Summary, general discussion and future perspectives
Chapter 10

Summary
In Part I, we investigated the role of malnutrition assessment in elective vascular surgery patients.

In Chapter 2, we aimed to assess the preoperative prevalence and associated factors of risk for malnutrition, determined by the Patient-Generated Subjective Global Assessment Short Form in elective vascular surgery patients. We found that 24% of the patients were at medium to high risk for malnutrition. Factors associated with this elevated preoperative risk for malnutrition included current smoking, female sex and being scheduled for amputation.

In Chapter 3, we investigated the relationship between this elevated risk for malnutrition prior to elective vascular surgery and postoperative complications. Occurrence of postoperative complications, length of hospital stay, 30-day readmission, and the Comprehensive Complication Index varied significantly between the patients with low, medium or high risk for malnutrition. After multivariate analysis, the medium risk for malnutrition group had an almost 1.5 times higher Comprehensive Complication Index than the low risk for malnutrition group.

In Part II, we focussed on the application of frailty assessment in vascular surgery patients. Frailty was measured using the Groningen Frailty Indicator (GFI), a screening tool covering 16 items in the domains of functioning. We aimed to assess the association between preoperative frailty status and postoperative complications. Finally, we investigated the dynamics of frailty before and after an elective vascular intervention.

In Chapter 4, we determined the influence of preoperative frailty status on short-term outcome after vascular surgery, with an emphasis on the specific frailty domains. Frailty was present in 22% of patients. Frail patients and patients with impaired cognition and reduced psychosocial functioning, two frailty domains covered in the GFI, had a significantly higher Comprehensive Complication Index. Also, frail patients had a significantly higher 30-day mortality rate and were more frequently discharged to a care facility.

Chapter 5 shows that preoperative frailty is associated with significantly increased long-term mortality risk after elective vascular surgery. After a follow-up of five years, 45% of frail patients died compared to 25% of non-frail patients. After adjusting for covariates such as age and comorbidities, the risk of five-year mortality remained almost twice as high for frail patients compared to non-frail patients.

In Chapter 6, a systemic review was performed to investigate the role of frailty and the association with outcomes in patients undergoing carotid endarterectomy (CEA). A systematic search, using Medline, Embase, Web of Science and Cochrane Database, led to
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a final inclusion of eight eligible articles. The Modified Frailty Index is the most frequently used frailty assessment tool in CEA patients. We found a pooled frailty prevalence of 24% and these patients are more prone to adverse outcomes such as post-operative complications and mortality.

To estimate whether the benefits of aortic aneurysm repair outweigh the risks in older patients, determining and diminishing individual risks is essential. Comprehensive Geriatric Assessment (CGA) determines the patient’s domains of functioning and enables a preoperative treatment plan. It would be helpful if patients who may benefit from CGA could be identified using a quick screening tool. The single-centre prospective cohort study in Chapter 7 compared the association of various quick screening tools with postoperative complications in older patients undergoing aortic aneurysm repair. We found that weak handgrip strength is significantly associated with the development of postoperative complications after aortic aneurysm repair.

The dynamics of frailty were investigated in Chapter 8 and 9. By approaching frailty as a dynamic, resilient state, more knowledge can be gathered about the postoperative course of frailty as a syndrome and the corresponding domains of frailty. The aim of the first study was to analyse the transitions in frailty state in elderly patients after vascular surgery over a period of one to three years and to evaluate influence of patient characteristics on this transition. We found that almost 21% of non-frail patients became frail and 9% of frail patients became non-frail after this follow-up time. Frail patients with comorbidities and those who underwent a major vascular intervention were at a significantly higher risk of remaining frail after intervention. In the last study, we evaluated the short-term trajectories of frailty and its domains with repeated measurements in the first six months after aneurysm repair in elderly patients. At three time points (baseline, and one month and six months postoperatively), four functional assessment tools were administered: the GFI; the Montreal Cognitive Assessment (MOCA); gait speed and handgrip strength. The GFI and handgrip strength remained the same over the time points. The MOCA score improved significantly after six months. In the open repair group, gait speed decreased significantly at one month, but returned to baseline at six months.
General discussion

