DOI:10.14753/SE.2024.2930

SEMMELWEIS EGYETEM

DOKTORI ISKOLA

Ph.D. értekezések

2930.

SZABÓ ANDRÁS

Szív- és érrendszeri betegségek élettana és klinikuma
című program

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DOI:10.14753/SE.2024.2930

DIFFERENT APPROACHES OF PREOPERATIVE FRAILTY AS A RISK FACTOR FOR LONG-TERM MORTALITY IN ELECTIVE CARDIAC AND VASCULAR SURGERY

PhD thesis

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Budapest

2023

DOI:10.14753/SE.2024.2930

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DOI:10.14753/SE.2024.2930

List of abbreviations

ADL	activities of Daily Living
AHR	adjusted hazard ratio
AIS	Athens Insomnia Scale
ASA	American Society of Anesthesiology
AUC	area under curve
BDI	Beck Depression Inventory
BMI	body mass index
CABG	coronary artery bypass grafting
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRP	C reactive protein
CSSDS	Caldwell Social Support Dimension Scale
FI	Frailty Index
GDS	Geriatric Depression Scale
HR	hazard ratio
HS	Hungarostudy
ICU	intensive care unit

IQR	interquartile range
MACCE	major adverse cardiac and cerebrovascular events
mCI	mild cognitive impairment
MMSE	Mini Mental State Examination
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
OR	odds ratio
PHQ	Patient Health Questionnaire 15
POSSUM	Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity
ROC	receiver operating characteristic
SD	standard deviation
STAI	State Trait Anxiety Inventory
TIA	transient ischaemic attack
V-POSSUM	Vascular Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity

1. Introduction

In this postdoctoral thesis, preoperative risk factors are investigated among cardiac and vascular surgical patients. During the risk estimation, the focus was on novel types of potential predictors whose importance is not sufficiently proven at the moment. Cardiac and vascular surgical procedures are one of the most complex and stressful interventions; therefore, physicians have a responsibility to perform accurate risk stratification and perioperative care.

1.1. Preprocedural risk estimation and stratification

Risk estimation is as old as humanity. Risk (or cost)-benefit analysis is a fundamental human activity that is one of our greatest evolutionary advantages. The ancient mystery of prophecy and knowledge of the future have always been desirable capabilities of societies. In the medical field, risk-benefit analysis has undergone a huge transformation. Various risk estimation methods have been developed for elective planned surgical health care.

Dr. Carson, an excellent neurosurgeon at Johns Hopkins Hospital, introduced a checklist to standardize the risk estimation. The following questions should be discussed during preprocedural evaluations. (1)

1. “What is the best thing that can happen if I take the risk?”
2. “What is the worst thing that can happen if I take the risk?”
3. “What is the best thing that can happen if I don’t take the risk?”
4. “What is the worst thing that can happen if I don’t take the risk?”

The risk estimation methods should be described with numbers to represent the chance of adverse events. This quantitative approach is necessary to provide correct and useful risk analysis. A well-known ascertainment by Lord Kelvin emphasizes this: ,,When you can measure what you are speaking about, and express it in numbers, you know something about it, when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind; it may be the beginning of knowledge, but you have scarely, in your thoughts advanced to the stage of science.” (2)

According to the current point of view the preoperative risk evaluation is performed by to the anaesthesiologist. During the preoperative visit, a holistic opinion should be developed and discussed with the patients and the surgeon to choose the best treatment method for the patient. Traditionally, the most well-known risk estimation method was the one developed by American Society of Anaesthesiologist, known as the ASA scoring system. This is a rough estimation of patients’ pre-anaesthesia conditions and coexisting diseases. The ASA scoring system has been in use for 60 years and is used worldwide to assess and communicate patients’ preprocedural conditions. It is important to note that the scoring system alone does not predict the perioperative risk other, supplementary estimation methods must be used. (3)

1.1.1. Surgical risk estimation methods

Surgical preoperative risk assessment has undergone substantial development in recent decades. Most surgical disciplines have risk estimation methods for special circumstances. Common disadvantages of these scores are the narrow spectrum of factors that could have an impact on outcome, such as current (preprocedural) clinical state and parameters, laboratory results and coexisting diseases. These mostly reflect a patient’s recent state and ignore the holistic aspect. The most common outcomes are mortality, surgical site infection and other frequent complications (e.g., renal failure or insufficiency, respiratory failure, circulatory failure). These are exact and important endpoints but do not provide any information about postprocedural quality of life and the length and degree of total recovery and rehabilitation. (4)

In vascular surgery, most risk stratification methods are used to estimate the success rate of the procedure. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System (Wound extent, Ischaemia, and foot Infection [WIfI]) was developed to stratify limb outcomes based on three major factors: ischaemia, wound extent, and foot infection. The Project or Ex-Vivo Vein Graft Engineering via Transfection III risk score was developed to assess patients based on expected amputation-free survival (AFS) after revascularization. (5) The Geriatric-Sensitive

Cardiac Risk Index (GSCRI), which is combined with NT-proBNP (N-terminal prohormone of brain natriuretic peptide), has an excellent predictive value for major adverse cardiac events of 0.830 with a 95% confidence interval. (6) Other widely used risk assessment methods in routine clinical practice include the Vascular POSSUM and the Goldman Cardiac Risk Index. (7)

In cardiac surgery, there are several risk stratification methods. The most commonly used are the Society of Thoracic Surgeons updated short-term risk calculator, the ACEF II risk score, the RiskE Score for infective endocarditis, the EuroScore II and the abovementioned Revised Cardiac Risk Index. (7-10) The CARE (Cardiac Anesthesia Risk Estimation) score is to estimate anesthesia risk regarding cardiac surgical procedures. (11)

1.2. Frailty definition and conception

Frailty is a health condition leading to potential clinical adverse effects. According to the ESC Consensus Document written in 2022, frailty is a "multidimensional and multisystem condition characterized by decreased functional reserves and increased vulnerability to stress and acute adverse events". (12, 13)

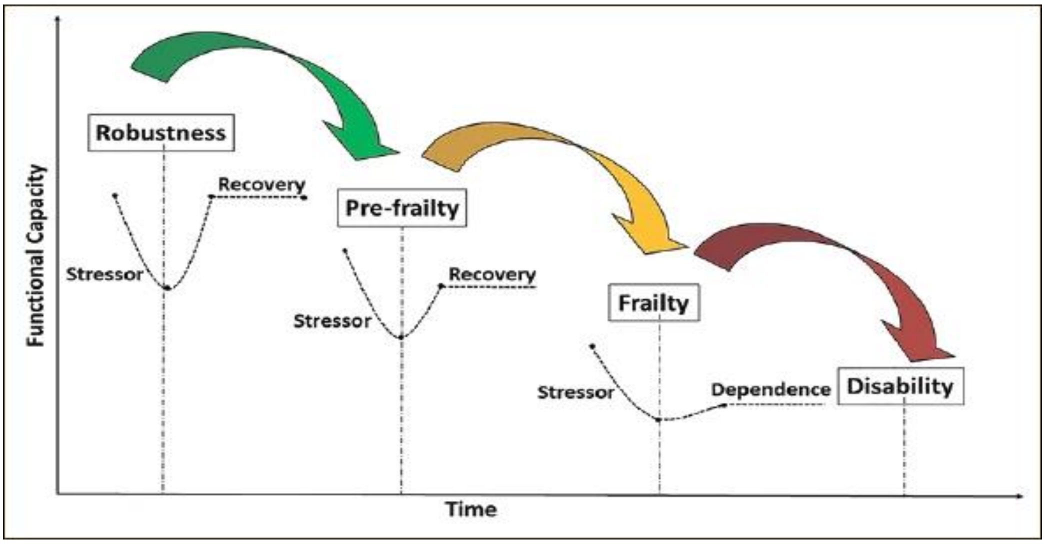


Figure 1. The cascade of functional decline in older adults from independence, through to frailty and disability (in the absence of intervention) [Based on concepts by Dapp et al., Hoogendijk et al., Clegg et al. and Fried et al.] publishes by Dent et al., in the Journal of Nutrition, Health and Ageing under Creative Commons license (14-18)

In recent decades, there have been various conceptions of frailty and numerous explanations of its etiology. Chronologically, the first well-accepted was the phenotype model by Fried et al. According to their phenotype-based frailty model, clinical frailty is determined by five indicators, such as sarcopenia (unintended weight loss), weakness, slowness, poor endurance, and low physical activity level. Frailty is diagnosed when three or more indicators are present. The presence of one or two indicators can represent prefrailty. (18)

The other models are based on deficit accumulation. These models are built with different scores or indicator systems using multidimensional approaches. In addition to physical disabilities, cognitive function (and sensorimotor abilities), psychological and sociological aspects were also included for evaluations. The most commonly used scores are the Clinical Frailty Scale, which was developed by Rockwood et al. (19) and the Essential Frailty Toolset for aortic valve replacement which was developed by Afilalo et al. (20)

As the population ages, ageing-related frailty and disability will have serious impacts on health care systems. This emphasizes the fact that frailty is a dynamic and reversible condition. The long-term follow-up (average of 4 years of follow-up) clinical studies reported an improvement in health status in 13.7% of patients (95% confidence interval 11.7-15.8%) and a worsening of health status in 29.1% of patients. (21)

1.2.1. Epidemiology of frailty

Recent research has applied various frailty scores and tools, which makes it difficult to estimate the prevalence and incidence of frailty. The results are not always appropriate for comparison. Ageing and the type of intended medical intervention make the issue more complicated. In the EXTEND-FRAILTY Study, patients with aortic valve disease were enrolled from three different US CoreValve Studies. Among 2,357 participants – with a mean age of 82.7±6.2 years – 64.9% were identified as frail according to the claim-based frailty index, which is based on the Fried model mentioned above. (22)

A review from Afilalo's lab found that the prevalence of frailty ranged from 20 to 60% among vascular surgical patients; the review included 23 articles that utilized a total of 14 frailty tools. (23) O'Neill et al. used the clinical impression method and found that 30.6% of patients were frail. However, the mortality risk was significantly elevated, and eye-balling methods always include a risk of subjectivity and error. (24)

According to a retrospective, multicentric, observational study by Turcotte et al., which enrolled almost 25,000 patients in 6 years, only 4.1% of patients in the general ICU population did not meet the criteria for frailty (their work used the Clinical Frailty Score, which is based on a deficit accumulation model). The Frailty Index – Acute Care tool and CHESS score were also used, and frailty was determined in 95.4% and 83.7% of the patients, respectively. (25)

1.2.2. Management of frailty

As frailty is a multidimensional clinical syndrome, it requires a multidisciplinary approach for management. One of the most emphasized parts is nutrition (quantitative and qualitative), i.e., the optimal intake of antioxidants and micronutrients. Many papers mention the importance of adequate dental care. (26) Measuring serum albumin level is the gold standard method for assessing nutrition, and normal albumin levels can improve functional outcomes. (27-36) Decreased albumin levels are associated with increased mortality in cardiac surgical patients. (37)

For treatment general strength and endurance regular exercises proved to be beneficial. (38, 39) However, higher functional state (measured by the 5-minute gate speed test, chair rise test, time up and go test, etc.) can decrease mortality, and merely measuring muscle mass (psoas muscle area, femoral muscle mass, etc.) leads to a limited ability to predict outcomes. (40, 41) The focus is on functionality. Special exercises for improving balance (such as tai-chi exercises) can be useful in aspects of muscle function, balance, and avoiding falls. (42-44)

Some ongoing trials are assessing the efficacy of using cognitive intervention trials in combination with other interventions to reverse frailty. (45-50) Although dementia is a hard-to-treat disease, strengthening an individual's social web and use of digital innovations (video monitoring, phone apps) seem to be useful methods for treating patients with severe cognitive decline.

The optimal medical therapy and the elimination of inadequate polypharmacy are another point of efficient interventions. (51-53) Choosing appropriate medication and identifying drug interactions can reduce harm. (54-56)

1.3. Cognitive functions

Based on clinical experience, some other factors that are not routinely evaluated might influence postoperative outcomes. Frailty has refined previous risk stratification methods based on clinically measured and previous medical data, thus enabling a more precise assessment of the length and difficulty of healing and recovery after surgery. Traditionally, an older age, current smoking status, lower educational level, certain ethnicities, an unmarried state, current use of postmenopausal hormone therapy, clinical depression/use of antidepressants, and mental disability are mentioned as the most relevant cofactors of frailty. (57-60)

A well-established tool was needed to measure the cognitive performance of patients. In the health care environment (emphatically), the most commonly used tools are the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). (61-63) Currently the MoCA is the most commonly used tool for detecting mild cognitive impairment among patients. (63) When our study was launched, the MoCA was not as widespread and validated as the MMSE. Furthermore, there were a few cases when the MMSE was made more specific for mild cognitive impairment with decreased thresholds. (64)

There are some other cases in which the surgical population’s cognitive dysfunction was mapped and analyzed according to mortality, but the data provide conflicting results. These findings prove the novelty and importance of our work.

