery challenging. Not only can HRQL vary largely between patients, it can also change over the course of time within an individual. This is known as a response shift. [14] For example, a patient may initially experience a worse mental HRQL after surgery. But, over time, the patient adapts and grows accustomed to the new circumstances and HRQL recovers to baseline. These variations in HRQL between and within patients can be random, making it difficult to predict and could partly explain the lack of strong associations with preoperative determinants. Postoperative complications can affect long term HRQL as well. In **Chapter 5** we investigated the impact of postoperative delirium on HRQL. Patients with a delirium had worse HRQL over the course of one year follow up. Not only delirium, but other postoperative complications could be a risk factor for worse long term HRQL too. Lastly, factors unrelated to surgery can have an impact on HRQL, especially when follow up time is longer. Comorbidities are more prevalent in elderly patients, and can worsen over time. Also, changes in social environment (loss of a partner of family member) influence HRQL and occur relatively often in elderly patients.

Yet, despite the difficulties in predicting HRQL it is essential to implement such measurements in perioperative practice. For one thing, HRQL is an important outcome measure in research studies, which was the main use of HRQL in this thesis. But more importantly, HRQL assesses the impact of an intervention on a patient's life, rather than just their body, or a single organ. Information which is very relevant when counselling a patient on expected recovery.

Disability

Disability can be defined as: *"an umbrella term for impairments, activity limitations and participation restrictions"*.[15] It is the combination of physical or mental impairments due to a health condition in relation to personal and environmental circumstances (i.e. social support, accessibility to healthcare, or participation in society). Patients often experience disability prior to cardiac surgery. As with quality of life, most patients improve as a result of the procedure, but a considerable proportion of patients develops new disabilities.

As a secondary outcome in the AGE study we assessed disability at three and twelve months following surgery. In this thesis the associations on preoperative frailty characteristics and disability one year after surgery were reported. One in five patients experienced disability one year after surgery. Preoperative frailty characteristics that had an association with disability independent from EuroSCORE II were polypharmacy, Nagi's scale, 5 meter walk test, timed get up and go test, preoperative mental and physical HRQL, living alone, and dependent living (**Chapter 3**). A multivariable model including EuroSCORE II, preoperative haemoglobin and five frailty characteristics (polypharmacy, 5 meter walk test Nagi's scale, HRQL, and living alone) was superior in identifying patients at high risk for three month disability compared to a model with EuroSCORE II and preoperative haemoglobin alone (**Chapter 4**). The impact of cardiac surgery associated acute kidney injury (CSA-AKI) on one year disability was described in **Chapter 5**. Cardiac surgery associated acute kidney injury was present in 15% of patients and increased the risk for disability at one year 1.6 fold.

An important note when comparing our results to previous studies are the differences in study design. Cohorts vary from patients undergoing a single procedure, such as isolated CABG, or minimal invasive procedures, such as transcatheter aortic valve replacement, to patients undergoing complex cardiac surgery. [16–19] Also, postsurgical disability was measured using different tools and no consensus existed on the definition used for disability. For example, questionnaires on impairments in activities in daily living were used to assess disability in some studies.[16,17] Whereas the composite of stroke, nursing home admission and recurrent hospital admissions was used in a different study.[18] As a result, it is too early for clinical recommendations regarding the predictive value of frailty on disability. Future research is needed to validate our findings, and those of others, using standardised endpoints for disability. In 2019 the Standardised Endpoints in Perioperative Medicine Initiative published recommendations on measuring patient reported outcomes. In line with our design, the WHODAS 2.0 was strongly recommended to measure disability and should be incorporated as an outcome measure in future research.[20]

The assessment of disability in the AGE study was performed after surgery and a comparison to preoperative measurements was not possible. Therefore, patients reporting disability in our cohort might suffer from new disability, or pre-existing disability that did not improve after surgery. Our cut-off point for disability free survival was based on the World Health Organisation International classification of functioning, disability and health, which defines a score of 25% as a moderate impairment.[21] However, at the time of analysing our data this definition was not yet validated in a surgical cohort. Validation was recently performed in a mixed surgical cohort including 5% cardiac surgeries. A minimally clinically important change was defined as a change of ≥5%, disability-free survival was set at a score <16%, and clinically significant disability as a score ≥35%.[22] Our cut-of value of 25% lies in between their definition of disability free survival and clinically significant disability. This could mean that we slightly overestimated clinically relevant disability rates in our population. The recent recommendations on disability questionnaires and clinically relevant cut/of values provide a framework for a uniform measuring of disability in future studies.[20,22]

Clinical applications

Multidisciplinary team care

With ageing of the population, the number of frail patients referred for cardiac surgery will increase. Management of this complex patient group requires expertise on surgery, comorbidity, geriatrics, and patient preferences. Because of the increasing specialisation of physicians weighing all options is difficult for a single physician. For complex cases a multidisciplinary team (MDT) meeting could be beneficial in forming a patient tailored treatment plan.[23,24] A team of perioperative specialists can interpret and discuss preoperative risk factors and construct a patient tailored treatment plan. Risk prediction scores can be a useful tool to summarise a patients' surgical risk. But, traditional risk prediction scores, such as EuroSCORE II or Parsonnet score, overlook frailty and were not designed to predict patient reported outcomes. This creates a gap in evidence on the prediction of relevant outcomes for frail elderly cardiac surgery patients. Clinical consensus reached in a MDT meeting (experienced based medicine) might be the best available evidence to guide treatment decisions.[23] In addition to risk prediction and treatment decisions, a MDT meeting based on a geriatric assessment can identify potentially modifiable risk factors. Examples could be combinations of nutritional support, physical therapy, or correction of preoperative anaemia. In other surgical fields prehabilitation has led to improved outcomes.[25,26] Within cardiac surgery several studies are ongoing on this subject and results have to be awaited before conclusions can be drawn.[27–29] Additionally, alternative, often less invasive treatment plans can be considered during a MDT meeting. For example a transcatheter instead of a surgical aortic valve replacement.[30] Or medical treatment in some cases of coronary artery disease. [31]