In this thesis the role of frailty and nutritional measurement in elderly vascular patients requiring elective surgery is investigated. The world is ageing and the care for this ageing population needs an adapted approach. To achieve the best possible care for the vulnerable vascular patient, collaboration between specialties is crucial. In the clinic, a vascular surgeon is needed to inform the patient about the different considerations between a surgical or conservative treatment to reach a joint decision. A geriatrician is needed to determine a patient’s functional status in terms of social, physical and functional domains to possibly optimize these domains preoperatively. A dietician is needed to identify and optimize the nutritional status before and after surgery. This multidisciplinary collaboration is even more essential in the complex academic medical field, consisting mostly of multimorbid tertiary referrals. Because in recent years much progress has been made in establishing associations between the different domains, the focus of future research should be on the implementation of validated assessment tools and the clinical benefit of the implementation.

The role of risk for malnutrition in vascular surgery patients

The assessment of risk for malnutrition used in this thesis, the PG-SGA SF, provides a global assessment, which identifies impairments in various nutritional domains such as weight loss, presence of nutrition impact symptoms and activities and function. We found that a quarter of the patients turned out to be at medium to high risk for malnutrition prior to the vascular intervention. With a prevalence in the general hospital population of 15-24%, the prevalence of 24% in vascular patients is on the high end. Because the PG-SGA SF identifies risk for malnutrition, a preventive preoperative treatment could be initiated, instead of a more reactive treatment for patients that are already malnourished. The associated risk factors we identified, i.e. current smoking, female gender and an amputation of the foot or leg, can be helpful in selecting patients that benefit most from nutritional preoperative screening.

The implementation of nutritional screening, and therefore preventive treatment in patients at risk for malnutrition, may lead to less adverse postoperative outcomes since a malnourished preoperative state is associated with postoperative complications such as infection and delayed wound healing. Consistent with the literature, our study showed that in elective vascular surgery patients, a medium risk for malnutrition is significantly associated with the development of postoperative complications. Malnutrition is shown to be reversible with adequate interventions that often consist of oral nutritional supplements in addition to dietary counselling. In elderly hospitalized patients at risk for malnutrition, such preventive nutritional interventions were also associated with improved functional and cognitive outcomes. When physical frailty and malnutrition occur simultaneously, there is an even higher risk for adverse outcomes, suggesting that frail patients with poor nutritional status are particularly suitable candidates for preventive interventions in terms of nutritional therapy and physical exercise.
The multi-faced implementation of frailty assessment in the vascular ward

The frailty syndrome describes an intolerance of the most vulnerable patients to stressors such as a surgical intervention, mostly explained by a diminished reserve in various domains like the physical, cognitive and psychosocial. Depending on the frailty tool used, the prevalence of frailty varies between 4-59% in the community-dwelling elderly and between 20-60% in vascular patients requiring a surgical intervention. We found that 29.2% of the vascular patients requiring an elective intervention were considered frail preoperatively. Frail patients had a higher risk of developing short-term post-operative complications and were more often discharged to a nursing home. The frailty domains mobility, nutrition, cognition and psychosocial condition seemed to have the strongest association with adverse outcomes. Two more recently published systematic reviews reported a similar association between frailty and adverse outcomes using meta-analyses. Beside the association with short-term outcomes, this thesis also showed that the risk of 5-year mortality after elective vascular surgery is almost twice as high for frail patients. Patients that undergo a major limb amputation were more often frail and had a worse long-term survival compared to other interventions, a finding that was previously reported. After excluding these patients, the association between frailty and 5-year mortality remained significant. The association between frailty and short- and long-term post-operative outcomes enables the possibility to enhance the specific frailty domains before the operation, hopefully leading to better outcomes. The knowledge of a patient's preoperative frailty state could also be helpful for shared decision-making. A patient's frailty state provides more information about the procedural risks and benefits and the possibility that a particular vascular intervention decreases the quality of life and increases mortality risk.

One of the vascular procedures studied in this thesis is carotid endarterectomy (CEA). The adverse post-operative outcomes for this patient category are slightly different since it also encompasses postprocedural disabling stroke and myocardial infarction. Therefore, we performed a systematic analysis to investigate the role of frailty in patients undergoing CEA. We found a pooled prevalence of 24%, which is on the low end compared to the general vascular surgery population. Carotid patients are less dependent on activities of daily living than for example patients with peripheral arterial disease and usually younger than patients treated for aneurysms, thereby leading to a smaller share of frail patients in this population. In CEA patients, impaired cognition has a pivotal role in becoming frail. The Modified Frailty Index (MFI) was the most used frailty assessment tool in this patient group, although it does not assess the domain cognition. We suggest that in CEA patients, a multi-domain frailty tool should be implemented in the clinical setting, and this tool should preferably also cover the cognition.

