Novel risk factors for poor outcome in frail cardiac surgery patients

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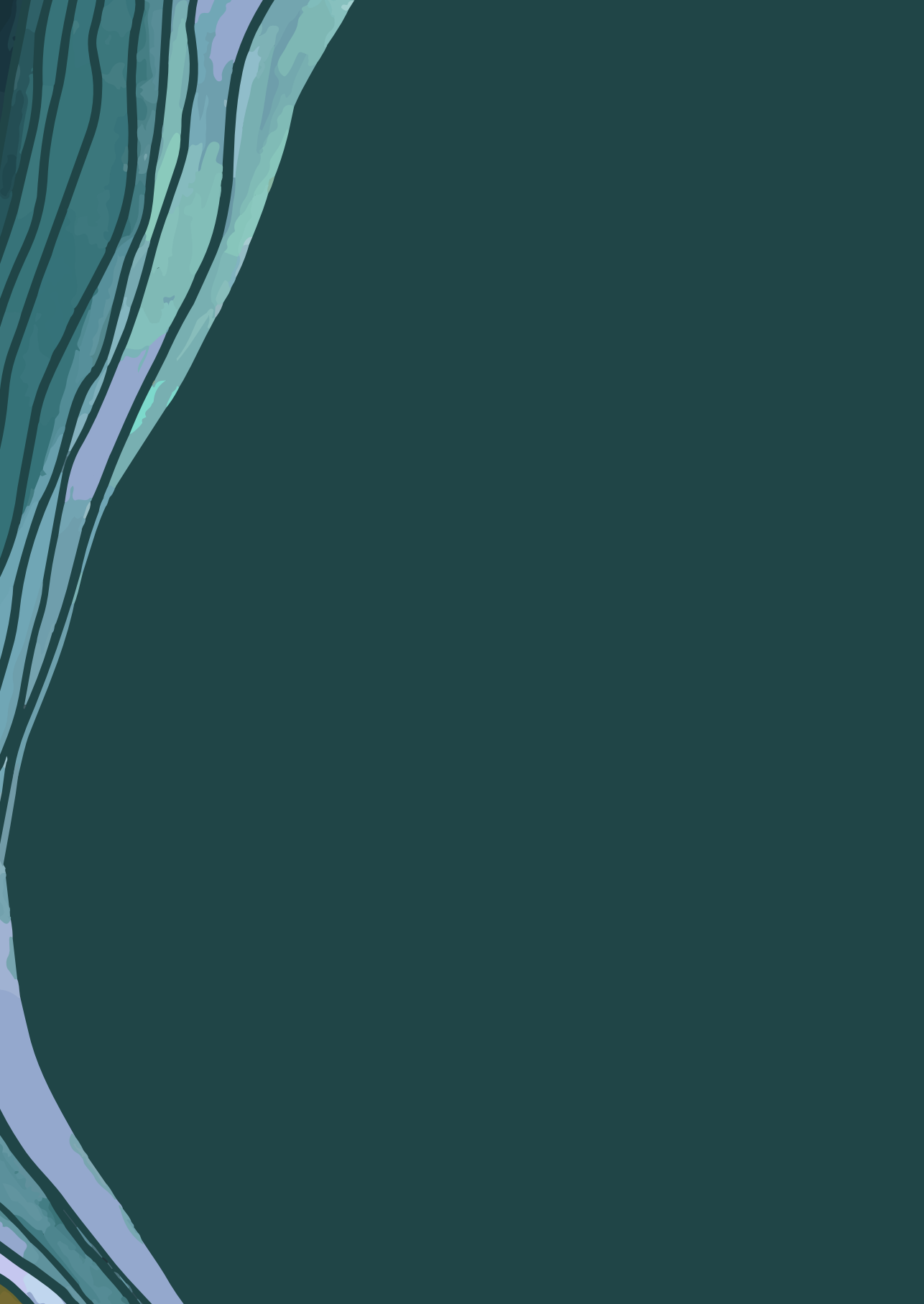


Chapter 1

General introduction

GENERAL INTRODUCTION

Population ageing reflects a human success story of increased longevity due to improved public health, medical innovations and scientific advances.[1] The elderly population grows as mortality rates decrease and people live longer. However, a longer life span has led to new challenges: with advanced age the prevalence of chronic diseases and frailty has increased. In the event of illness, or after major surgery, older patients are at risk for new disabilities and loss of independence. Although surgery in the elderly is relatively safe, maintaining quality of life and self-reliance of surgical patients pose major future challenges for surgeons and anesthesiologists.