Although a MDT provides several benefits there are also drawbacks. Inappropriate referral to a MDT can lead to a treatment delay, additional screening can be an unnecessary patient burden, and it requires a substantial investment of time and hospital resources.[23] To minimize these disadvantages, accurate selection of high-risk complex cases is essential (**Chapter 4**). For example, patient A from our clinical scenarios had a low risk profile with few frailty characteristics. His surgery was uncomplicated and his HRQL was improved at follow up. A MDT meeting would have been an unnecessary investment of the patients' time and hospital resources. Contrastingly, patient B had several impairments in frailty characteristics. She experienced several complications, and reported significant disabilities at follow up. As a results of a MDT meeting, an alternative and less invasive procedure could be considered and discussed with the patient. Also, factors that influence the risk of complications could be optimised, in this case nutritional status, anaemia, physical performance, and possibly anxiety.

During the course of the AGE study a weekly MDT meeting was set up in the St. Antonius Hospital for high risk surgical patients with abdominal malignancies or abdominal aneurysms. And, after completion of the AGE cohort also for patients undergoing cardiac surgery. Patients are referred to the MDT by the surgeon. Prior to the meeting an Anaesthesia Geriatric Evaluation is performed. This includes a routine anaesthesia assessment, tests or questionnaires on frailty characteristics in four domains, and an interview of patient preferences and treatment goals. For cardiac surgery at least one representative of the following specialities attends: anaesthesia, cardiac surgery, geriatrics, cardiology, clinical pharmacy, physiotherapy, and nutritional therapy. The discussion includes several topics: severity of comorbidities and frailty, possibility of prehabilitation, indication for treatment, expected prognosis with and without treatment, burden of disease, patient motivation, and risks and benefits of treatment.

After the MDT meeting the treatment plan is discussed with the patient by the surgeon and nurse according to shared decision making principles.

Future directions

From this thesis and our experiences with the MDT meetings some clinical and research considerations follow. First, by careful patient selection, MDT care (which is costly, time demanding, and an additional patient burden) can be provided for frail patients. The selection method proposed in **chapter 5** resulted in an average referral of two patients a week for MDT care in a centre with 2000 cardiac surgeries per year. Alternatively, literature proposes the use of the Clinical Frailty Scale for referral to MDT care.[8] Second, a complete risk profile of the patient is needed to facilitate an in-depth discussion during MDT meetings.[5] Routine preoperative screening evaluates mainly somatic issues and overlooks important physical, mental and social risk factors. An assessment of all four domains needs to be performed prior to MDT meeting.[5] Third, patient reported outcomes should be measured before and after surgery. Preoperative HRQL is the main contributing factor to HRQL after surgery. It can be used in counselling patients on what can be expected during recovery. Last, up to date MDT care is not implemented in most clinics. A restricting factor is the lack of evidence for its benefit. Studies comparing MDT care with regular care are needed to assess potential benefit on complications, mortality, patient reported outcomes and costs. This period, in which MDT meetings are not yet standard care, provides the opportunity to design studies investigating their added value on outcomes.

Frailty could play a large role in the clinical implementation of patient selection for MDT and patient specific risk assessment. However, choosing the most appropriate frailty instruments to use in clinical practice from the more than 40 that are available in literature is challenging.[8] A frailty instrument for patient selection has different requirements compared to prehabilitation. The first needs to be quick and inexpensive in order to be feasible in clinical practice. The second needs to be thorough and precise to achieve complete risk assessment on all domains. To combine these two requirements a two-step frailty assessment seems logical.[8,23] At first a quick frailty assessment is performed using a frailty scale, followed by a full geriatric assessment on all four domains in high risk patients only. Future research could be to investigate the ideal frailty instrument for both purposes. This could assist physicians in implementing frailty screening in clinical practice. And, it would improve homogeneity and enable comparisons of different studies, leading to higher quality research.

Routine measurement of patient reported measures has clinical and research benefits. They are more relevant to a patient than traditional outcomes because they measure the impact on a patients' life rather than just the body. Registration of complications, mortality, or length of stay is widely used to monitor quality of care and to improve health care. Patient reported outcome measures could be a valuable addition to these purposes. Automated digital questionnaires per email could be considered since they are patient friendly and require few hospital resources. Recent recommendations suggest the EuroQol 5 questionnaire for HRQL and the 12-item WHODAS 2.0 for disability.[20]

Lastly, evidence on the benefits of multi-disciplinary team care could be a focus for future research. A randomised controlled trial (RCT) is the most common study design to investigate an intervention. However, a regular RCT is prone to contamination bias. [32] Which means that the patients in the control group inadvertently receive recommendations meant for the intervention group because care-givers gain experience during the course of the study. This could reduce the true effect of the intervention. A before-after trial eliminates this problem. But this type of study design can be biased because health care can change over time. Measured effects could then be due to the intervention, or to the changes in health care.[33] A step wedge design can reduce both forms of bias and can more accurately investigate complex interventions such as a prehabilitation program.[32,33] It is a multi-centre design. Each centre includes a part of the control group first, then implements the intervention and includes the intervention group. This reduces contamination bias. Bias caused by changes in health care is reduced because each centre implements the intervention at a different time point. The first centre to implement the intervention contributes mostly to the intervention group, and the last centre to the control group. Therefore, during the course of the study, both control and intervention patients are included.