Various frailty and/or risk assessment tools have been developed and subsequently validated in the surgical population. In the guideline of the American College of Surgeons and the American Geriatrics Society (ACS NSQIP Collaborative), CGA (Comprehensive Geriatric Assessment)-based interventions are recommended.
undergoing aortic aneurysm repair, we found that weak preoperative handgrip strength, a tool that can be administered in less than 5 minutes, has the strongest association with the development of postoperative complications compared to other quick assessment tools. As CGA could be too time-consuming, and therefore expensive to perform for every older vascular patient, we suggest to implement a quick assessment like handgrip strength in the outpatient setting. This enables the possibility to identify vascular patients that may benefit from a CGA-based intervention, like physical prehabilitation, at an early stage.

In most studies, frailty is measured at one time point, assuming that it is a static state. Over the past years, an increasing amount of studies is observing the dynamic nature of frailty. In community-dwelling elderly patients, 8% transitioned from pre-frail to frail and 1% from non-frail to frail over a timespan of three years. We found that in the first one to three years after elective vascular surgery, almost 21% of the elderly patients transitioned from non-frail to frail. Frail patients with comorbidities had a significantly higher risk of remaining frail. Hopefully the implementation of prehabilitation will also support frail patients in transitioning to a non-frail state after a vascular intervention.

At last, we investigated the short-term frailty trajectories of elderly patients undergoing aneurysm repair. The GFI remained the same after the intervention, but the MOCA improved significantly. When stratifying the patients per type of aneurysm repair, gait speed declined after one month, but returned to baseline after six months in the patients that underwent open repair. After dividing the patients in preoperatively frail or non-frail, we found that non-frail had a significant improvement in GFI and MOCA. In the upcoming months, the data collection will be finalized and the final analysis will be executed. The results will hopefully lead to a better prognosis of trajectories in the physical and cognitive status of elderly patients and will support in developing the optimal intervention strategy for all affected domains.
Future perspectives

As stated in the introduction of this thesis, one of the main challenges in the vascular clinic in the upcoming decades is the ageing population. Despite that surgical interventions are known to be expensive and invasive, a study found that 32% of the elderly undergo a surgical intervention in the last year of their life, with the majority in the last month. Limiting factors of this study are that it is hard for clinicians to estimate if a patient is reaching the end of life, and this study does not reflect the care provided to patients that survived. Still, this finding supports the idea that our care for the elderly requires a revision. Another study found that if a treatment that restores current health has a low-burden, 98.7% of the patients aims to receive this treatment. But this percentage reverses if the outcome is survival but with severe functional or cognitive impairment, since 74.4% and 88.8% of the patient then prefer to refrain from treatment. One year after a vascular intervention, frail patients that are subjected to high surgical stress, based on the Operative Severity Score, have a higher risk of loss of functional independence and mortality compared to non-frail patients. It is therefore important that during preoperative shared-decision making, clinicians take the wishes of the patient into account and discuss not only the possibility of extending life but more importantly preserve quality and autonomy. Although minimally invasive surgical approaches, such as endovascular interventions, rise in popularity, it remains pivotal to achieve proper surgical outcomes for high-risk patients due to the growing prevalence of elderly patients with multiple co-morbidities, malnutrition and/or frailty.