1.4. Preoperative opioid usage

Opioid derivatives are an essential part of everyday clinical pain management practice. They have excellent analgesic effect and distinct sedative and sympatholytic effects. Thanks to these properties they are widely used in various conditions.

According to its definition, opioids are generally synthetic or organic substances that act on opioid receptors (μ, κ, δ) and can be antagonized by naloxone. Administration could be by different routes (intravenous, intrathecal, oral, transdermal, etc.) and their pharmacokinetic parameters can vary widely. (65)

In addition to their positive effects, these medicines have several negative side effects that are linked to long-term usage. The biggest drawbacks are the financial load that drug addiction causes and the potential loss of years of life from opioid overdose. (66, 67) The largest yearly prevalence of opioid addiction is seen in North America, Australia, and Southwest Asia, where prevalences range from 2.5 to 3.5% annually, greatly exceeding the global average for those aged 15 to 64 (1.2% annually). 3.7% of Americans aged 12 and over (10.3 million persons) misused opioid derivatives in the US in 2018. Nearly 50,000 individuals in the US passed away in 2019 from opioid overdoses, according to the WHO drug report. (68) These fatalities were linked to opioid compounds, primarily the synthetic opioid fentanyl. Since the beginning of the pandemic, there has been an increase in opioid overdose deaths in North America. (69) Opioid abuse is closely linked to psychological, societal, and criminal issues in addition to mortality. (70)

The main risk factors for postoperative opioid use disorders, according to a previous review, are a history of substance misuse (of any sort), any physical ailment, a history of mental health issues, and the use of sedatives or hypnotics. However, the best way of handling the opioid problem is vigilance rather than severely restricting the use of these powerful analgesics. (71)

1.5. Comprehensive frailty approach

Since the deficit accumulation frailty model was described various frailty indices have been used. The clinical frailty scale (CFS) is a simple method to define patients' frailty status and it has a good predictive value for mortality and other outcomes. (72)

During the recent COVID pandemic CFS was one of the best predictors for fatal outcome. (73) CFS is easy to use and has a massive prediction, but it uses some subjective approach. In dedicated cases objectivity could be more important, in this manner comprehensive, frailty scoring methods have their roles. Projects, such as Lee’s Comprehensive Geriatric Assessment are based on deficit accumulation, but they mapped patients’ performance along different axes. (74, 75)

2. Objectives

2.1. Cognitive impairment in vascular surgical patients (Study A)

In the current article, we focused on factors including cognitive, mental, social, and psychological aspects rather than the traditional scoring system.

With patients undergoing vascular surgery, this study sought to preoperatively identify the most significant psychological and social factors that could affect postoperative results.

Overall mortality was the primary endpoint. To discover potential variations in psychosocial attitudes, a comparison between our patient group undergoing vascular surgery and a representative control population cohort was made.

The hypotheses were as follows:

A/1. Mild cognitive dysfunction (measured by the MMSE) is related to higher mortality

A/2. The MMSE with modified cut-off values is an appropriate tool for detecting mild cognitive deficit

A/3. No differences in socioeconomic variables will be observed between the general population and the vascular surgical group

2.2. Chronic opioid use among vascular surgical patients

The long-term opioid use among patients who had vascular surgery was the focus of the current investigation. Patients who receive prescriptions for opioid derivatives frequently have persistent pain, a decline in quality of life, and restricted mobility. The impact of prolonged preoperative opioid usage on overall mortality was the primary endpoint. The use of opioid derivatives prior to surgery and the surgical risk determined by the vascular POSSUM score were compared. In addition to looking at the negative effects brought on by these medicines, several psychological and cognitive test results were analyzed. Additionally, total frailty scores were contrasted between patient populations.

Resolving opioid addiction issues will need a multidisciplinary strategy. Over the social and psychological support, it may be necessary to use additional treatments, such as neuromodulators like antiepileptics and antidepressants, in addition to different combinations of minor and major analgesics.

The hypotheses were as follows:

B/1. Chronic opioid use patients have an increased preoperative risk of mortality

B/2. Chronic opioid use is correlated with depression and anxiety in vascular surgical patients

2.3. *Comprehensive frailty approach in cardiac and vascular surgical patients (Study C)*

Using a multidomain assessment and modelling of its impact on postoperative mortality, our goal was to examine patients' preoperative frailty. Analysis was done on the impact of various frailty factors behind the overall effects. Our endeavour to assess the summary accuracy of both sorts of scores included comparing and modifying conventionally employed risk estimating methodologies.

The hypotheses were as follows:

C/1. A comprehensive frailty assessment could detect an increased preoperative risk of morality

3. Methods

3.1. Study design and participants

This thesis presents a single center, prospective, observational clinical research. The patients were enrolled in the research between September 2013 and August 2017, in the Heart and Vascular Centre, Semmelweis University, Budapest. The investigation was registered on clinicaltrials.gov (ID: NCT02224222) and approved by the Semmelweis University Regional and Institutional Committee of Science and research Ethics (TuKEB 250/2013).

The participants in this study were recruited from Vascular Surgery and Cardiac Surgery Departments during the preoperative anesthesiology visit. Criteria for selecting the subjects were as follows: age over 18 years, native Hungarian speaker and undergoing elective vascular (procedures on arterial system or caval veins) or cardiac surgery. Pregnant women, untreated psychiatric disorders, acquired or congenital mobility disorders, aphasia, and patients deemed to have a restricted capacity to comprehend the study procedures and give ethical approval were among the exclusion criteria. Written consent was obtained because all clients were able to decide whether or not to participate in the study. During their outpatient anesthesia meeting, a study nurse, medical student, or postdoctoral fellow offered patients to take part in the study. Each member of the hired team received quick training from a psychologist on how to do accurate cognitive mapping and evaluations. Prior to surgery, baseline surveys were done five to thirty days beforehand.

3.1.1. Studies settings

In this work synthesis of three different original papers were performed and presented. For the research settings and results described in the articles are marked with A, B and C as follows:

A: The effect of cognitive dysfunction on mid- and long-term mortality after vascular surgery

DOI:10.14753/SE.2024.2930

B: Effect of preoperative chronic opioid use on mortality and morbidity in vascular surgical patients

C: Comprehensive frailty assessment with multidimensional frailty domains as a predictor of mortality among vascular and cardiac surgical patients

During the enrollment period 303 patients were invited as the study schematic flow chart shows on Figure 2.

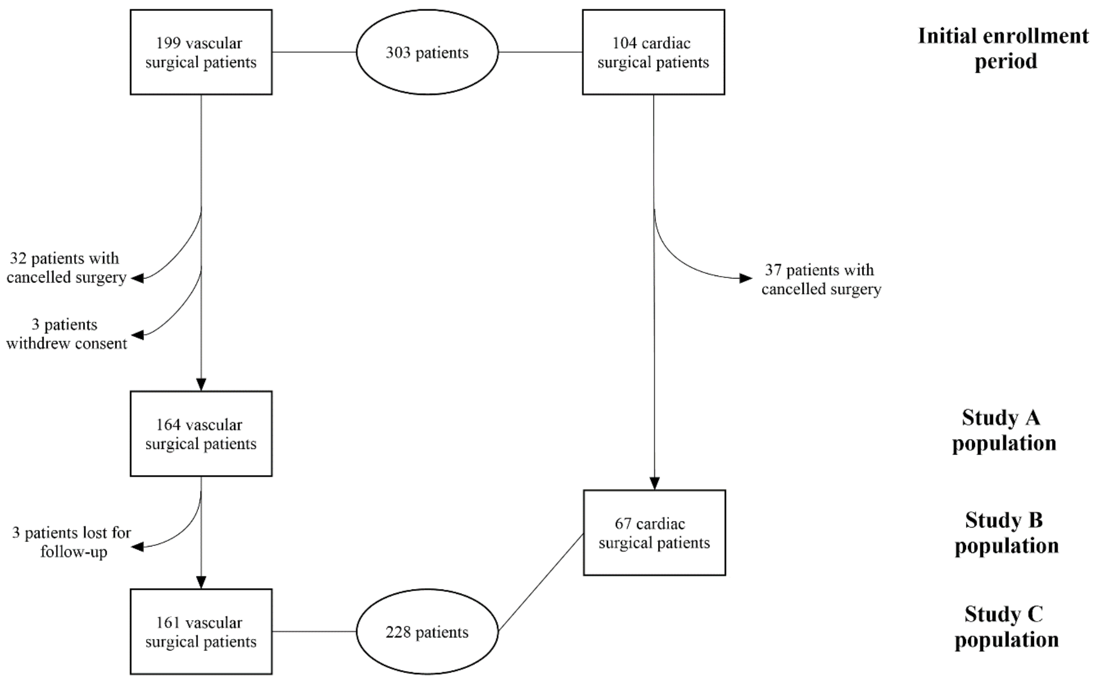


Figure 2. The flow chart of studies

3.2. Preoperative biological variables

Numerous clinical and other biological parameters were evaluated as potential influencers of the result. Clinical variables included preoperative laboratory values (blood counts, renal function assessments, ion levels, etc.), intraoperative variables (operation time, cross-clamp time, blood loss, need for transfusions, and fluid balance medications), postoperative variables (blood loss, medications, etc.), outcomes, and the frequency and severity of postoperative complications (major cerebrovascular or neurological event; acute or chronic heart failure defined as pulmonary oedema, atrial fibrillation, arrhythmias, cyanosis, metabolic disorders, need for inotropes, respiratory failure;

infection; acute renal failure/need for renal replacement therapy; length of mechanical ventilation; length of ICU and in-hospital stay and in-hospital mortality rate). The American Society of Anesthesiologists risk score (ASA score) (76) and the Vascular Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (vascular POSSUM) (77-80) were computed. Two components make up the vascular-POSSUM: a physiological score and an operational score. The operative score concentrates on intraoperative blood loss, peritoneal contamination, potential malignancy, the length and urgency of the surgery, as well as age and the main vital markers (cardiac, renal, haematological, and neurological function).

3.3. Psychosociological estimation tools

Age, gender, living conditions, smoking, alcohol consumption, and education were among the psychosocial and demographic data collected. The Beck Depression Inventory (BDI), the Spielberger State and Trait Anxiety Inventory (STAI-S and STAI-T), the Mini-Mental State Examination (MMSE), the Geriatric Depression Scale, the Somatic Symptom Severity Scale, the Devins Illness Intrusiveness Rating Scale, the Caldwell Social Support Dimension Scale, and specific parts of the Hungarostudy Query (a representative national questionnaire from 2013) were then given to participants.

The Mini-Mental State Examination (MMSE) was used to assess cognitive function for mapping. The MMSE is a well-known scale for detecting cognitive deficits and signs of dementia. It includes simple questions and problems in a variety of areas, such as temporal-spatial orientation, short-term memory, arithmetic computation (such as decreasing serial sevens), language use and comprehension, and basic visual-motor skills. The questionnaire had a point value ranging from 0 to 30. For mild, moderate, and severe cognitive impairment, the cut-off values are 23, 18, and 9 points, respectively. (81, 82) In addition to evaluating the raw MMSE results, age and education level adjustments were made, so patients with higher levels of education and younger ages had a lower threshold for cognitive impairment. Patients were classified as having cognitive impairment when there was a difference of more than two standard deviations between expected (age and education level adjusted) and MMSE scores. (81) According to previous research, modified cut-off values were used to detect the mildest cognitive impairment. (64, 83, 84)

A cut-off value of 27 or lower indicated mild cognitive impairment in these studies, while a score of 23 or lower indicated severe cognitive impairment.