Concluding remarks

This thesis provides new understandings on preoperative frailty in elderly patients undergoing elective cardiac surgery and the relation with patient reported outcomes. Findings from this thesis could be used to design new studies in the field of geriatric cardiac surgery and inspire fellow health care providers to further improve care for elderly patients using a multidisciplinary approach.

References

1. Afilalo J, Eisenberg MJ, Morin J-F, et al. Gait speed as an incremental predictor of mortality and major morbidity in elderly patients undergoing cardiac surgery. *J Am Coll Cardiol*. 2010;56(20):1668-1676.
2. Afilalo J, Mottillo S, Eisenberg MJ, et al. Addition of frailty and disability to cardiac surgery risk scores identifies elderly patients at high risk of mortality or major morbidity. *Circ Cardiovasc Qual Outcomes*. 2012;5(2): 222-228.
3. Lee DH, Buth KJ, Martin BJ, Yip AM, Hirsch GM. Frail patients are at increased risk for mortality and prolonged institutional care after cardiac surgery. *Circulation*. 2010;121(8):973-978.
4. Chow WB, Rosenthal RA, Merkow RP, Ko CY, Esnaola NF. Optimal Preoperative Assessment of the Geriatric Surgical Patient : A Best Practices Guideline from the American College of Surgeons National Surgical Quality Improvement Program and the American Geriatrics Society. *J Am Coll Surg*. 2012;215(4):453-466.
5. Nederlandse vereniging voor klinische geriatrie nvkg. Richtlijn behandeling kwetsbare ouderen bij chirurgie. 2016:980.
6. Alvarez-Nebreda ML, Bentov N, Urman RD, et al. Recommendations for Preoperative Management of Frailty from the Society for Perioperative Assessment and Quality Improvement (SPAQI). *J Clin Anesth*. 2018;47(February 2018):33-42.
7. Griffiths R, Beech F, Brown A, et al. Peri-operative care of the elderly 2014 : Association of anaesthetists of great britain and Ireland. *Anaesthesia*. 2014.
8. McIsaac DI, Macdonald DB, Aucoin SD. Frailty for Perioperative Clinicians: A Narrative Review. *Anesth Analg*. 2020;130(6):1450-1460.
9. World Health Organization. Constitution of the World Health Organization. April 7. https://www.who.int/about/who-we-are/constitution. Published 1948. Accessed December 20, 2019.
10. Huber M, Knottnerus JA, Green L, et al. How should we define health? *BMJ*. 2011;343:d4163.
11. Kurfirst V, Mokráček A, Krupauerová M, et al. Health-related quality of life after cardiac surgery - the effects of age, preoperative conditions and postoperative complications. *J Cardiothorac Surg*. 2014;9(1):1-8.
12. Blokzijl F, Houterman S, van Straten BHM, et al. Quality of life after coronary bypass: a multicentre study of routinely collected health data in the Netherlands†. *Eur J Cardio-Thoracic Surg*. 2019;56(3):526-533.
13. Rumsfeld JS, Magid DJ, O'Brien M, et al. Changes in health-related quality of life following coronary artery bypass graft surgery. *Ann Thorac Surg*. 2001;72(6):2026-2032.
14. Sprangers MA., Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. *Soc Sci Med*. 1999;48(11):1507-1515.
15. World Health Organization. World report on disability. https://www.who.int/publications/i/item/world-report-on-disability. Published 2011. Accessed July 13, 2020.
16. Afilalo J, Lauck S, Kim DH, et al. Frailty in Older Adults Undergoing Aortic Valve Replacement. The FRAILTY-AVR Study. *J Am Coll Cardiol*. 2017;70(6):689-700.
17. Hoogerduijn JG, de Rooij SE, Grobbee DE, Schuurmans MJ. Predicting functional decline in older patients undergoing cardiac surgery. *Age Ageing*. 2014;43(2):218-221.
18. Sun LY, Tu J V., Lee DS, et al. Disability-free survival after coronary artery bypass grafting in women and men with heart failure. *Open Hear*. 2018;5(2):1-12.
19. Hosler QP, Maltagliati AJ, Shi SM, et al. A Practical Two-Stage Frailty Assessment for Older Adults Undergoing Aortic Valve Replacement. *J Am Geriatr Soc*. 2019;67(10):2031-2037.
20. Moonesinghe SR, Jackson AIR, Boney O, et al. Systematic review and consensus definitions for the Standardised Endpoints in Perioperative Medicine initiative: patient-centred outcomes. *Br J Anaesth*. 2019;123(5):664-670.

21. International Classification of Functioning, Disability and Health (ICF) Practical Manual V.0.9. https://www.who.int/classifications/icf/en/. Published 2013. Accessed September 11, 2019.

22. Shulman MA, Kasza J, Myles PS. Defining the Minimal Clinically Important Difference and Patient-acceptable Symptom State Score for Disability Assessment in Surgical Patients. *Anesthesiology*. 2020;(6):1362-1370.