Cardiovascular disease and stroke are among the leading causes of death for the population aged 60 years and older.[1] Cardiac surgeries, such as coronary artery bypass grafting and heart valve replacement are part of the most commonly performed surgeries globally in adults.[2] With the ageing population and innovations in healthcare, the elderly represent the fastest growing group of patients referred for cardiac surgery.[3] Elderly patients have consistently shown to derive benefits from cardiac surgery.[4–9] However, perioperative care for older patients is complex, as advanced age is frequently accompanied by a larger burden of comorbid conditions, polypharmacy and frailty.[10–12] A considerable number of elderly experience a postoperative complication and old age is associated with a 2- to 4-fold increased risk of postoperative morbidity and mortality.[10–12]

Major complications after surgery will inevitably lead to loss of independence and disability.[3,10,12] This indicates that identifying elderly patients at a higher risk of adverse outcome may allow for more enhanced perioperative health care. Frailty is an age related state of functional decline, characterized by an accumulation of age- and disease-related deficiencies (**Figure 1**).[13]

Frailty has a multidimensional etiology, which includes deficits related to physical performance, nutritional status, mental health and cognition, and is an emerging risk factor for adverse postoperative outcomes. Frail patients may therefore have limited physiological reserves and low resilience, making them more prone to postoperative complications and poor functional recovery.[3,14,15] Also, frail patients are often exposed to polypharmacy to treat multiple comorbidities. However, the potential harm from multiple medications might outweigh their benefits. Polypharmacy in elderly can result in a burden of treatment including medication interactions, side effects such as increased risk of falls, or errors in medication management, affecting overall health and quality of life. Quality of life is important at all ages, but as we grow older, it becomes crucial for the remaining years ahead.

Figure 1. Frailty, an age related state of functional decline.

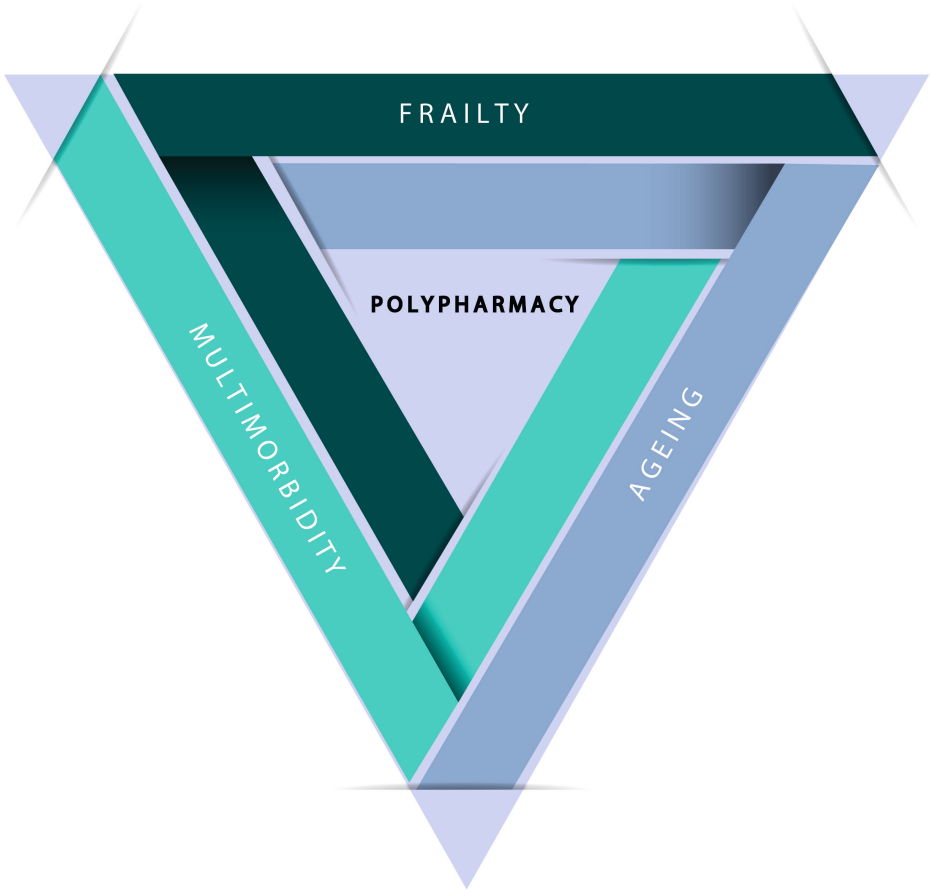
Exploring the implications of polypharmacy in the high risk elderly patient