Patients were asked to rate their own happiness and satisfaction on a scale of 1 to 10. These self-reported parameters were identified as an important factor influencing long-term mortality in healthy adult individuals. (85)

The State-Trait Anxiety Inventory (STAI) was used to assess patients' anxiety. The inventory consists of two sections: the STAI-S and the STAI-T. The first 20 questions concern the transitional emotional status induced by a stressful circumstance (STAI-S), such as hospitalization or surgical intervention. The STAI-T score demonstrates individual differences in susceptibility to chronic anxiety. Based on four-level Likert items, each group receives a score ranging from 20 to 80 points. (86, 87) In the Hungarian population, the STAI, a test with high reliability and validity, is well documented. (88) (STAI-T and S Cronbach's α=0.638 and 0.763, respectively)

For affective disorders, the Beck Depression Inventory (BDI) was used. The Beck Depression Inventory (BDI), a 21-item questionnaire, is a well-established tool for screening depression, with each item evaluating different symptoms of depression, such as a bad mood, a pessimistic outlook, feelings of guilt, and loss of appetite. The item in question contains four sentences indicating the severity of that specific symptom. The responses are four-level Likert items, and the entire inventory is scored from 0 to 63 points. (89-91) The validity and reliability of the BDI are also well documented in the Hungarian population (Cronbach's α=0.787). (92)

The Geriatric Depression Scale is a 30-item yes-or-no question-based inventory used to assess depression in the elderly. The GDS short form, which includes 15 questions, was used in our study. Each question is scored 0 or 1. In the range of 0 to 5 points depression is unlikely. (Cronbach's α=0.704). (93)

The Somatic Symptom Severity Scale (Patient Health Questionnaire - PHQ15) rates the severity of various symptoms such as gastrointestinal dysfunction, dizziness, chest pain, and dyspnea. It is calculated by determining scores of 0, 1, and 2 to the response categories "not at all", "bothered a little", and "bothered a lot" for each of the 13 somatic symptoms, respectively. Furthermore, two mood module items (fatigue and sleep) are scored as 0 ("not at all"), 1 ("several days"), or 2 ("more than half the days" or "nearly every day"). To improve comparability, we did not include questions about menstrual pain or dysmenorrhea. As a result, the inventory is graded from 0 to 28 points. Cut-off points for low, medium, and high somatic symptom severity are 5, 10, and 15, respectively. (Cronbach's α=0.730). (94-96)

The Devins Illness Intrusiveness Rating Scale assesses how illness affects various social issues. The 13-item questionnaire was developed to screen for illness-induced changes in lifestyle, activities, and interests that may jeopardize psychosocial well-being and contribute to emotional distress in chronic disease patients. The responses are seven-level Likert scale items, and the inventory is scored from 13 to 91 points. (Cronbach's α=0.854). (97, 98)

The Caldwell Social Support Dimension Scale was used to analyze the patient's social web structure. This scale is an updated version of the Social Support Questionnaire, which was first published in 1987. (99) The questionnaire represents the intensity of various social connections and supports, such as direct relatives, colleagues, and friends. Following the initial score summary, a distinct familial (parents, spouse, grandparents, children, and other relatives) and nonfamilial (neighbor, schoolmate, workmate, other social or sacral company) support score was created. All answers are presented as four-level Likert scale items. (Cronbach's α=0.570). (100-102)

Finally, the Athens Insomnia Scale Inventory (AIS-5) was taken to identify mild or severe insomnia. The AIS-5 cut-off score is 4, which is associated with potential insomnia (Cronbach's =0.630). (103)

The data was contrasted against the Hungarostudy (HS) population. Every ten years, Hungary conducts free-access, nationally representative, face-to-face household surveys; present one (n=2,000) was conducted in 2013. (104, 105) The BDI, STAI, CSSDS, Devins Illness Intrusiveness Rating Scale, PHQ15, and AIS, as well as standard inquiries about age, sex, marital status, religion, education level, and physical status, are all included in the Hungarostudy, which is constructed from the aforementioned inventories. Additional inquiries about smoking, drinking alcohol, and some inquiries regarding the participant's income are made in HS. In our survey, a condensed version of the HS 2013 form was adopted, making the two populations comparable. The propensity score matching method was used to compare analogous questions.

To describe the connection between traditional frailty syndrome and cognitive decline, our results were adjusted to a thorough frailty score that Shi et al. published. (106) Based on our data, the modified frailty index included recurrent angina pectoris, atrial fibrillation, congestive heart failure, chronic coronary disease, diabetes mellitus, hypertension, past myocardial infarction, peripheral vascular disease, stroke or TIA, anxiety (as measured by the STAI score), asthma or COPD, depression (as measured by the GDS score), cognitive impairment (as measured by the MMSE score), malnutrition (BMI<21) and medication (using ≥5 medications daily). The MMSE categories used in the comprehensive frailty score were applied according to the modified cut-off values described before.

3.4. Conventional risk estimation tools

American Society of Anesthesiologist score system is the best known and most widely used risk estimation method during the preoperative risk assessment. Its accuracy is based on some basic aspects, such as coexisting diseases, the patient’s current status and type and location of surgery. Traditionally, its simplicity and wide understandability kept it in clinical routine, and it is a basic language to communicate preoperative risk between disciplines. However, strictly the scoring method does not include any summarizing point calculation process such as the following ones. (3, 76, 107)

There are two domains in the V-POSSUM (POSSUM: Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity): 1. physiological variables (age, respiratory disease, heart rhythm, systolic blood pressure, pulse rate, cardiac failure, hemoglobin level, white blood cells, blood urea nitrogen, serum potassium and sodium levels, Glasgow Coma Scale level) and 2. operative parameters (type of the procedures, planned blood loss, peritoneal contamination, concomitant malignancy, urgency).

Three fundamental domains make up EuroScore II: 1. the patients' attribute, such as age, sex, respiratory disease, endocarditis, renal dysfunction or insufficiency, atherosclerosis, limited mobility, preoperative critical state, diabetes mellitus treated with insulin, 2. cardiac-related factors (congestive heart failure, angina severity, current myocardial infarction, left ventricular ejection fraction, pulmonary hypertension), and 3. operation-related factors (urgency, weight of procedures (e.g. valve replacement with coronary artery bypass grafting) and the involvement of thoracic aorta. (108)

The estimated mortality in percentages was determined for the comparability of the mortality risk calculation scores, and this value was utilized in the adjustment techniques.

3.5. Building a comprehensive frailty index

Four key domains were used to construct the comprehensive frailty score. As shown in Figure 3, each domain featured a large number of indicators. The values of each indicator ranged from 0 to 1. The existence of the condition got 1 point for binomial indicators (such as atrial fibrillation or diabetes). The original score was calculated to get a value between 0 and 1 in the case of continuous variables (such as self-rated scales). Asthma or chronic obstructive pulmonary disease (COPD), arthritis, degenerative spinal disorders, chronic renal insufficiency, and neoplasia were included in the biological frailty domain along with cardiovascular risk factors (hypertension, congestive heart failure, chronic coronary syndrome, atrial fibrillation, diabetes, previous myocardial infarction or stroke). Chronic medication use was taken into account, and taking more than five medications on a regular basis was determined to be a possible risk factor. The functional domain includes nutritional markers (body mass index (BMI) lower than 20, serum albumin level lower than 35 g/L, and unplanned weight loss (more than 10% within the last six months) as well as functional indications (ability to carry heavy objects, participate in sports, and do housework). Cognitive impairment, depression, anxiety, and self-reported happiness and satisfaction were the essential cognitive and psychological headings. Education, living alone, the Caldwell Social Support Dimension Scale, and self-reported financial difficulties were all included in the sociological frailty domain.

Low levels (elementary and high school) and high levels (college and higher education) were identified in the education index.

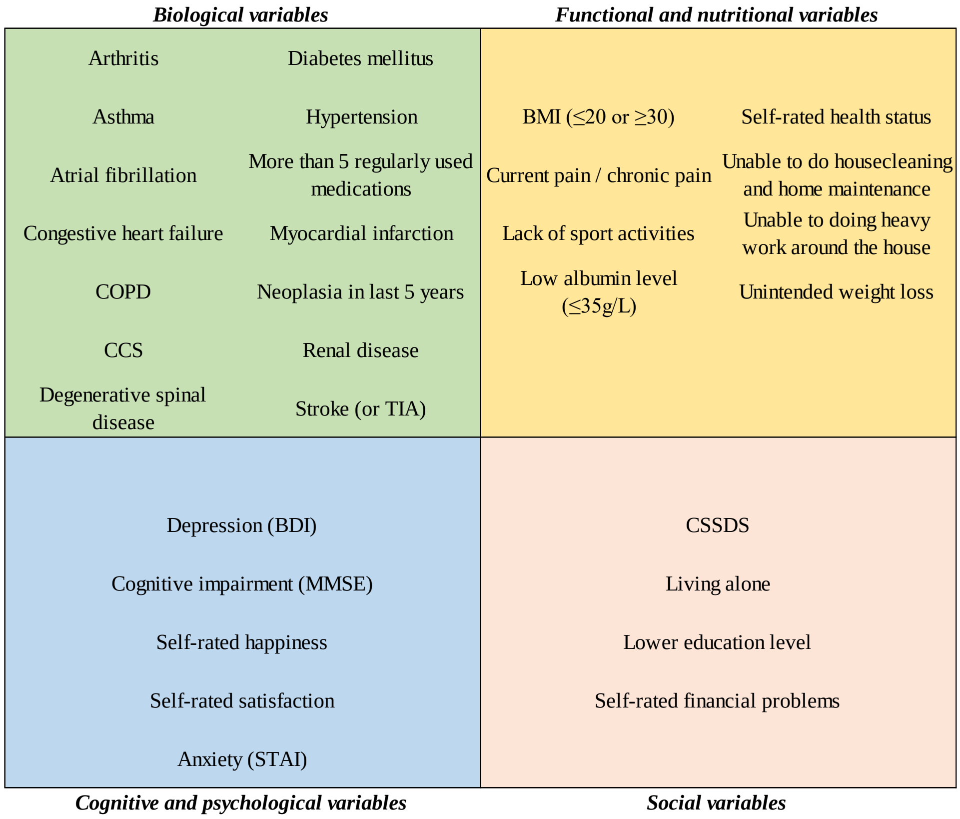


Figure 3. variables in comprehensive frailty index according to domains (COPD – chronic obstructive pulmonary disease, CCS – chronic coronary syndrome, TIA – transient ischaemic attack, BMI – body mass index, BDI – Beck Depression Inventory, MMSE – Mini-Mental State Examination, STAI – State Trait Anxiety Inventory, CSSDS – Caldwell Social Support Dimension Scale)

Self-reported physical function tests

There were self-reported physical status markers in the functional domain. Our indications, such as moving heavy objects and doing housekeeping on one's own, were taken from the activities of daily life questionnaire. More than one exercise session per week was considered as a normal sports activity in the world of sports. Its drawback is that some patients' medical issues, such as severe lower-limb artery stenosis, prevented them from performing any workouts.

Mini Mental State Examination

The Mini-Mental State Examination (MMSE) was utilized to assess the patients' cognitive functioning. The MMSE has a high degree of specificity for cognitive impairment despite being developed to identify dementia, and multiple studies have demonstrated its clinical significance. (82) The test includes questions that correspond to cognitive function, such as linguistic proficiency, short-term memory, and computing prowess. According to the original scores of 27–30, 24-26, 21–23, and below 21, the MMSE was given in the current context a score of 0, 0.3, 0.7, and 1, respectively. (106)

Beck Depression Inventory

Aaron T. Beck developed the Beck Depression Inventory (BDI) in 1961, which consists of 21 multiple-choice items. (89) The inventory underwent multiple changes; now, the BDI-II, a version created in 1996, is used. Additionally, it has updated cutoff values: 14 to 19 points are related to mild depression, 20 to 28 points are related to moderate depression, and over 29 points are related to severe depression.(90) In the current study, a score of 13 or higher on the BDI was considered to be depressive.

State-Trait Anxiety Inventory

The State-Trait Anxiety Inventory (STAI) was used to assess anxiety. It has two axes - trait anxiety and state anxiety - each of which is made up 20 items on a 4-point Likert scale. (88) The trait axis was mapped in this study, and general anxiety was defined as achieving at least a 40 on the STAI-T. (109)

Caldwell Social Support Dimension Scale

The Caldwell Social Support Dimension Scale (CSSDS) is a self-report questionnaire used to evaluate the social network and support system of patients. It includes information on both family and nonfamily members' support. (110) The overall social support dimension measure was utilized in the current investigation.

Other self-reported indicator scales

Simple self-rated questions were applied to map happiness, satisfaction, current health state, and everyday financial concerns in the functional, psychological, and social domains. The patients could select values between 1 and 10 on a continuous scale. In past investigations, the effectiveness of these straightforward questions' predictive capacity for mortality and morbidity was demonstrated. (111, 112) Absolute values (1-original value/10) were used to calculate the indicator (patients who self-rated as 7/10 received 1-7/10=0.3 points, for example).

Living alone was selected as an indicator in the social frailty main domain since it is a well-established risk factor for mortality, particularly in elderly people. (113, 114)

Preoperative surgical risk

The Vascular POSSUM was used for vascular surgery patient risk assessment, and Euroscore II was utilized for cardiac surgery patient risk assessment. (115-117) Estimated mortality was converted from the original score to percentages. The comprehensive frailty index was adjusted in the Cox regression model to account for anticipated mortality.

3.6. Statistical methods and tools

All continuous variables were presented with descriptive statistics (means, standard deviations, medians, and interquartile ranges). Kolmogorov-Smirnov test and the Shapiro-Wilk test were used to determine the type of distribution. For variables having a normal distribution, means and standard deviations were employed. The non-normal distributions were described by medians and interquartile ranges 25-75 (IQR). For categorical variables, Pearson χ^2-test was used; nonparametric tests were used for continuous variables, with the Mann-Whitney U test as the default. In some special cases categorical variables were calculated from continuous scales, with well-proven cut-off values as it described in detail before. Univariate and multivariable logistic regression (Cox regression) models were also used for estimation hazard in aspect of different outcomes. In study C multivariable Cox regression models were used as the primary analysis to discover independent risk factors for mortality with adjustment for the Euroscore II and Vascular POSSUM scores. Kaplan-Meier analysis with the log-rank tests was used to investigate different survival rates. In study B bootstrapping was used for crosstabulation and logistic regression methods.(118) The two-sided alpha level of 0.05 was applied ($p < 0.05$ was considered statistically significant).