23. Whiteman AR, Dhesi JK, Walker D. The high-risk surgical patient: A role for a multi-disciplinary team approach? *Br J Anaesth*. 2016;116(3):311-314.

24. Quinn TD, Wolczynski P, Sroka R, Urman RD. Creating a Pathway for Multidisciplinary Shared Decision-Making to Improve Communication During Preoperative Assessment. *Anesthesiol Clin*. 2018;36(4):653-662.

25. Prestmo A, Hagen G, Sletvold O, et al. Comprehensive geriatric care for patients with hip fractures: A prospective, randomised, controlled trial. *Lancet*. 2015;385(9978):1623-1633.

26. Partridge JSL, Harari D, Martin FC, et al. Randomized clinical trial of comprehensive geriatric assessment and optimization in vascular surgery. *Br J Surg*. 2017;104(6):679-687.

27. Yau DKW, Wong MKH, Wong WT, et al. PREhabilitation for improving QUality of recovery after ELective cardiac surgery (PREQUEL) study: Protocol of a randomised controlled trial. *BMJ Open*. 2019;9(5):1-9.

28. Stammers AN, Kehler DS, Afilalo J, et al. Protocol for the PREHAB study-Pre-operative Rehabilitation for reduction of Hospitalization After coronary Bypass and valvular surgery: a randomised controlled trial. *BMJ Open*. 2015;5(3):e007250.

29. Hartog J, Blokzijl F, Dijkstra S, et al. Heart Rehabilitation in patients awaiting Open heart surgery targeting to prevent Complications and to improve Quality of life (Heart-ROCQ): Study protocol for a prospective, randomised, open, blinded endpoint (PROBE) trial. *BMJ Open*. 2019;9(9):1-11.

30. Lazkani M, Singh N, Howe C, et al. An updated meta-analysis of TAVR in patients at intermediate risk for SAVR. *Cardiovasc Revasc Med*. 2019;20(1):57-69.

31. Maron DJ, Hochman JS, Reynolds HR, et al. Initial Invasive or Conservative Strategy for Stable Coronary Disease. *N Engl J Med*. 2020;382(15):1395-1407.

32. Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. *Contemp Clin Trials*. 2007;28(2):182-191.

33. Ho AMH, Phelan R, Mizubuti GB, et al. Bias in before?after studies: Narrative overview for anesthesiologists. *Anesth Analg*. 2018;126(5):1755-1762.

Addendum

Summary
Nederlandse Samenvatting
List of abbreviations
Dankwoord
About the author

Summary

A growing number of elderly patients is referred for cardiac surgery. Improvements in surgical techniques and perioperative care made cardiac surgery feasible for elderly patients. But, older age remains associated with an increased risk for mortality or postoperative complications. This is particularly the case for patients characterised by advanced age, multi-morbidity, and frailty. Frailty can be described as *"a biologic syndrome of decreased functional reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, thereby causing vulnerability to adverse outcomes"* (Fried et. al. 2001). The main research focus of this thesis was to investigate the relation between preoperative frailty characteristics and one year functional outcomes after elective cardiac surgery in elderly patients. Additionally, we looked into the relation between a preoperative biomarker panel with cardiac surgery associated acute kidney injury (CSA-AKI). And, preoperative frailty as a predictor for postoperative delirium.

First, in **Chapter 2** clinically available preoperative determinants of HRQL were investigated in a retrospective cohort of 658 patients undergoing elective coronary artery bypass grafting (CABG). Physical HRQL improved in 22.8% of patients, did not change in 61.2% of patients and worsened in 16.0% of patients. Mental HRQL improved in 49.8% of patients, remained unchanged in 34.5% of patients and worsened in 15.7% of patients. The main finding was that preoperative HRQL was the most important risk factor for a change in HRQL after one year. Patients with higher preoperative HRQL were more likely to worsen and patients with low physical HRQL more likely to improve.

Clinically available factors only poorly predicted one year HRQL. This led to our research in **Chapter 3** where the associations of preoperative frailty characteristics on HRQL and disability one year after surgery were investigated. A prospective two-centre cohort study was performed in 555 patients aged 70 years or older and referred for elective cardiac surgery. Frailty characteristics in three additional domains (physical, mental, and social) were assessed in all patients concurrent with routine preoperative anaesthesia assessment. The majority of older cardiac surgery patients had one or more frailty characteristics and over half of all patients had were frail in multiple domains. At one year follow up one in four patients reported worse HRQL, and one in five patients reported disability. Preoperative frailty was associated with adverse functional outcome in general. Individual frailty characteristics were more closely related with postsurgical disability than worse HRQL.

In **Chapter 4** the preoperative assessment of frailty characteristics was used to guide patient selection for a preoperative multidisciplinary team meeting (MDT). A preoperative MDT meeting can be useful to weigh the risks and benefits of surgery, interpret frailty assessment, discuss alternative treatments, and investigate possibilities for prehabilitation. However, it requires a considerable effort of hospital resources and perioperative staff, and increases patient burden. Careful selection of patients at high risk for adverse outcomes could limit these disadvantages. A model with five frailty characteristics improved risk stratification between elderly patients with and without disability at 3 months after cardiac surgery compared to a model consisting of clinical factors alone. Applying this model to the St. Antonius Hospital, a centre with 2000 cardiac surgeries annually, would lead to two or three patients being referred for a preoperative MDT meeting weekly.