Identifying preoperative frailty can improve risk stratification in older cardiac surgery patients.[3,16,17] However, many barriers exist to implement preoperative frailty assessments, as these assessments are time-consuming and there is a lack of clarity on which frailty assessment to choose.[10,18,19] A focus on specific frailty domains is more straightforward and can guide preoperative interventions to improve surgical outcomes. Polypharmacy for example, the use of multiple medications, is a known risk factor in elderly patients for impaired physical functioning, decreased postoperative survival and increased risk of complications and mortality.[20-22] The relationship between frailty, multi-morbidity, older age and polypharmacy is complex (**Figure 2**).[23]

Older people are the main users of medications as a result of multi-morbidity, and polypharmacy appears to increase the risk of frailty.[23] Besides, it is unclear whether frailty is a cause or consequence of multi-morbidity and there is an increasing recognition that biological changes of frailty affect pharmacokinetics and pharmacodynamics.[23]

Hence, disease-drug and drug-drug interactions can lead to heterogeneity in medication responses and increased adverse drug effects.[7,24] Polypharmacy also contributes to medication non-adherence, for example resulting in a suboptimal effect of prescribed analgesic perioperative pain management and more postoperative pain.[25] Unfortunately, the risk of postoperative pain is high in cardiac surgery patients and chronic postoperative pain affects 37% of patients in the first 6 months after surgery.[26] Moreover, patients after cardiac surgery with controllable pain, recover faster and have lower risk of postoperative complications.[27] Identifying preoperative risk factors such as polypharmacy and providing individualized perioperative pain treatment in frail elderly are both examples of perioperative risk management to improve surgical outcome.

Figure 2. Complex relationship between frailty, multi-morbidity, ageing and polypharmacy.



Bridging the gap between ICU and the surgical ward: risk monitoring of frail elderly patients

Given the significance of identifying risk factors to enhance postoperative care, it is essential to note that nearly half of all adverse events in hospitalized patients commonly arise in the early postoperative recovery phase at the general ward.[28-30] In addition, the European Surgical Outcomes Study[31] (EuSOS) stated that about three quarters of post-surgery in-hospital deaths occurred without intensive care unit admission, emphasizing the substantial risk inherent to general wards in postoperative patient care.

The failure to identify and act on physiological signs of deteriorating patients is a longstanding issue that was recognized over a decade ago.[32] To improve early recognition and adequate treatment for deteriorating patients, the (modified) early warning score (MEWS) was implemented.[33] The MEWS is measured by nurses and enables to differ between normal physiological changes and pathologic variation in vital signs. In case of deterioration, this score leads to intensification of monitoring, activation of rapid response teams and/or therapeutic interventions. Nowadays, intensive monitoring on the ward is limited and clinicians rely on intermittent spot checks using MEWS by nurses usually once every 6 – 8 hours.[34] This leaves patients unmonitored for most of the time and patients can deteriorate between observation sets. For example, in hospitalized patients recovering from non-cardiac surgery, one third of patients experienced severe hypoxemia (SpO_2 < 90% for one hour or more) and the occurrence and duration was seriously underestimated with spot check monitoring by nurses.[35] A different study regarding the systematic measurement of vital signs in patients on the general ward, demonstrated that completeness of MEWS in the first 3 days after major surgery was only 17%.[36] This calls into question whether intermittent spot check monitoring is adequate to address the changing profile of patients on general wards today. Increasing the intensity of spot checks by nurses may seem a sensible solution, but is unlikely given the fact that manual measurements are time-consuming and health personnel and hospital budgets are limited.