For the statistical analysis, IBM SPSS Statistics 24.0 (SPSS Inc., Chicago, Illinois) with the R plugin (version 3.2.1) for PS matching was used. Forest plots were generated using 1. GraphPad Prism version 8.0.1 software for Windows, GraphPad Software, San Diego, California, USA, www.graphpad.com or 2. jamovi. (119) Following jamovi extensions were used: ClinicoPathDescriptives, deathwatch, felxplot, jjstatsplot, jsurvival, medmod and scatr.

To compare the vascular population and the Hungarian patient cohort, a propensity-matching analysis was performed. Pairs were established from the HS representative group and the vascular surgical group during propensity score matching based on age, sex, and place of residence. Absolute standardized differences were used to assess what degree the initial variables between the treatment and control groups were balanced. A standardized bias was considered acceptable if it was less than 0.1. To examine the disparities in psychological views and social moods between the general and surgical populations, identical questions were examined as the pairings were being produced.

3.6.1. Outcomes

The primary outcome of the studies was the risk of overall mortality. In a further analysis, the interactions between potential risk factors (chronic opioid use, cognitive dysfunction, depression, and anxiety) were described using MMSE, BDI, GDS, and STAI-T scores, respectively.

4. Results

4.1. Cognitive dysfunction among vascular surgical patients (Study A)

4.1.1. Descriptive and outcome data

Information from 164 patients was examined. A total of 35.97% of the patients were female, with a mean age of 67.05 years (SD±9.49). 20.73% of the patients were treated in the ICU during the postoperative phase, and the average stay was 1.5 days (IQR: 1.0–2.0). The surgical ward stay was 6.0 days on average (IQR 5.0-9.0 days). 42 patients (25.61%) died during the follow-up period (1,312 days, IQR: 924-1,582 days), with the 30-day mortality rate being 0.61% and the 1-year death rate being 4.88% (8 individuals). The non-surviving group had a higher vascular POSSUM score (16 points [IQR: 14.00-18.00] vs. 17 points [IQR: 15.00-22.00], p=0.025]. There were more previous vascular operations in the non-surviving group (43.44% vs. 66.67%, p=0.009). Results are shown on Table 1.

Table 1. Preoperative variables and overall mortality (BMI – body mass index (kg/m^2), ASA – American Society of Anesthesiologist score, POSSUM – Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity, CABG – coronary artery bypass grafting, TIA – transient ischemic attack, MMSE – Mini-Mental State Examination, BDI – Beck Depression Inventory, STAI-T – State Trait Anxiety Inventory, trait axis)

		All patients (n=164, 100%)						
		Survivors (n=122, 74.39%)			Nonsurvivors (n=42, 25.61%)			
Preoperative Variable		n (%)	Mean/ Median	Standard Deviation/ IQR	n (%)	Mean/ Median	Standard Deviation/ IQR	p-value[b]
Sex	male	77 (63.11)			28 (66.67)			0.679
Age			66.87	9.98		67.60	7.96	0.874
BMI			27.52	4.72		26.03	3.82	0.092
ASA	1	1 (0.82)			0 (0.00)			0.783[c]
	2	46 (37.70)			10 (24.39)			
	3	72 (59.02)			29 (70.73)			
	4	3 (2.46)			2 (4.88)			
Vascular POSSUM[a]			16.00	(14.00-18.00)		17.00	(15.00-22.00)	0.025
Medical variables								
Ischaemic Heart Disease		43 (35.25)			15 (35.71)			0.956
Myocardial infarction		23 (18.85)			5 (11.90)			0.302
Diabetes Mellitus		35 (28.69)			19 (45.24)			0.049
Obesity		31 (25.41)			5 (11.90)			0.068
Hypertension		108 (88.52)			34 (80.95)			0.214
CABG		10 (8.20)			4 (9.52)			0.791
Previous vascular surgery		53 (43.44)			28 (66.67)			0.009
Stroke or TIA		20 (16.39)			11 (26.19)			0.162
Thyroid disorder		7 (5.74)			2 (4.76)			0.811
Haemoglobin (g/l)			140.33	14.63		129.8	19.7	0.020
Platelet number (G/l)			235.37	81.04		251.9	111.9	0.632
Glomelural filtration rate (ml/min)			84.39	13.56		86.20	10.24	0.537
C reactive protein (mg/L)			3.00	(1.16-6.18)		12.35	(4.46-33.50)	<0.001
Psychologycal variables								
Cognitive impairment by MMSE		11 (9.02)			10 (23.81)			0.013
Depression by BDI		41 (35.96)			15 (36.59)			0.943
Anxiety by STAI-T		47 (38.52)			18 (42.86)			0.621

[a] = not normally distribution

[b]= Pearson chi square test for categorical variables and Man-Whitney U test for continous variables

[c]= Kolmogorov-Smirnov Z test

We contrasted the research patients to the participants from the Hungarostudy. 159 pairs were made after propensity score matching (adjusting participants based on age, sex, and place of residence). Over the past year, the vascular surgery patient group visited medical facilities more frequently (26.6% vs. 11.8%, p=0.001). The patient group had reported more intense social support [CSSDS scores were 20 (15.00-23.00) vs. 23 (19.00-27.00), p<0.001 for the population group and the patient cohort, respectively]. Following propensity score matching, Table 2 compares the socioeconomic characteristics of our vascular surgery sample to the population of the Hungarostudy survey.

Table 2. Comparison between the propensity score-matched pairs (Hungarostudy vs. vascular surgery group, n=159 pairs) (BMI – body mass index, ASA – American Society of Anesthesiologist score, POSSUM – Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity, CABG – coronary artery bypass grafting, TIA – transient ischemic attack, MMSE – Mini-Mental State Examination, BDI – Beck Depression Inventory, STAI-T – State Trait Anxiety Inventory, trait axis)

		Hungarostudy			Vascular surgery group			
		n (%)	Median	IQR	n (%)	Median	IQR	p-value
No medical contact - last year*		42 (26.58)			18 (11.76)			<0.001
Actual bodily pain*		85 (53.46)			85 (53.46)			0.545
Self reported health condition (1-10)			3	(3.00-4.00)		3	(3.00-3.00)	0.471
Patient Health Quality			21	(16.00-26.00)		20	(17.00-24.00)	0.637
Devins Illness Intussiveness Rating Scale			32.50	(26.00-39.00)		19.00	(13.00-27.00)	0.109
Life satisfaction (1-10)			7	(5.00-8.00)		7	(5.00-8.00)	0.472
Happiness (1-10)			7	(5.00-8.00)		7	(5.00-9.00)	0.119
In-hospital-days - last year			0	(0.00-0.00)		1	(0.00-10.00)	<0.001
Alternative health care - last 3 years*		4 (2.53)			18 (11.32)			0.002
Caldwell Social Support Dimension Scale			20	(15.00-23.00)		23	(19.00-27.00)	<0.001
Caldwell Social Support Dimension Scale - family			10	(8.00-12.00)		12	(10.00-15.00)	<0.001
Caldwell Social Support Dimension Scale - other			9	(7.00-12.00)		10	(7.00-13.00)	0.001
Smoking	Never	74 (46.54)			23 (14.74)			<0.001
	Used to smoking	44 (27.67)			80 (51.28)			
	Active smoker	41 (25.79)			53 (33.97)			
Pack year unit			28.50	(17.50-40.00)		23.00	(13.75-40.00)	0.411
Physical exercise/week			5	(4.00-7.00)		2	(0.00-6.00)	<0.001
Other, non sport physical activity/week			3	(1.00-4.00)		1	(1.00-4.00)	<0.001
Drinking alcoholic beverages (1-5)			2	(1.00-4.00)		2	(1.00-3.00)	0.310
Not religious*		50 (32.05)			75 (47.17)			0.024
Education level*	Primary school	9 (5.66)			7 (4.40)			0.375
	Secondary school	30 (18.87)			25 (15.72)			
	High school levels	97 (61.01)			89 (55.97)			
	Collage	23 (14.47)			38 (23.90)			
Family stage*	Unmarried, without partner	7 (4.43)			4 (2.53)			0.002
	Unmarried, with partner	2 (1.27)			7 (4.43)			
	Married	74 (46.54)			88 (55.35)			
	Married but living alone	3 (1.90)			15 (9.49)			
	Divorved, without partner	17 (10.76)			8 (5.06)			
	Divorced, with partner	8 (5.06)			31 (19.62)			
	Widow, without partner	46 (29.11)			5 (3.16)			
	Widow, with partner	1 (0.63)			0 (0.00)			
Number of person in the same household			2	(1.00-2.00)		2	(1.00-2.00)	0.618
Financial difficulties*		28 (18.18)			19 (11.95)			0.083

*=categorical variable, chi square test were used for statistics, on continuous variable Man Whitney U test were used.

4.1.2. Main results

11.59% of the patients (n=19) met the criteria for a cognitive impairment in the conventional MMSE categories (normal range of 24 points or higher). The prevalence of cognitive dysfunction increased to 25.00% (n=41) as a novel cut-off value for the MMSE score (normal range 27 points or higher) was used and published by She et al. (106) The minimum and maximum MMSE scores were 18 and 30, respectively.

The three curves from a Kaplan-Meier analysis of survival are presented in Figure 4. A list of the categories used is provided in Part A. Figure 4/C uses the more sensitive, modified cut-off value as a definition of cognitive dysfunction while Figure 4/B uses age- and education-adjusted cut-off values. All MMSE categories produced using the aforementioned method had significantly different survival rates (see figures for log-rank p-values, each at the corresponding Kaplan-Meier curve).

Each worse MMSE-cluster, which was generated as shown in Figure 4/A, was linked to a higher risk of long-term mortality after adjustment to the vascular POSSUM score (HR: 1.659, 95% CI: 1.129-2.439, p=0.010).

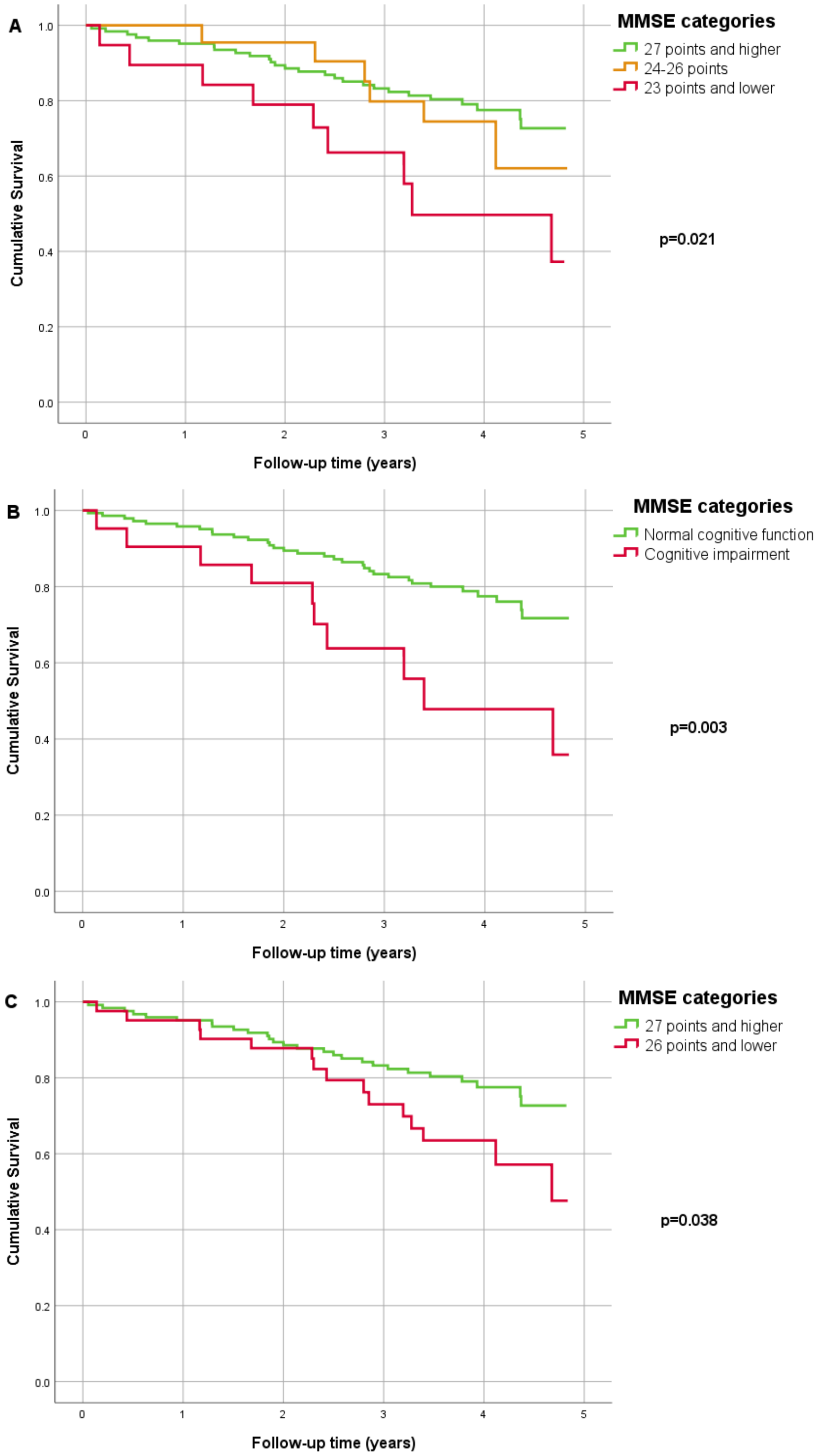
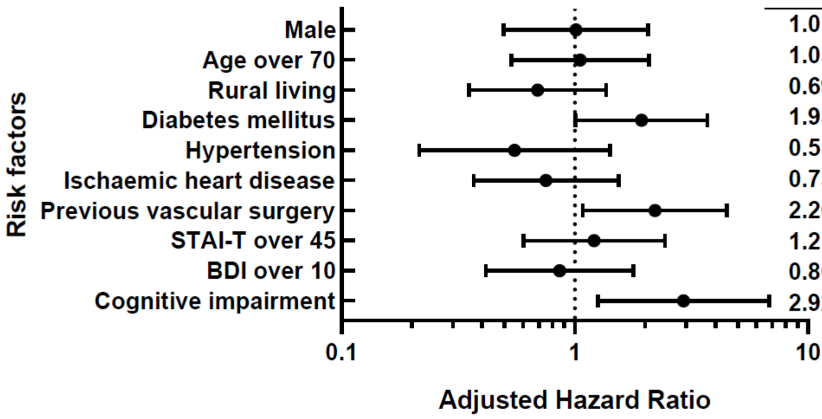