Nutritional status in vascular surgery patients

Over the past years, more attention is given to the pre-operative nutritional status in vascular surgery patients. The European Society for Clinical Nutrition and Metabolism (ESPEN) recommends in their guideline to assess the nutritional status before major elective surgery. Following this, the European Society for Vascular Surgery recommends to measure the concentration of serum albumin, assuming that hypoalbuminemia is a measure of malnutrition.Clinicians should be cautious with this assumption since the synthesis of albumin by the liver is reduced not only due to inadequate protein and caloric intake but also inflammation. Low serum albumin concentrations are therefore not helpful in solely selecting patients for nutritional interventions. The implementation of validated nutritional risk assessment tool might be more indicative. When comparing four malnutrition screening tools in vascular surgery patients, neither of the tools were able to accurately estimate the presence of malnutrition, diagnosed by a clinical dietician. This is probably due to the parameters included in each of these tools, like BMI and unintentional weight loss, which are less relevant in vascular surgery patients. The elevated risk of malnutrition in this category of patients is more due to suboptimal mobility and micronutrient status such as lack of protein intake and vitamin D deficiency. Therefore, a nutritional tool that identifies patients at risk for malnutrition, developed solely for the vascular population, that includes at least the above mentioned parameters, should be implemented in the outpatient setting. Health care workers could use a recently published
algorithm for the screening, diagnosis and follow-up of malnutrition, based on the ESPEN guidelines. The identification of malnourished vascular patients is crucial due to the association with adverse postoperative outcomes like postoperative infection and out-of-hospital mortality. The ESPEN recommends that perioperative nutritional support is initiated, preferably by the enteral route or otherwise oral nutritional supplements or tube feeding, in malnourished and at risk patients. In 2022, the ESPEN published a guideline on clinical nutrition in geriatrics and they recommend to screen all elderly patients for malnutrition. In elderly patients, nutritional interventions, varying from the prescription of supplements such as vitamin D to environmental and organizational programs, resulted in an improvement in energy and protein intake, as well as better outcomes. The ESPEN advises individualized and comprehensive interventions for elderly patients that are part of a multimodal and multidisciplinary team approach. A study investigating the optimal preoperative nutritional support in vascular patients at risk for malnutrition is currently lacking.

So concluded, although current guidelines advise to screen, especially elderly, elective surgical patients for malnutrition, no nutritional assessment tool fitted for the vascular population has been developed yet. Secondly, a study investigating the optimal preoperative nutritional support, possibly leading to improved postoperative outcomes, is currently lacking in vascular patients at risk for malnutrition.

Consensus about a frailty assessment tool in the vascular clinical setting

Besides the lack of a nutritional assessment tool in vascular clinical practice, consensus about the most fitting frailty assessment tool is also missing. Although several systematic reviews over the past years have extensively proved the association between frailty and adverse outcomes, until now there is no universal implementation of a preoperative frailty assessment. Several frailty assessment tools, with a variety in included functional domains and administration time, have been validated in vascular surgery patients. The 9-level Clinical Frailty Scale is the quickest way to determine the presence of frailty. The modified Frailty Index consists of 11 prognostic comorbidities and has the advantage to retrospectively determine frailty, and its severity, using patient data. The Groningen Frailty Indicator, the tool used in this thesis, encompasses all the domains of functioning in a questionnaire that can be administered in less than 5 minutes. Sarcopenia, measured using the psoas muscle area, is sometimes used as a surrogate for frailty although recently published data from vascular surgery patients showed that only frailty, and not sarcopenia, was an independent predictor of mortality and had the strongest prognostic significance. Therefore, we suggest that sarcopenia should not be used as a surrogate for frailty and that a multi-domain frailty tool, covering all the domains of functioning, should be applied in the preoperative vascular setting. This implementation could facilitate risk stratification and the aforementioned shared decision making for the elderly.
Resilience

As previously stated, frailty is a rather dynamic than static state. Another concept that is gaining popularity in the research field of frailty is resilience: the capability of a patient to adapt and bounce back after a stressor. The more resilient a patient is preoperatively, the higher the chances are that this patient will come out of the so-called ‘critical zone’ postoperatively. Resilience comprises a complex, dynamic process of recovery. To measure the resilience of patients, it is important to execute multiple repeated measurements around a stressor that provide insight into the dynamic response to stressors and to observe the dynamic interactions between physiological and physical subsystems. Until now, no study has been performed on (physical) resilience in vascular surgery patients. Currently, we are preparing a manuscript about repeated measurements of various functional domains before and after vascular surgery. This knowledge will ultimately lead to better prognosis of transitions in the functional status of elderly patients and will support in developing the optimal interventions to strengthen resilience preoperatively.