A

In addition to frailty assessment, biomarkers can provide preoperative insight into a patients´ functional reserve. In **Chapter 5** the association of a preoperative biomarker panel on CSA-AKI was described. Since the pathophysiology of CSA-AKI is multifactorial twelve preoperative biomarker representing cardiac dysfunction, inflammation, renal dysfunction and metabolic disorders were investigated. Cardiac surgery associated acute kidney injury was a frequent complication and occurred in 80 (15%) patients in our population. Patients with CSA-AKI were at increased risk of mortality or disability one year after surgery. A preoperative panel of five biomarkers (a cardiac, inflammatory, renal and two metabolic) was associated with CSA-AKI and improved risk stratification beyond a model using clinical factors.

Physical frailty has been associated with postoperative delirium after cardiac surgery. In **Chapter 6** the associations of physical, mental and social frailty were investigated. Postoperative delirium occurred in 18% of patients and was associated with three out of six frailty characteristics in the physical domain, three out of four in the mental domain and two out of three in the social domain. When used to classify patients to a risk group for postoperative delirium, a frailty model with seven characteristics from all domains correctly identified patients at high risk 8% better, and patients at low risk 17% better than clinical factors alone. Overall reclassification improved 25% ($p<0.001$). Patients with a postoperative delirium experienced worse physical HRQL during one year follow up.

To place the findings of the research presented in this thesis in a larger context **Chapter 7** provides a reflection on our results and offers recommendations for clinical care and further research.

Nederlandse samenvatting

Er is een toename van oudere patiënten die electieve hartchirurgie ondergaan door algemene vergrijzing in de populatie en verbeteringen in chirurgische en anesthesiologische technieken. Ondanks verbeteringen in zorg rondom operaties brengt een hogere leeftijd meer risico op complicaties of overlijden met zich mee. Dit risico is het meest uitgesproken voor patiënten met meerdere aandoeningen of kwetsbaarheid. Kwetsbaarheid (in het Engels aangeduid als *frailty*) is een achteruitgang van verschillende orgaansystemen waardoor de functionele reserve afneemt en de kans op slechte uitkomsten toeneemt. Het hoofddoel van dit proefschrift is om de relatie tussen preoperatieve kwetsbaarheid en functionele uitkomsten één jaar na de operatie te onderzoeken in oudere patiënten die een electieve hartoperatie ondergaan. Een uitgebreide inleiding op het probleem wordt gegeven in **hoofdstuk 1.**

Voorafgaand aan een operatie worden alle klinische gegevens van een patiënt verzameld om risico's rondom een operatie in te schatten. In **hoofdstuk 2** onderzoeken we de relatie van deze standaard beschikbare gegevens (zoals leeftijd, sekse, comorbiditeiten of laboratoriumwaarden) op verandering in kwaliteit van leven een jaar na een cardiale bypass operatie. Hiervoor hebben we gegevens gebruikt van 658 patiënten met leeftijden tussen 47 en 87 jaar oud die een cardiale bypass operatie ondergingen. Fysieke kwaliteit van leven verbeterde in 22,8% van de patiënten, veranderde niet in 61,2% van de patiënten en verslechterde in 16,0% van de patiënten. Mentale kwaliteit van leven verbeterde in 49,8% van de patiënten, was gelijk in 34,5% en verslechterde in 15,7% van de patiënten. De klinisch beschikbare gegevens bleken kwaliteit van leven maar matig te voorspellen. De sterkste voorspeller voor fysieke en mentale kwaliteit van leven was de preoperatieve kwaliteit van leven. Patiënten met een hoge kwaliteit van leven hebben een hogere kans op achteruitgang terwijl patiënten met een lage kwaliteit een hogere kans op verbetering hebben.

Kwetsbaarheidskenmerken komen regelmatig voor bij ouderen. Eerder onderzoek heeft aangetoond dat kwetsbare patiënten een groter risico hebben op postoperatieve complicaties en overlijden. De relatie met functionele uitkomsten zoals kwaliteit van leven of beperkingen in functioneren is nog niet duidelijk. In **hoofdstuk 3** onderzoeken we de relatie tussen preoperatieve kwetsbaarheid en kwaliteit van leven of beperkingen in functioneren een jaar na een hartoperatie. In een prospectieve observationele cohort studie in 555 patiënten is kwetsbaarheid voor de operatie gemeten als aanvulling op de routinematige preoperatieve screening. Patiënten waren allen 70 jaar of ouder en verwezen voor electieve hartchirurgie. Kwetsbaarheidskenmerken werden gemeten in een fysiek, mentaal en sociaal domein. Een meerderheid van patiënten had een of meerdere kwetsbaarheidskenmerken en ongeveer de helft van de patiënten werd gezien als kwetsbaar. Een jaar na de operatie gaf een kwart van de patiënten aan dat ze een verslechtering hadden van hun kwaliteit van leven, en een vijfde ervoer beperkingen in functioneren. Kwetsbaarheid was geassocieerd met een slechte functionele uitkomst in het algemeen. De relatie van kwetsbaarheidskenmerken was sterker tussen beperkingen in functioneren dan tussen een verslechtering in kwaliteit van leven.