Figure 4. Kaplan Meier curve for Mini-Mental State Examination (MMSE) categories and mortality:
In part A log-rank pairwise comparison was performed: an MMSE score of 27 points or higher vs. *24-26 points, p=0.531; B: 27 points or higher* vs. *23 or fewer points, p=0.007; C: 24-26 points and 23 points and below, p=0.120.*

All-cause mortality was reduced by having a higher MMSE score (OR: 0.883, 95% CI: 0.802-0.973, p=0.012). After adjusting for the vascular POSSUM score, the cohort with cognitive dysfunction (MMSE score 24 points) had a greater risk of overall mortality (AHR: 2.918, 95% CI: 1.380-6.170, p=0.005). Cognitive impairment had no discernible effects on the one-year survival rate (AHR: 2.360, 95% CI: 0.476-11.692, p=0.293).

In addition to these fundamental risk factors, the multivariate Cox regression model demonstrated that cognitive impairment was a significant, independent risk factor (AHR: 2.928, 95% CI: 1.258-6.819, p=0.013) when adjustment to the age and education were performed. Other independent risk factors for overall mortality were diabetes mellitus and prior vascular surgery (AHR: 1.930, 95% CI: 1.006-3.702, p=0.048 and AHR: 2.206, 95% CI: 1.082-4.498, p=0.030, respectively). The results of the multivariate Cox regression analysis are shown in Figure 5.



AHR	Lower 95% CI	Upper 95% CI	p value
1.012	0.496	2.063	0.975
1.053	0.533	2.079	0.883
0.692	0.352	1.360	0.286
1.930	1.006	3.702	0.048
0.551	0.215	1.415	0.215
0.752	0.368	1.537	0.435
2.206	1.082	4.498	0.030
1.210	0.602	2.431	0.593
0.860	0.415	1.779	0.684
2.928	1.258	6.819	0.013

Figure 5. Effects of variables on overall mortality in the multivariate Cox regression model (AHR – adjusted hazard ratio, CI – confidence interval, BDI – Beck Depression Inventory, STAI-T – State Trait Anxiety Inventory, trait axis)

4.1.3. Other analyses

The non-surviving group had lower levels of self-rated factors (happiness, satisfaction, and current health state). Significant differences were seen between the results for happiness (median=8.0 IQR: 5.0-10.0 vs. 6.0 IQR: 5.0-8.0, p=0.046) and satisfaction (median=7.0 IQR: 5.0-8.0 vs. 6.0 IQR: 5.0-7.0, p=0.122).

Between the non-surviving and surviving groups, there were no appreciable differences in the BDI, GDS, STAI-T Patient Health Quality 15 and the Caldwell Social Support Dimension Scales.

4.2. Chronic medication before vascular surgery (Study B)

4.2.1. Participants

164 patients' data were examined. The participants' mean age was 67.05 years, with a standard deviation of 9.48 years, and 64.02 percent of them were male. The interquartile range of the follow-up time was 930 to 1582 days, with 1312 being the median. 42 patients died throughout the follow-up period (25.61%); males represented 66.67% of those who did not survive.

4.2.2. Descriptive data

The procedures were divided into four major categories: procedures on the carotid arteries, iliac system, peripheral arteries, and descendent aorta. The carotid arteries (43.56%) received the majority of the operations. The descending aorta accounted for 22.09%, the iliac region for 14.11%, and the peripheral artery operations accounted for 20.24%. Crosstabulation analysis was used to see whether the type of operation had any significant effects on either the primary or secondary result.

4.2.3. Main results – Relationship between long term mortality and comprehensive frailty index estimation

In the study group, opioid derivative use occurred 3.66% (6 individuals). Transdermal fentanyl or tramadol was applied by the patients. It was not possible to capture the precise indication of opioid derivative use. Opioid use was substantially greater in the non-survivors' group (1.64% vs. 9.52%, p=0.019). The differences in demographic and preoperative medical treatments between survivors and non-survivors are shown on Table 3.

Table 3. The registered anthropometric data, previous diseases and medical therapies according to mortality in Study (BMI – body mass index, POSSUM – Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity, CABG – coronary artery bypass grafting, TIA – transient ischemic attack, COPD – chronic obstructive pulmonary disease, OAC – oral anticoagulants, PDE – phosphodiesterase, SSRI – selective serotonin reuptake inhibitor, ACEI – angiotensin converting enzyme inhibitor, ARB – angiotensin receptor blocker, OAD – oral antidiabetics)

		Survivor (n=122, 74.39%)				Non-survivor (n=42, 25.61%)				
		N	%	Median	IQR	N	%	Median	IQR	p-value
Sex	male	77	63.11%			28	66.67%			0.679
Age (years)				68.00	60.00-74.00			68.50	62.00-73.00	0.874
BMI				27.39	24.20-30.80			25.30	23.18-28.73	0.092
Vascular POSSUM				16.00	14.00-18.00			17.00	15.00-22.00	0.030
Ischaemic heart disease		43	35.25%			15	35.71%			0.956
Diabetes mellitus		35	28.69%			19	45.24%			0.049
Hypertension		108	88.52%			34	80.95%			0.214
Obesity (BMI≥30)		31	25.41%			5	11.90%			0.068
Neoplasia		28	22.95%			10	23.81%			0.909
Psychiatric anamnesis		5	4.10%			3	7.14%			0.430
Previous vascular surgery		53	43.44%			28	66.67%			0.009
Stroke or TIA		20	16.39%			11	26.19%			0.162
COPD		25	20.49%			14	33.33%			0.092
Acetylsalicylic acid		70	57.38%			26	61.90%			0.607
Clopidogrel		32	26.23%			6	14.29%			0.114
Apixaban		3	2.46%			0	0.00%			0.305
Other antiplatelet drug		2	1.64%			0	0.00%			0.404
OAC		5	4.10%			2	4.76%			0.854
PDE inhibitor		9	7.38%			3	7.32%			0.99
Benzodiazepine		34	27.87%			9	21.43%			0.413
SSRI		7	5.74%			2	4.76%			0.811
Other antidepressants		4	3.28%			0	0.00%			0.235
Beta blockers		63	51.64%			15	35.71%			0.075
Ca channel blockers		46	37.70%			13	30.95%			0.432
ACEI		55	45.08%			21	50.00%			0.581
ARB		17	13.93%			6	14.29%			0.955
Diuretics		54	44.26%			25	59.52%			0.088
Digitalis		3	2.46%			3	7.14%			0.163
OAD		20	16.39%			12	28.57%			0.086
Insulin		7	5.74%			5	11.90%			0.186
Antiepileptics		3	2.46%			1	2.38%			0.977
Steroid		9	7.38%			4	9.52%			0.657
Statin		68	55.74%			19	45.24%			0.240
Opioid derivate		2	1.64%			4	9.52%			0.019

According to the univariate Cox regression model (hazard ratio (HR): 2.49, 95% CI: 1.20-5.18, p=0.014) and V-POSSUM score-adjusted Cox regression model (adjusted hazard ratio (AHR): 2.40, 95% CI: 1.15-5.01, p=0.020), the use of opioid derivatives appeared to be an independent risk factor for overall mortality.

Opioids have been found to be an independent risk factor for all-cause death in a multivariate Cox regression model (AHR: 4.31 95%CI: 1.77-10.55 p=0.001). According to research, taking beta-blockers had a beneficial effect (AHR: 0.48 95% CI: 0.27-0.85, p=0.012). Overall mortality was significantly predicted by the vascular POSSUM score (HR: 1.12, 95% CI: 1.04-1.21, p=0.003). The entire model was represented as a forest plot on Figure 6.

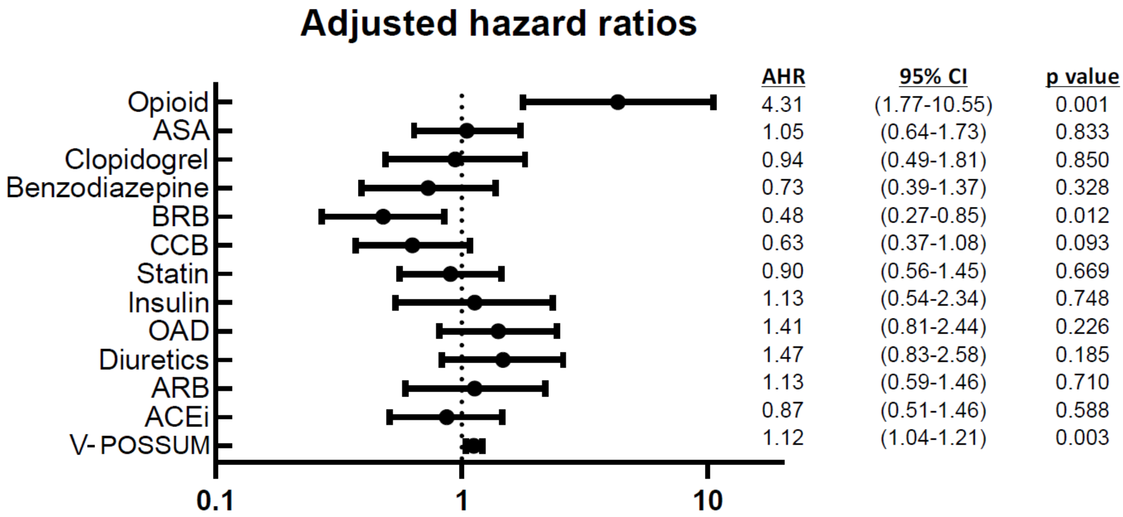


Figure 6. Multivariate Cox model for all-cause mortality (AHR – adjusted hazard ratio, CI – confidence interval, ASA – acetyl salicylic acid, BRB – beta receptor blocker, CCB – calcium channel blocker, OAD – oral antidiabetics, ARB – angiotensin receptor blocker, ACEi – angiotensin converting enzyme inhibitor, V-POSSUM – vascular Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity score

4.2.4. Relationship between psychological variables and opioid use

Numerous psychological factors relating to opioid use were examined. Opioid users scored worse on the MMSE score [25.50 (IQR: 24.50-26.00) vs. 28.00 (IQR: 27.00-29.09 p=0.008]. On the BDI, opioid users performed worse (15.50 [IQR:10.00-18.00] vs. 6.00 [IQR:3.00-11.00], p=0.030]. The results of all completed inventories are shown in Table 4.