Empowering the surgical ward: the promise of continuous monitoring

Continuous monitoring of vital signs is a promising approach to early identify the deteriorating patient. Although complications often become clinically apparent as acute cardiac or respiratory failure, it has long been known that subtle abnormalities in vital signs typically precede these conditions, sometimes by 6 – 12 hours.[34,37] A recent meta-analysis evaluated the effect of continuous monitoring in general wards and indicated a 39% lower risk of mortality among continuously monitored patients compared to those receiving standard care (spot checks).[37] Furthermore, continuous monitoring was associated with a reduced need for patient rescue events,

reduced intensive care unit transfers and a reduced length of stay.[37] While continuous monitoring is not yet the standard of care, the technology for vital signs monitoring is advancing rapidly and promising. Especially in frail elderly patients, who are less resilient and more prone to adverse drug effects and postoperative complications, postoperative monitoring of vital signs may have the potential to early detect clinical deterioration. However, evidence for the effectiveness of continuous monitoring of vital signs in identifying postsurgical patients at risk is still scarce. We aimed to determine risk factors for postoperative deterioration at the general ward in frail elderly patients following cardiac surgery, using continuous monitoring.

Titration of analgesic medication in the frail elderly patient to reduce complications following cardiac surgery

The Anesthesia Patient Safety Foundation recommended already a decade ago that "Continuous electronic monitoring of oxygenation and ventilation would reduce the likelihood of unrecognized clinically significant opioid-induced depression of ventilation in the postoperative period".[38] Postoperative administration of opioids is essential in preventing and managing postoperative pain. However, the significant variation in how individuals respond to opioid doses complicates treatment to ensure safe and efficient pain relief. The challenges surrounding prescription of these high risk medications in older people are further amplified in the presence of frailty, as there is few data to support evidence-based decisions in such patients.[7,39] Moreover, opioid therapy in the elderly is often associated with adverse effects because of excessive respiratory depression.[7] The risk of clinically significant respiratory depression for hospitalized patients in their seventh, eight, and ninth decades of life is respectively 2.8, 5.4 and 8.7 times higher, than for younger patients.[39] Therefore, most opioid dosing regimens, especially in elderly patients or patients with limited physiologic reserves (e.g. frailty), tend to lean towards smaller doses or longer intervals, often leading to insufficient dosing. Consequently, the fundamental question arises "What is the correct dose for this frail elderly patient"?

Optimal pain control is a multifaceted and intricate challenge but essential given the high demand for analgesia in these patients following cardiac surgery. As the global population ages and frailty becomes more prevalent, understanding the pathophysiological mechanisms, including pharmacokinetics and pharmacodynamics in frail elderly patients, and their impact on drug therapy is essential. With this knowledge, it might be possible to facilitate customized care for every frail elderly patient following cardiac surgery. Additionally, implementing continuous monitoring for early detection of clinical deterioration at the general ward, might offer a secure environment for the administration of medication in this high risk population.

Therefore, this thesis will study novel risk factors for postoperative complications and poor functional outcomes using systematic analysis of continuous monitoring data and pharmacokinetic models collected in a high-risk surgical population.

Objectives of this thesis

I. To better understand the relationship between frailty domains, especially polypharmacy, and postoperative functional outcome after cardiac surgery.
II. To study the clinical utility of continuous postoperative monitoring of vital signs after ICU discharge in relation to early signs of clinical deterioration and side effects of high risk medication.
III. To study the pharmacokinetics and analgesic response of morphine in frail elderly patients following cardiac surgery, to identify strategies for safer medication use.

Outline of this thesis

Chapter 2 describes the association of polypharmacy with functional decline in frail elderly patients following cardiac surgery. **Chapter 3** assesses which preoperative frailty domains are associated with chronic pain and functional outcome one year after cardiac surgery in older patients. In **chapter 4** the association between vital signs and clinical deterioration using continuous remote monitoring on the general ward in frail elderly patients after cardiac surgery is prospectively studied. **Chapter 5** describes the effects of high risk medication on postoperative vital signs in frail elderly cardiac surgery patients, using continuous monitoring. In **chapter 6** we report the analysis of the pharmacokinetics and analgesic response of morphine treatment in frail older cardiac surgery patients. Lastly, in **chapter 7**, the results and overall conclusions of this thesis are summarized and discussed. In this chapter, perspectives are given concerning perioperative management in frail elderly patients. Finally, ideas are provided for further interventions or studies regarding optimizing patients safety and clinical outcome.

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