Een klinische toepassing van kwetsbaarheid is om patiënten te selecteren voor een uitgebreid preoperatief multidisciplinair overleg (MDO). Door de complexiteit van problemen bij een oudere patiënt biedt een MDO de mogelijkheid om risico's en voordelen van een operatie af te wegen, de kwetsbaarheidsscreening te interpreteren, alternatieve behandelingen te overwegen en risicofactoren te optimaliseren voor de operatie. Nadelen van een MDO zijn de investering van tijd en kosten voor ziekenhuis en personeel en de extra testen die een last kunnen zijn voor de patiënt. Om deze nadelen te beperken is het belangrijk alleen hoog risico patiënten te verwijzen naar een MDO. In **hoofdstuk 4** onderzoeken we of de kwetsbaarheidskenmerken hoog risico patiënten kunnen identificeren. Een kwetsbaarheidsprofiel van 5 kenmkern

In **hoofdstuk 4** is de kwetsbaarheidsscreening gebruikt om patiënten te selecteren die baat kunnen hebben bij een preoperatief multidisciplinair overleg (MDO). Door de complexiteit van problemen bij een oudere patiënt biedt een MDO de mogelijkheid om risico's en voordelen van een operatie af te wegen, de kwetsbaarheidsscreening te interpreteren, alternatieve behandelingen te overwegen en risicofactoren te optimaliseren voor de operatie. Nadelen van een MDO zijn de investering van tijd en kosten voor ziekenhuis en personeel en de extra testen die een last kunnen zijn voor de patiënt. Om deze nadelen te beperken is het belangrijk alleen hoog risico patiënten te verwijzen naar een MDO. Vergeleken met een standaard preoperatieve screening kon een kwetsbaarheidsscreening met vijf kenmerken beter inschatten welke patiënten beperkingen in functioneren hadden drie maanden na de operatie.

Naast kwetsbaarheidskenmerken kunnen biomarkers aanvullende informatie geven over de functionele reserve van een patiënt. **Hoofdstuk 5** beschrijft de relatie tussen een preoperatief biomarker panel en acuut nierfalen kort na de operatie. De pathofysiologie van acuut nierfalen kent meerdere factoren. Om zoveel mogelijk factoren mee te nemen zijn twaalf biomarkers bepaald die cardiaal functioneren, inflammatie, renaal functioneren en metabole aandoeningen representeren. Acuut nierfalen kwam voor in 80 van de 537 patiënten. Patiënten met acuut nierfalen hadden een verhoogd risico op overlijden en beperkingen in functioneren een jaar na de operatie. Een combinatie van vijf biomarkers (één cardiale, inflammatoire en renale en twee metabole) verbeterde de risico inschatting voor acuut nierfalen ten opzichte van een model met enkel klinische factoren.

Fysieke kwetsbaarheid is door eerdere onderzoekers geassocieerd met het optreden van een delier na hartchirurgie. In **hoofdstuk 6** onderzoeken we de associatie van fysieke, mentale en sociale kwetsbaarheidskenmerken met het optreden van een postoperatief delier. 18% van de patiënten had een delier na de operatie. Drie van de zes fysieke, drie van de vier mentale en twee van de drie sociale kwetsbaarheidskenmerken waren geassocieerd met een delier. Patiënten met een postoperatief delier werden 8% vaker als een hoog risico patiënt geclassificeerd door zeven kwetsbaarheidskenmerken aan een klinisch model toe te voegen. En patiënten zonder een postoperatief delier werden 17% vaker als laag risico patiënt geclassificeerd. In het algemeen verbeterde de risicoclassificatie in 25% van de patiënten door kwetsbaarheidskenmerken aan een klinisch model toe te voegen. Patiënten met een postoperatief delier rapporteerden vaker een slechtere fysieke en mentale kwaliteit van leven een jaar de hartoperatie.

De bevindingen van dit proefschrift worden in **hoofdstuk 7** in een bredere context geplaatst. Daarnaast worden aanbevelingen gegeven voor toekomstig onderzoek en de klinische toepassing van kwetsbaarheidsscreening.

A

List of abbreviations

5MWT	5-Meter Walk Test
95% CI	95% Confidence Interval
AGE	Anaesthesia Geriatric Evaluation
AKI	Acute Kidney Injury
AUC	Area Under the Curve
CABG	Coronary Artery Bypass Grafting
CGA	Comprehensive Geriatric Assessment
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COPD	Chronic Obstructive Pulmonary Disease
CSA-AKI	Cardiac Surgery Associated Acute Kidney Injury
c-statistic	Concordance Statistic
DOS	Delirium Observation Screening
eGFR	estimated Glomerular Filtration Rate
euroSCORE	European System for Cardiac Operative Risk Evaluation
GDF-15	Growth Differentiation Factor-15
Hb	Haemoglobin
HRQL	Health Related Quality of Life
hs-CRP	high sensitive C Reactive Protein
hs-cTnT	high-sensitive Cardiac Troponin T
ICDSC	Intensive Care Delirium Screening Checklist
ICU	Intensive Care Unit
IL-6	Interleukin-6
IQR	Interquartile Range
LVEF	Left Ventricular Ejection Fraction
MDT	Multidisciplinary Team

MI	Myocardial Infarction
MMSE	Mini Mental State Examination
MNA	Mini Nutritional Assessment
NRI	Net Reclassification Index
NT-proBNP	N-Terminal pro B-type Natriuretic Peptide
NYHA	New York Heart Association
OR	Odds Ratio
RCT	Randomised Controlled Trial
REML	Restricted Maximum Likelihood Estimation
RR	Relative Risk
SD	Standard Deviation
SF-12	Short Form 12
SF-36	Short Form 36
STS	Society of Thoracic Surgeons score
TCA	TriCyclic Antidepressant
TGUGT	Timed Get Up and Go Test
TIA	Transient Ischaemic Accident
WBC	White Blood cell Count
WHO	World Health Organization
WHODAS	World Health Organization Disability Assessment Schedule