Table 4. Psychological variables, in-hospital and ward length of stay (LOS) regarding to opioid usage (IQR – interquartile range, MMSE – Mini-Mental State Examination, GDS – Geriatric Depression Score, BDI – Beck Depression Inventory, STAI-T – State Trait Anxiety Inventory, trait axis, LOS – length of stay)

	Use of opioid derivates						
	No			Yes			
	Median	IQR 25-75		Median	IQR 25-75		p-value
MMSE Score	28.00	27.00	29.00	25.50	24.00	26.00	0.008
GDS Score	5.00	2.00	7.00	5.50	5.00	7.00	0.626
BDI Score	6.00	3.00	11.00	15.50	10.00	18.00	0.030
STAI-T Score	40.50	35.00	51.00	42.50	29.00	51.00	0.830
Self-rated satisfaction (1-10)	7.00	5.00	8.00	5.50	1.00	6.00	0.118
Self-rated happiness (1-10)	7.00	5.00	9.00	5.00	4.00	6.00	0.036
Athens Insomnia Scale 5	1.00	0.00	3.00	2.00	0.00	4.00	0.462
Comprehensive Frailty Score	4.00	3.00	6.00	6.80	5.30	8.00	0.018
In-hospital LOS (days)	7.00	5.00	10.00	12.00	7.00	15.00	0.120
Ward LOS (days)	6.00	5.00	9.00	12.00	7.00	13.00	0.062
Vascular POSSUM	16.00	14.00	19.00	15.00	13.00	24.00	0.689

Self-rated life satisfaction was not significantly different [7.00 (IQR: 5.00-9.00) vs. 5.50 (IQR: 1.00-6.00), p=0.116], while self-rated happiness was lower in the opioid user group [7.00 (IQR: 5.00-9.00) vs. 5.00 (IQR: 4.00-6.00), p=0.036].

Chronic opioid derivative users had a higher estimated comprehensive frailty score (4.00 (IQR: 3.00-6.00) vs. 6.80 (IQR: 5.80-8.00), p=0.018].

The in-hospital length of stay (LOS) showed a significant trend [6 days (IQR: 5-9) vs. 12 days (IQR: 7-13), p=0.068].

4.3. Comprehensive frailty index in vascular and cardiac surgical patients (Study C)

4.3.1. Participants, Descriptive Data

228 participants' data were used in the statistical analysis. 67 individuals had cardiac surgery, while a total of 161 patients had vascular surgery. The median age of the whole cohort was 68.00 years, and the interquartile range was 60.50-73.00 years. The median BMI was 27.44 (IQR 24.30-29.75), while the 64.07% of patients were male. The median follow-up time was 2012 days, with the IQR 1471-2413 days. A significant difference between these parameters was not confirmed. 95 individuals passed away (41.667%) during the follow-up. The death rates at one, two, three, and four years were, respectively, 6.140% (14), 10.088% (23), 18.421% (42) and 23.246% (53). The incidence of different indicators of the comprehensive frailty index was showed on Table 5.

Table 5. The incidence of different indicators of the comprehensive frailty index (CCS – chronic coronary disease, TIA – transient ischemic attack, COPD – chronic obstructive pulmonary disease, BMI – body mass index, STAI – State Trait Anxiety Inventory, BDI – Beck Depression Inventory, CSSDS – Caldwell Social Support Dimension Scale)

		Count	%	Median	Interquartile range
Biological variables	Atrial fibrillation	25	10.960%		
	Congestive heart failure	23	10.090%		
	CCS	83	36.400%		
	Diabetes mellitus	90	39.470%		
	Hypertension	206	90.350%		
	Myocardial infarction	41	17.980%		
	Stroke (or TIA)	61	26.750%		
	Arthritis	128	56.140%		
	Asthma	6	2.630%		
	Neoplasia in last 5 years	14	6.140%		
	Renal disease	42	20.790%		
	COPD	80	35.090%		
	Degenerative spinal disease	35	15.350%		
	More than 5 regularly used medications	137	60.090%		
Biological domain subindex				0.286	0.214-0.385
Functional and nutritional variables	BMI (≤20 or ≥30)	26	11.400%		
	Unintended weight loss	22	10.050%		
	Current pain / chronic pain	98	44.950%		
	Self-rated health status[a]			0.400	0.400-0.400
	Low albumin level (≤35g/L)	46	23.710%		
	Lack of sport activities	87	41.230%		
	Unable to doing heavy work around the house	115	50.660%		
	Unable to do housecleaning and home maintenance	96	42.860%		
Functional frailty domain subindex				0.300	0.200-0.425
Cognitive and psychological variables	Cognitive impairment	52	22.807%		
	Self-rated happiness[a]			0.300	0.100-0.500
	Self-rated satisfaction[a]			0.300	0.200-0.500
	STAI (≥40 points)	112	51.610%		
	BDI (≥ 13 points)	37	18.500%		
Cognitive and psychological frailty domain subindex				0.245	0.100-0.400
Social variables	CSSDS	100	43.860%		
	Living alone	50	21.930%		
	Lower education level	111	48.680%		
	Self-rated financial problems	22	10.000%		
Social frailty domain subindex				0.250	0,250-0.500
Comprehensive frailty index				0.393	0.331-0.465
Ratios	Biological frailty domain			24.950%	18.445-34.795%
	Functional frailty domain			26.759%	19.222-34.512%
	Cognitive and pychological frailty domain			20.703%	11.949-31.134%
	Social frailty domain			23.730%	14.531-32.511%

Outcome data regarding the type of surgery

Vascular surgery group had a significantly higher follow-up mortality rate than cardiac surgery (47.826% vs. 26.866%, p=0.003). The estimated mortality prior to surgery was similar (median: 2.700, IQR: 2.000-4.900 vs. 3.000, IQR: 1.140-6.000, p=0.266) and did not differ significantly. Significant and striking differences were seen in the comprehensive frailty index (0.400, IQR: 0.358-0.467 vs. 0.348, IQR: 0.303-0.460, p=0.001). Table 6 provides a summary of the indicators by type of surgery. The biological domains (0.357, IQR: 0.214-0.429 vs. 0.357, IQR: 0.214-0.429, p=0.001) and functional domains (0.325, IQR: 0.200-0.425 vs. 0.325, IQR: 0.200-0.450, p=0.011) showed a significant difference between the two groups.

Table 6. *The incidence of different indicators of the comprehensive frailty index regarding type of surgery (CCS – chronic coronary disease, TIA – transient ischemic attack, COPD – chronic obstructive pulmonary disease, BMI – body mass index, STAI – State Trait Anxiety Inventory, BDI – Beck Depression Inventory, CSSDS – Caldwell Social Support Dimension Scale)*

		Vascular surgical patients				Cardiac surgical patients				
		Count	%	Median	Interquartile range	Count	%	Median	Interquartile range	p-value
Biological variables	Atrial fibrillation	15	9.320%			10	14.930%			0.217
	Congestive heart failure	17	10.560%			6	8.960%			0.714
	CCS	55	34.160%			28	41.790%			0.275
	Diabetes mellitus	65	40.370%			25	37.310%			0.667
	Hypertension	144	89.440%			62	92.540%			0.471
	Myocardial infarction	35	21.740%			6	8.960%			0.056
	Stroke (or TIA)	57	35.400%			4	5.970%			0.001
	Arthritis	108	67.080%			20	29.850%			0.001
	Asthma	4	2.480%			2	2.990%			0.830
	Neoplasia in last 5 years	11	6.830%			3	4.480%			0.500
	Renal disease	27	19.850%			15	22.730%			0.637
	COPD	58	36.020%			22	32.840%			0.646
	Degenerative spinal disease	15	9.320%			20	29.850%			0.001
	More than 5 regular used medicine	108	67.080%			29	43.280%			0.001
Biological domain subindex				0.357	0.214-0.429			0.214	0.214-0.357	0.001
Functional and nutritional variables	BMI (≤20 or ≥30)	43	26.710%			15	22.390%			0.306
	Unintended weight loss	18	11.840%			4	5.970%			0.183
	Current pain / chronic pain	85	52.800%			13	22.810%			0.001
	Self-rated health status[a]			0.400	0.400-0.400			0.400	0.400-0.600	0.577
	Low albumin level (≤35g/L)	3	2.360%			43	64.180%			0.001
	Lack of sport activities	67	41.880%			20	39.220%			0.737
	Unable to doing heavy work around the house	97	60.250%			18	27.270%			0.001
	Unable to do housecleaning and home maintenance	68	43.040%			28	42.420%			0.933
Functional frailty domain subindex				0.325	0.200-0.450			0.275	0.175-0.425	0.011
Cognitive and psychological variables	Cognitive impairment	40	24.845%			12	17.910%			0.299
	Self-rated happiness[a]			0.300	0.100-0.500			0.200	0.100-0.500	0.666
	Self-rated satisfaction[a]			0.300	0.200-0.500			0.300	0.200-0.500	0.126
	STAI (≥40 points)	82	50.930%			30	53.570%			0.733
	BDI (≥ 13 points)	27	17.760%			10	20.830%			0.633
Cognitive and psychological frailty domain subindex				0.260	0.120-0.400			0.200	0.080-0.400	0.098
Social variables	CSSDS	67	41.610%			33	49.250%			0.290
	Living alone	33	20.500%			17	25.370%			0.418
	Lower education level	83	51.550%			28	41.790%			0.179
	Self-rated financial problems	20	12.420%			2	3.390%			0.048
Social frailty domain subindex				0.250	0.250-0.500			0.250	0.000-0.500	0.807
Comprehensive frailty index				0.400	0.358-0.467			0.348	0.303-0.460	0.001
Ratios	Biological frailty domain			25.231%	19.582-34.924%			24.829%	17.575-33.944%	0.651
	Functional frailty domain			27.526%	20.000-33.796%			24.623%	17.339-35.233%	0.607
	Cognitive and pychological frailty domain			20.741%	12.516-31.818%			20.664%	8.7363-30.270%	0.348
	Social frailty domain			23.529%	15.953-31.028%			24.87%	0.000-40.698%	0.599
Estimated mortality				2.700	2.000-4.900			3.000	1.140-6.000	0.266

4.3.2. Main results – Long-term mortality regarding differences in comprehensive frailty index

The biological, functional, and sociological domain subindex scores were significantly higher in patients who died during the follow-up period. Additionally, there was an increase in the overall frailty index (0.371, IQR: 0.316-0.445 vs. 0.423, IQR: 0.365-0.500, p0.001). The psychological and cognitive domain subindices, however, did not differ significantly, and the non-survivor cohort had worse cognitive impairment (16.541% vs. 31.579%, p=0.029) and self-rated happiness (0.200, IQR: 0.000-0.500 vs.

0.300, IQR: 0.100-0.500, p=0.045). The differences between the non-survivor and survivor populations are shown on Table 7.

Table 7. *The incidence of different indicators of the comprehensive frailty index regarding type of surgery (CCS – chronic coronary disease, TIA – transient ischemic attack, COPD – chronic obstructive pulmonary disease, BMI – body mass index, STAI – State Trait Anxiety Inventory, BDI – Beck Depression Inventory, CSSDS – Caldwell Social Support Dimension Scale)*

		Survivor (n=133)				Non-survivor (n=95)				
		Count	%	Median	Interquartile range	Count	%	Median	Interquartile range	p-value
Vascular surgical patients		84	57.174%			77	42.826%			0.003
Cardiac surgical patients		49	73.134%			18	26.866%			
Biological variables	Atrial fibrillation	12	9.023%			13	13.684%			0.267
	Congestive heart failure	8	6.015%			15	15.789%			0.016
	CCS	51	38.346%			32	33.684%			0.471
	Diabetes mellitus	44	33.083%			46	48.421%			0.019
	Hypertension	122	91.729%			84	88.421%			0.404
	Myocardial infarction	22	16.541%			20	21.153%			0.385
	Stroke (or TIA)	29	21.805%			32	33.684%			0.046
	Arthritis	67	50.376%			61	64.211%			0.038
	Asthma	4	3.008%			2	2.105%			0.675
	Neoplasia in last 5 years	11	8.271%			3	3.158%			0.113
	Renal disease	21	17.500%			21	25.610%			0.163
	COPD	40	30.075%			40	42.105%			0.061
	Degenerative spinal disease	20	15.038%			15	15.789%			0.877
	More than 5 regularly used medications	76	57.143%			61	64.211%			0.283
Biological domain subindex				0.286	0.214-0.357			0.357	0.231-0.429	0.002
Functional and nutritional variables	BMI (≤20 or ≥30)	12	9.023%			14	14.737%			0.181
	Unintended weight loss	11	8.594%			11	12.088%			0.397
	Current pain / chronic pain	51	40.157%			47	51.648%			0.093
	Self-rated health status[a]			0.400	0.200-0.400			0.400	0.400-0.400	0.572
	Low albumin level (≤35g/L)	31	26.496%			15	19.481%			0.261
	Lack of sport activities	42	35.000%			45	49.451%			0.035
	Unable to doing heavy work around the house	62	46.970%			53	55.789%			0.190
	Unable to do housecleaning and home maintenance	55	41.985%			41	44.086%			0.754
Functional frailty domain subindex				0.300	0.175-0.425			0.343	0.233-0.450	0.018
Cognitive and psychological variables	Cognitive impairment	22	16.541%			30	31.579%			0.029
	Self-rated happiness[a]			0.200	0.000-0.500			0.300	0.100-0.500	0.045
	Self-rated satisfaction[a]			0.300	0.200-0.500			0.300	0.200-0.500	0.142
	STAI (≥40 points)	65	51.587%			47	51.648%			0.993
	BDI (≥ 13 points)	17	14.912%			20	23.256%			0.132
Cognitive and psychological frailty domain subindex				0.240	0.100-0.375			0.260	0.120-0.480	0.152
Social variables	CSSDS	52	39.098%			48	50.526%			0.086
	Living alone	26	19.549%			24	25.263%			0.304
	Lower education level	58	43.609%			53	55.789%			0.070
	Self-rated financial problems	12	9.375%			10	10.870%			0.715
Social frailty domain subindex				0.250	0.000-0.333			0.250	0.250-0.500	0.007
Comprehensive frailty index				0.371	0.316-0.445			0.423	0.365-0.500	<0.001
Ratios	Biological frailty domain			24.829%	18.132-34.924%			25.025%	19.017-34.167	0.828
	Functional frailty domain			28.020%	18.503-35.484%			25.607%	19.958-32.300	0.351
	Cognitive and pychological frailty domain			20.741%	11.523-31.542%			20.108%	12.160-30.894	0.827
	Social frailty domain			22.846%	0.000-32.169%			25.253%	15.709-33.397	0.415
Estimated mortality				2.400	1.700-4.000			3.200	2.300-5.700	<0.001