Comprehensive Geriatric Assessment and prehabilitation

One way to strengthen resilience and optimize the functional status of a patient is to implement a Comprehensive Geriatric Assessment (CGA), defined as “a multidimensional interdisciplinary diagnostic process focused on determining a frail older person’s medical, psychological and functional capability in order to develop a coordinated and integrated plan for treatment and long-term follow-up.” Although CGA is associated with less postoperative complications, according to two trials performed in vascular surgery patients, cost-effective and recommended in the guideline of the ACS NSQIP Collaborative, it is not universally implemented in the vascular clinic. Older adults with insufficient levels of physical activity are more prone to become frail. Such an extensive assessment of an elderly patient like CGA, where all the domains are evaluated, opens the door for the enhancement of these domains with individualized tailored interventions, for example with the use of prehabilitation. Prehabilitation is “the process of enhancing an individual’s functional capacity to enable the possibility to withstand a forthcoming stressor, e.g. major surgery”. Between the moment at the outpatient clinic that the decision for surgery is being made, and the intervention itself, several weeks or months can go by. During this time span, a prehabilitation program could be implemented. At first, the prehabilitation programs mainly consisted of physical exercises, i.e. unimodal, but in the recent practice, a more multimodal approach is followed. This means that the program includes physical exercise but also medical, nutritional and physiological support. The programs, varying in duration between four and eight weeks, are generally delivered in a home-based setting or at the outpatient clinic. In abdominal cancer patients, a meta-analysis including several randomized controlled trails (RCTs) proved that multimodal prehabilitation improves preoperative functional capacity, measured by the 6 minute walking distance, and leads to a reduction in hospital length of stay. However, the outcomes remain conflicting in this patient group, because
in frail patients undergoing resection of colorectal cancer, improved outcomes were not found after prehabilitation, compared to rehabilitation postoperatively. Although the oncological population is different from the vascular population, these promising results show potential for implementing prehabilitation in the vascular population.

In vascular surgery patients, no randomized controlled trials have been performed to determine the effects of prehabilitation versus usual care on patient-centred and clinical outcomes. Preoperative physical exercise in terms of gait training in patients with lower-limb peripheral arterial disease is well-known and shown to increase the walking distance. It could be that, beside extending the walking distance, it could also contribute to an improved preoperative physical fitness of the patient, i.e. in terms of cardiopulmonary condition. Although in patients with an abdominal aortic aneurysm (AAA) several studies showed beneficial effects of pre-operative exercise therapy, meta-analysis was not able to confirm these favourable effects. The inclusion of trials with small sample sizes and heterogeneity in measurements was a limiting factor, which seems to be a common limitation in other reviews on prehabilitation. The National Institute for Clinical Excellence guidance on management of AAA states that future research should focus on the optimal form and effectiveness of prehabilitation. In the prehabilitation programs of vascular patients, there should also be attention for smoking cessation. Vascular surgery patients smoke more often compared to other surgical patients groups. Smoking cessation in the preoperative period may support the pulmonary prehabilitation.

Regarding initiating prehabilitation in vascular surgery patients, first reporting templates for the exercises and interventions should be developed to diminish the heterogeneity in the performed studies. Second, multicentre RCT’s with large sample sizes including these templates should be conducted. Following this, a sufficient meta-analysis could be performed to determine a possible association between prehabilitation and outcome in vascular surgery patients. Hopefully, the implementation of prehabilitation will lead to increased physical activity in the long-term. Research showed that cardiac rehabilitation may play a protective role in the expansion of small AAAs. Eventually, prevention is better than cure. If we are able to possibly slow the expansion of AAAs with physical exercise, less vascular interventions are needed. This means that maybe in the future, we will not only offer prehabilitation to patients listed for aneurysm repair, but also to patients whose aneurysm does not meet the size threshold for surgery yet.

**Overall conclusion**

This thesis investigates the role of frailty and nutritional measurement in elderly vascular patients and the association with adverse outcomes, leading to a better estimation of postoperative outcomes in terms of complications and functioning. The growing share of elderly patients in the vascular clinic demands an adapted, multidisciplinary approach. As a future first step, we are hopefully able to execute a multidisciplinary risk assessment, using an adapted CGA for vascular patients, in order to identify modifiable risk factors before the intervention. Secondly, during shared decision making we will inform the
patients about these risks and take the wishes of the patient into account. We will discuss not only longer survival but more importantly the preservation of quality of life and physical functioning. Then, we use the information from the CGA to start a multimodal prehabilitation program, adjusted for the vascular population, to enhance affected domains. In this way, the future care for vulnerable vascular surgery patients can be improved. Because in the end, achieving the most optimal outcomes for the frail vascular patient “takes a village”.

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