Dankwoord

Na ongeveer drieduizend verzonden brieven, een paar duizend vragenlijsten, bijna veertigduizend woorden en liters koffie is mijn proefschrift klaar om gedrukt te worden. Het is een veelgehoorde opmerking: ‘promoveren doe je niet alleen’. Ik kan me hier alleen maar bij aansluiten. Veel personen hebben een rol gespeeld bij het schrijven van dit proefschrift en hieronder wil ik een deel bedanken.

Ten eerste **alle patiënten** die de moeite hebben genomen om mee te doen aan de AGE studie. Van iedere patiënt heb ik wel iets geleerd en een aantal zie ik nog helder voor me zitten in kamer 7 op de poli.

Ik wil natuurlijk mijn promotieteam bedanken voor al hun inzet en begeleiding de afgelopen jaren.

Professor Van Klei, beste **Wilton**, dankjewel voor je expertise en bijdragen aan mijn proefschrift. Je academische kijk vulde de perifere gedachten mooi aan. Je hulp in de laatste fase om mijn eigen verhaal op te schrijven in de discussie was ik erg blij mee.

Dr. Van Dongen, beste **Eric**, je bent denk ik de rustigste van de drie. “Uiteindelijk komt het allemaal neer op endotheel”, was een van je paradepaardjes. In niet veel stukken kwam het letterlijk terug, maar in het AKI stuk kon het nog mooi verwerkt worden. Je bescheidenheid siert je en je bent een rolmodel als anesthesioloog.

Dr. Noordzij – beste **Peter,** onze samenwerking begon ergens in 2013 toen ik mijn onderzoeksstage in het St. Antonius wilde volgen. Ik kon een van de eerste onderzoeksstudenten worden. Hoe passend dat ik daarna ook de eerste fulltime onderzoeker van de anesthesie in het Antonius mocht worden. Ik ben trots op wat we neergezet hebben en kijk met plezier terug! Op het gebied van de wetenschap wil ik je bedanken voor je geduldige begeleiding. Tijdens drukke OK dagen kwam je in het blauwe pak even binnenwandelen en sparren over welke kant een bepaald stuk op moest. Ik heb het ook erg gewaardeerd dat ik in de kliniek bij je terecht kon toen ik twijfelde over mijn carrière toekomst en je me bijstond met adviezen. Het was een lastige tijd waarin je me gesteund heb. Bedankt daarvoor.

Mijn mede-onderzoekers wil ik bedanken voor alle gezelligheid. **Ellen**, als internist kwam je ons anesthesie clubje vergezellen. We hebben heel wat gedeeld over onderzoeksperikelen maar ook over onze persoonlijke levens. Ik wens je heel veel succes met de laatste loodjes want je bent er bij-na! Er staat een pot met goud aan het einde van de regenboog. **Rosa** en **Britta**, met jullie twee erbij werd het een heuse onderzoeksgroep. Heel veel succes daar op 'de camping' en 'de sauna' en blijf vooral op vrijdagmiddagen Abba uit de speakers knallen. **Ingeborg**, je bent een onmisbare radar in de anesthesie onderzoeksmachine. Bedankt voor onze samenwerking en koffies op de vide.

Ik wil de volledige **assistentengroep** bedanken. Het hebben van goede collega's is zoveel waard. Als onderzoeker, maar vooral als AIOS was het een hele fijne groep om bij te horen. Wat was het fijn om van de ouderejaars te kunnen leren en met jaargenoten ervaringen te kunnen delen. Daarnaast zijn de borrels en skiweekenden natuurlijk legendarisch geweest.

Ook de **stafleden van de maatschap** wil ik bedanken en de opleiders in het bijzonder. Natuurlijk voor alle buizen bloed die ik tijdens inleidingen af kwam nemen voor de AGE studie. Maar vooral voor alles wat ik van jullie geleerd heb tijdens mijn AIOS tijd. Ook van de **anesthesiologen in het JBZ** heb ik veel mogen leren.

A

Mijn onderzoek speelde zich vooral af op de preoperatieve screening. Beste **POS dames**, zonder jullie waren al mijn studiepatiënten ertussen door geglipt in de drukke kliniek van de poli. Bedankt voor jullie inzet tijdens de AGE studie. **Ingrid**, jou wil ik in het bijzonder bedanken voor de warmte die je creëert en natuurlijk voor de eindeloze voorraden snoep waarmee je iedereen de dag doorsleept.

Naast alle samenwerkingen met collega's was dit proefschrift nooit afgekomen zonder de steun van mijn persoonlijke omgeving.

Mijn familie is belangrijk voor me. De 'patiënt' op de kaft zijn mijn opa en oma van moederskant. Ze staan voor mij symbool voor de band die ik heb met mijn beide families van **Verwijmeren** en **Brouwers**.