4.3.3. Comprehensive frailty index and prediction of long-term mortality

Four subgroups were formed in accordance with the comprehensive frailty index quartiles for the analysis of mortality risk. An odds ratio of 1.449 (95% CI: 1.199-1.751, p0.001) was discovered in univariate Cox regression. The estimated mortality was used to account for traditional surgical risk, and the calculated OR was 1.384 (95% CI: 1.140-1.680, p=0.001). The adjusted odds ratios calculated according to the comprehensive frailty index quartiles in the multivariate Cox regression are shown in Figure 7.

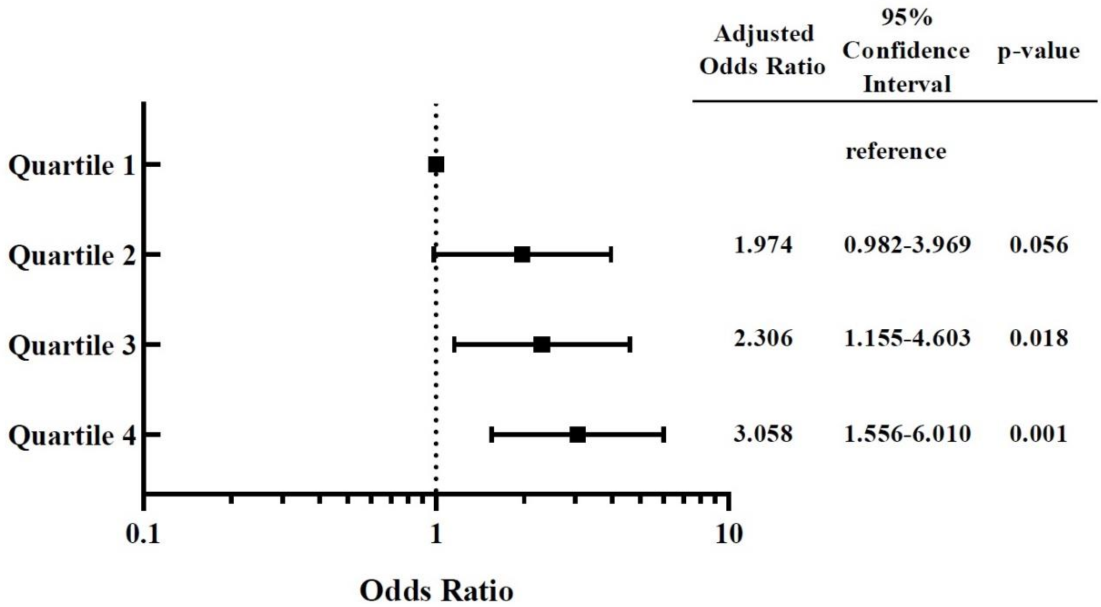


Figure 7. The adjusted odds ratios for morality according to the comprehensive frailty index quartiles in the multivariate Cox regression model

Kaplan–Meier analysis regarding to the comprehensive frailty index quartiles represented a significant difference in mortality as it showed on Figure 8. (Mantel–Cox log-rank test, p=0.001).

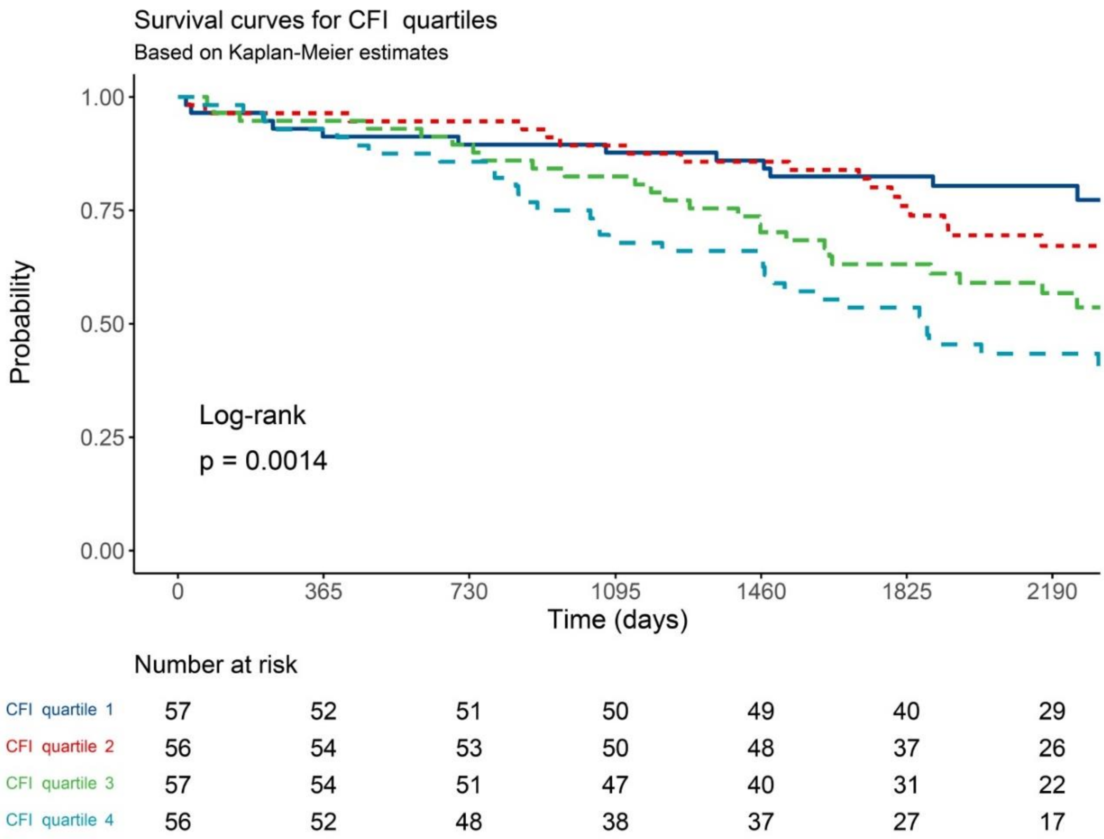


Figure 8. Kaplan–Meier analysis according to the comprehensive frailty index (CFI) quartiles

4.3.4. Psychological variables according to surgical discipline

As in Study B psychological variables were compared it is important to highlight some similarities and differences here. In the vascular surgical group, there are no significant differences between anxiety (measured by STAI-T) and depression (measured by BDI) according to mortality. In the cardiac surgical group, a significantly higher BDI score and non-significantly higher STAI score was identified in the non-survivor group.

DOI:10.14753/SE.2024.2930

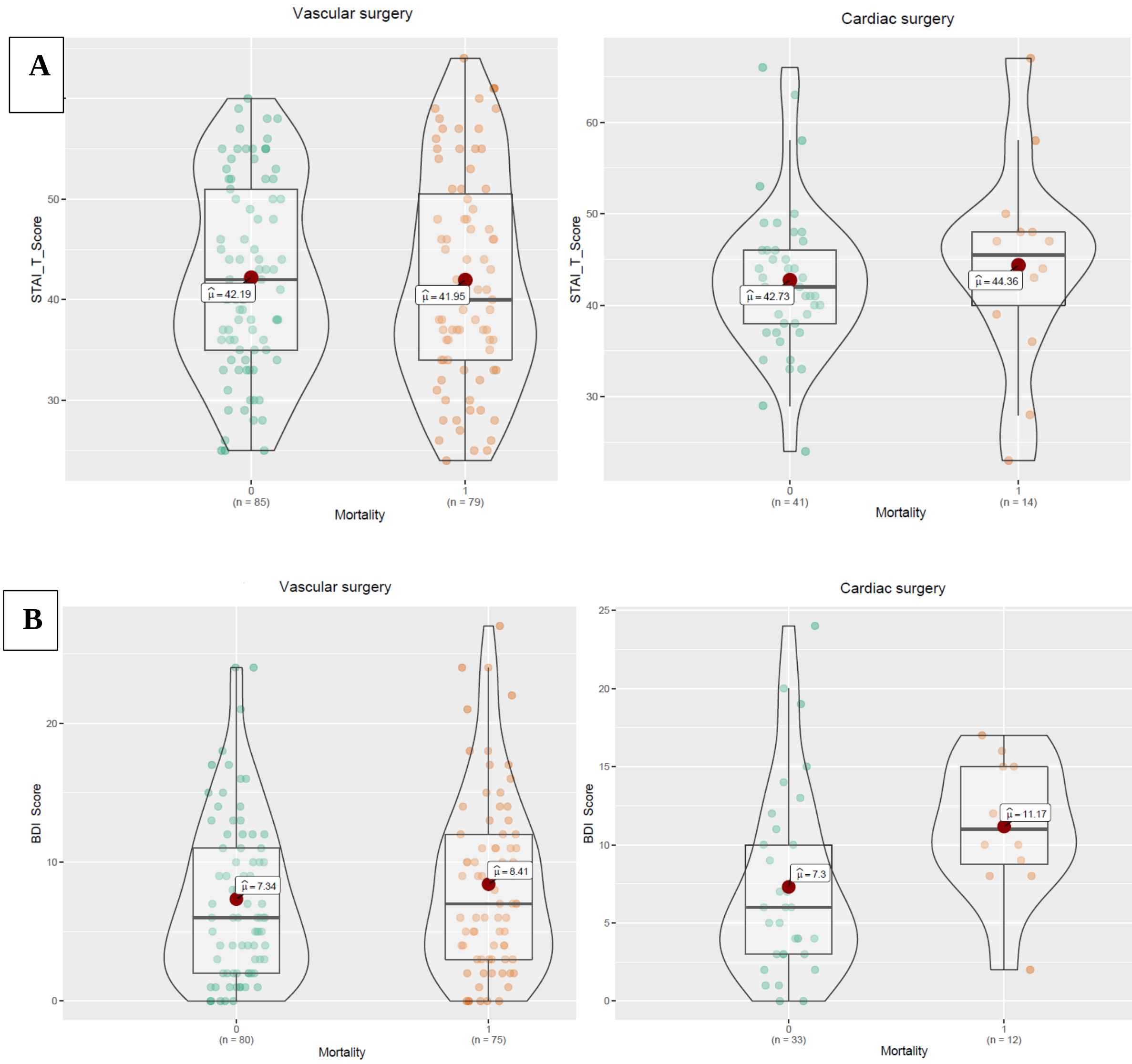


Figure 9. Violin plot diagrams about psychological variables according to surgery type and mortality. (A: Anxiety measured by STAI-T, B: depression measured by BDI) Difference in anxiety was not proven (STAI score 42.19 vs. 41.96, p=0.775 - in vascular surgery population and 42.73 vs. 44.36, p=0.514 – iv cardiac surgery population), in aspect of depression higher BDI score was found in cardiac surgery group (7.30 vs. 11.17, p=0.003), but no difference in vascular surgery group (7.34 vs. 8.41, p=0.294)

4.3.5. Reliability of our comprehensive frailty index model

Using receiver operating characteristic (ROC) analysis reliability of our model was tested. Reliability of comprehensive frailty index, traditional risk estimation methods (Euroscore II and vascular POSSUM) and the combined method were analyzed. Area under curve was found 0.632 according to the comprehensive frailty index, and 0.635 according to the traditional risk scores. The combination of the two methods raised the AUC to 0.654. The result was summarized on the Table 8.