Sascha, Lenna, Maartje en Robin, sinds de middelbare school kennen we elkaar. Inmiddels is dat bijna 22 jaar, al geven we liever niet toe dat we al zo oud zijn. Vaak is een blik al genoeg om de ander door te hebben. Bedankt voor alle steun tijdens het schrijven van dit proefschrift. Maar vooral bedankt voor alle pret die we hebben beleefd in alle jaren. **Susanne**, de kaft is prachtig geworden. Bedankt dat je dit voor me wilde ontwerpen. Ik vind het zo tof dat al dat binnenwerk nu wordt omgeven door een combinatie van familie en vriendschap. Ik kijk uit naar toekomstige kampeer- en wandelavonturen, bij voorkeur in de Lofoten. **Anne Peters** (bij jou hoort je achternaam er op een of andere manier gewoon bij), al je bemoedigende woorden in die laatste fase hebben me geholpen mijn discussie af te schrijven.

Sinds geneeskunde deel ik lief en leed met een aantal intelligente en sterke vrouwen. Dankjewel **Sarah** en **Chantal**, als PhDiva's delen we al ons PhD 'plezier'. Ik ben blij dat we bij elkaar terecht kunnen voor een luisterend oor op alle gebieden. Laten we als het weer mag vooral blijven borrelen. **Lisanne**, ook al woon je in Culemborg, je bent en blijft een echte Van Lieflander. Ook jij hebt de academische eindstreep bijna gehaald en ik kijk ernaar uit jouw boekje te bewonderen. **Biaina** en **Annelinne**, jullie zijn goud! Waar is de volgende logeerpartij?

Hockey en hoepelen zijn mijn sportieve uitlaatkleppen. **Marchien**, **Rozemarijn** en **Irene**, jullie bedank ik in het bijzonder. Als harde kern van de fietsclub kijk ik elke keer weer uit naar de winderige en natte fietstochten naar Maarssen. Maar ik heb ook genoten van alle uren samen in de bibliotheek (of in de rij) waar uiteindelijk de laatste delen van dit proefschrift zijn geschreven. **Mariska**, ik vind het zo toevallig hoe we eerst collega's waren maar door het hoepelen ook een vriendschap hebben opgebouwd. Dankjewel voor alle gezelligheid en steun en dat we samen zo gek zijn om op hoepelkamp te gaan.

Karin, Eric en **Rachel**, bij jullie als schoonfamilie voel ik me thuis. Dankjewel voor de goede gesprekken, kritische vragen en steun die mij (en Daryo) verder helpen.

Ineke, bedankt voor je vriendschap, goede gesprekken en onderdak in Utrecht. Wat fijn dat ik bij jou ook een 'thuis' heb.

Alle anderen wiens naam hier niet specifiek genoemd wordt, dankjewel!

Ten slotte, de belangrijkste personen om me heen en zonder wie ik me geen promotie voor kan stellen;

Lieve **pap** en **mam**, jullie hebben me altijd aangemoedigd om mijn eigen ding te doen. Annemarie, bedankt dat je mijn paranimf wil zijn. Na al die jaren dat je figuurlijk achter me staat, sta je nu naast me. Lieve pap, jij bent de oorspronkelijke onderzoeker van het gezin. Je hebt met je enthousiasme voor ontdekken in de natuur altijd mijn nieuwsgierigheid weten op te wekken. Ik kan me geen fijnere ouders voorstellen.

Zeergeleerde broers **Mart** en **Thijs**, vanaf nu graag mijn nieuwe titel gebruiken als je mij aanspreekt: dokter doctor Verwijmeren. Maar laten we ook stoppen met het verzamelen van wetenschappelijke titels, anders moeten we alle drie nog professor worden. Lieve schoonzussen **Lisette** en **Judith**, ik ben blij dat mijn broers zo'n goede smaak hebben.

Eefje, bedankt voor je vriendschap en voor al je steun tijdens dit traject. Je bent nooit bang om te zeggen wat je echt vindt, jaagt je dromen na, staat altijd klaar voor degenen om je heen en bent ook een beetje gek. Ik was met trots je paranimf en ben blij dat je dat ook bij mij bent.

Lieve **Daryo**, eigenlijk ken je me niet anders dan dat ik aan het promoveren ben. Snel nadat we elkaar leerden kennen ging ik in het Antonius werken. Soms snapte je niets van de ziekenhuiswereld maar je deed altijd je best om je in te leven. Vooral dit laatste jaar hebben we veel beleefd en wordt onze relatie steeds hechter. Ik wil nog jaren lang met je de bergen in trekken, de zee in rennen, moestuinieren in weer en wind en eindeloos avonturen beleven. Maar soms wil ik ook niets liever dan gewoon op de bank zitten met je. Gelukkig kan het allemaal.

About the author

Lisa Verwijmeren was born on the 14th of November 1987 in Tilburg, The Netherlands where she also attended primary and secondary school. In September 2007 her medical training at Utrecht University started. Her interest in research developed in her last year of medical training during a science internship under the supervision of dr. Noordzij. After her graduation in 2015 she started working as a physician in the Intensive Care Unit at the Jeroen Bosch Hospital ('s Hertogenbosch). In the beginning of 2015 dr. Noordzij reached out with a PhD opportunity within the Anaesthesia Geriatric Evaluation project at the St. Antonius Hospital (Nieuwegein) which she gratefully accepted. For two and a half years she worked full-time on the AGE-study. In January 2018 she started an anaesthesia residency and combined her PhD research with clinical work. After careful deliberation she decided in 2019 that working as a doctor outside of the hospital fitted her better and she resigned her residency. She took up working on her thesis full time until half of 2020. She will start working as an occupational physician in the beginning of 2021.