DOI:10.14753/SE.2024.2930

Table 8. Receiver operating characteristic analysis of the different risk estimation scores

Test Result Variable(s)	Area	Std. Error	p-value	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Comprehensive frailty index	0.632	0.037	0.001	0.559	0.705
Estimated mortality	0.635	0.036	<0.001	0.564	0.706
Combined method	0.654	0.036	<0.001	0.583	0.724

5. Discussion

5.1. Study A

In our prospective study, cognitive dysfunction (measured by the Mini Mental State Examination) was found an independent risk factor for postoperative mortality in vascular surgical cohort. The MMSE score adjusted for age and education was associated with an increased mortality rate independently. Vascular surgical patients reported more social net support and more frequent use of alternative health care opportunities than the Hungarostudy population. (120)

Psychological features are essential elements of frailty syndrome, whose relative importance has increased in recent decades. (121, 122) The daily functioning state, polypharmacy, sarcopenia, and other comorbidities are examples of factors other than physical domains that are included in frailty syndromes that are now being recognised by healthcare professionals. (123) In our article, we try to emphasise how crucial the psychological effects of frailty syndrome, such as cognitive impairment.

It is obvious that having a poor functional status and being physically frail will lead to higher postoperative mortality rates. (62, 124-126) Recent research has, however, increasingly concentrated on the connection between preoperative cognitive abilities and postoperative mortality. (106, 127) According to our recent findings, using the MMSE score identifying cognitive dysfunction was associated with worse mid- and long-term survival. Nevertheless, a lower level of education was associated with worse survival in our previous study of patients undergoing cardiac surgery. A higher prevalence of depression or anxiety was not observed in this group, which could explain the results.

An established, well-known, and frequently used cognitive scale is the MMSE. Tools with greater sensitivity are currently available to detect mild cognitive impairment (e.g., MCI), despite its benefits. However, the MMSE has a high level of specificity for detecting cognitive decline. (128) Studies have reported utilizing modified cut-off values to improve the sensitivity of the test and thus increasing the tool's ability to identify cognitive deficits at an earlier phase. (83, 84) For the classification of cognitive functions, we used a different cut-off score for the MMSE to detect cognitive disabilities in a more precise manner. (64) The original and modified cut-off values for cognitive impairment cohorts (MMSE scores below 24 in the traditional group and less than 27 in the modified group) were associated with worse survival.

Contrarily, short-term survival was not significantly or directly impacted by preoperative cognitive deficits. After approximately 1,000 days of follow-up, patients with a mild cognitive deficit (MMSE score of 24-26) have a slightly different risk than those without cognitive dysfunction (MMSE score of 27–30) (result shown in Figure 1). Patients with MMSE scores of 23 points or less were found to have the highest mortality risk.

Previous studies that highlighted the significance of mental health issues like depression and anxiety contend that these concerns have a significant impact on short- and midterm survival. (109, 129) Our current dataset, however, was unable to demonstrate a strong correlation between the observed BDI, GDS, or STAI scores and the primary and secondary outcomes because the severity of depression is recognized as an important risk factor. In a recent article, Morin et al. concluded that the severity of depression may be a potential predictor of cognitive dysfunction and physical frailty. (130) Our prior study concluded a negative correlation between the severity of anxiety and survival in patients who underwent cardiac surgery. (109) Our most recent research led us to the conclusion that cognitive impairment primarily had a detrimental impact on patients undergoing vascular surgery's mid- and long-term survival.

Comparing the vascular surgical population to the general, healthy population was another goal of our study. After propensity score matching, the analysis demonstrates explicitly that the vascular surgical population has lower mobility, decreased physical activity, and worse smoking attitudes (Table 2). In various clinical contexts, the value of social support has been emphasized in a number of papers. (131-133) One unanticipated finding was that vascular surgical patients had higher self-reported social support scores. According to our research, patients undergoing vascular surgery or those with any other health issues perceive or at least experience higher levels of social support.

5.2. Study B

According to our most recent research, chronic opioid use prior to surgery may be a separate risk factor for mortality following vascular surgery. Additionally, long-term use of opioid derivatives was linked to both a decline in cognitive function as measured by the MMSE and more frequent depressive symptoms as measured by the BDI. Patients who had used opioids repeatedly saw an increase in the total frailty index. To find late complications and mortality, a lengthy follow-up was conducted. (134)

According to the earlier study, using opioids and their derivatives is linked to higher rates of morbidity and mortality following colorectal surgery (HR for morbidity: 1.43), [95% CI 1.07-1.91], $p<0.05$] and HR for mortality 1.48 [95% CI 1.05-2.08]). (135) Similar findings were found in our dataset, with a preoperative opioid user's mortality risk being significantly higher (AHR: 4.31 [95% CI: 1.77-10.55], p=0.001). Patients undergoing vascular surgery who used preoperative opioids reported longer hospital stays, but there was no discernible difference in postoperative mortality, according to Aizpuru et al. (136) The striking difference in our dataset is the elevated mortality risk. An extended hospital stay was also mentioned in a similar manner. The unfavorable effects of pharmacological substance use following heart surgery have been revealed in a prior study. (137)

Previous research has demonstrated that opioid users are more likely to experience cognitive impairment. This is in accordance with the results of the current study. (138) In individuals who had used opioids continuously before surgery, we discovered considerably poor scores on the MMSE.

Previous studies have indicated that opioid usage affects the severity of depression and health-related quality of life, but neither the GDS score nor the anxiety axis as measured by the STAI-T clearly showed a link. (139) On the basis of GDS and BDI scores, we evaluated the effects of chronic opioid usage on depressive symptoms. Our findings showed that BDI scores were considerably higher among opioid users, which is consistent with prior research.

The risk of postoperative morbidity and mortality can be estimated by using a commonly utilized risk stratification tool known as vascular POSSUM. (77, 80) The estimation improved with the frailty score was significantly better for the prediction of long-term mortality. Our current findings suggest that the concurrent use of multiple risk estimation scales and various markers could be useful in the short- and long-term prediction of mortality and mental health complications.

5.3. Study C

According to the results of the current investigation, the comprehensive frailty index is a significant, independent, and trustworthy predictor of the long-term mortality of vascular and cardiac surgery patients. Any increase in the patient's frailty index, regardless of how slight, could have negative effects. The current frailty index was created using biological, functional, sociological, cognitive, and psychological components, which were then grouped into four basic frailty domains. (140)

In summary, the most frail patient population had a mortality risk that was more than three times higher than that of the least frail cohort. (140)

There was no evidence of the comprehensive frailty index having any effect on short-term mortality in the clinical context according to the study. The estimated postoperative mortality calculated by using Euroscore II and V-POSSUM showed a positive connection with the comprehensive frailty index. (140)

A growing number of original studies discuss frailty in certain categories, like people with vascular and cardiac surgery. The generic frailty concept's fundamental mechanisms should have broad applications. In the present study, a comprehensive frailty index was developed based on a comprehensive geriatric assessment. (123) The significance of frailty and the preoperative diseases and illnesses that we included in our frailty index was recently highlighted in a meta-analysis. (141) That article clearly showed significant elevated risk of mortality among patients undergoing transcatheter aortic valve implantation caused by frailty (TAVI or TAVR) (HR: 2.16, 95% CI: 1.57–3.00). Our current findings confirmed the increased risk for mortality (AHR=1.384, 95% CI: 1.140-1.680, p=0.001) in our vascular and cardiac surgical cohort.

An article by Afilalo et al. that examined a group similar to our own was published. The authors of this study compared 7 different frailty tools. In the cohort of 1020 patients who underwent surgical or transcatheter aortic valve replacement (TAVR) procedures, there was a prevalence of frailty ranging from 26% to 68%. The Essential Frailty Tool (EFT) – a multidimensional but condensed approach like ours – was among the strongest tools. It had a significant impact on one-year mortality (adjusted odds ratio: 3.72; [95% CI: 2.54 to 5.45]), improving the C-statistic by 0.071 ($p<0.001$) and the integrated discrimination by 0.067 ($p<0.001$). (20)

It is hypothesized that as time passes after surgery, the comprehensive frailty index's mortality prediction gets stronger. Frailty parameters after endovascular techniques for aortic repair did not demonstrate any association with short- and mid-term mortality, according to a recently published article. (142) Short-term mortality is strongly influenced by preoperative physical and surgical factors, as well as by the type of surgery, perioperative risk factors, and postoperative complications.

Shi et al. investigated Lee score and frailty in patients who had artificial aortic valve implantation to see if they could predict mortality and functional decline with severe symptoms. (106) Their frailty index accurately predicted mortality in the surgical group but was unable to predict mortality in a cohort of patients who underwent transcatheter intervention. In the surgical population, however, the Lee score had a more precise predictive value. In addition, compared to our findings (AHR (95% CI) in quartiles 2, 3 and 4 compared to quartile 1 as a reference: 1.974 (0.982-3.969), 2.306 (1.155-4.603), and 3.058 (1.556-6.010), respectively), they reported a marginally higher adjusted hazard ratio for poor outcomes.

There was no difference in 30-day mortality or complications among patients with severe aortic stenosis who underwent TAVR or valve replacement surgery, but there was a difference in the length of hospital stay and the 1-year all-cause mortality. When the frail and fit groups were clustered in this study, the adjusted hazard ratio for mortality in the frail group was 3.51 (95% CI 1.4-8.5, $p=0.007$). The fourth quarter of the comprehensive frailty index, which represents our most frail group, is where these findings most closely match our findings. (143)

A similar single-centre prospective cohort examination represented slightly matching findings (OR: 3.68 [95% CI 1.21–11.19], $p=0.02$) using their own comprehensive frailty assessment built up with cognitive, psychological, and functional tests in TAVR patients. Furthermore, they verified a strongly elevated risk for 30-day mortality and major adverse cardiovascular and cerebral events (MACCEs) and 1-year MACCEs. (144)

Our models are consistent with the findings in the literature in terms of reliability. The c-statistic was found to be between 0.632 and 0.654 as the accuracy of our unadjusted and adjusted models were checked by receiver operating characteristic (ROC) curves. The general population admitted to the intensive care unit (ICU) was found to have nearly the same reliability in a previous retrospective cohort study with 24,499 patients. They assessed the accuracy of various frailty scoring systems in predicting mortality over 30-, 90-, and one-year periods. Using the c-statistic, they compared the performance of the Clinical Frailty Score, the Frailty Index - Acute Care, and the Changes in Health, End-Stage Disease, Signs, and Symptoms Scale (CHESS). Their prediction model was more accurate among ICU patients without a need for mechanical ventilation (c- stat: approx. 0.64) and slightly weaker in the mechanically ventilated group (s- stat: approx. 0.62). (25)

Clustering in this study was done artificially using the comprehensive frailty index quartiles. Exact cut-off values for different categories have not been shown in the literature to produce the different content of the described indices. To define and understand the variations in the patient's frailty status, categorization is practical. On the other hand, we cannot rule out regional variations in things like psychosocial status and access to healthcare. We can therefore rationalize employing quartiles in our multidimensional frailty approach rather than cut-off values.

5.4. Significance of the studies

Identifying patients' frailty has become a common practice in risk assessment. Recent literature claims and findings suggest that more risk estimation techniques are being developed in addition to the fact that clinicians are more frequently working with a population that is significantly frail. A thorough risk estimation method is more necessary than ever as the general population ages and as the prevalence of sarcopenic obesity, diabetes, and cardiovascular diseases rises. (145) The importance of our work is further highlighted by the fact that complex invasive interventions are being carried out on the elderly population more frequently.

5.4.1. Strengths of this study

The idea of frailty and knowledge of preoperative risk management are becoming more important in our everyday work. In the current study, regardless of the type of cardiovascular surgery, the significance of various unconventional risk factors was emphasised and demonstrated in terms of long-term mortality.

5.5. Limitations

The relatively small sample size must be mentioned as a limitation. We lacked the necessary participant numbers in particular fields to achieve the required statistical power. Due to the low prevalence of opioid use, there was insufficient statistical power and rigid/strict power of adjustment. To distinguish between these psychological variables, which have a fairly large variance, further investigation is required.

Because this was a single-centre study, the results should be interpreted with caution.

Another limitation is the lack of examining of patients’ physiological frailty and physical states. Our patient cohort generally has poor mobility. Usually, the absence of mobility is caused by a minimal (sometimes zero) effort threshold to pain due to extensive arterial circulation insufficiency. Therefore, physical tests like walking or chair-raising may have produced inaccurate results in cases of peripheral arterial disease and lower limb ischaemia.

The comprehensive frailty estimation process's length is a further downside. Depending on each patient's ability, limitations, and current health status, the comprehensive method that is being presented could require a lot of time. To find the most accurate but comprehensive frailty estimation method, further research should be carried out.

6. Conclusions

The purpose of my research work was to investigate risk factors in preoperative settings. Among vascular and cardiac surgical patients, various factors were examined and evaluated as potential risk factors for mortality. During the process, the focus was on those factors that had not received much interest at the time in the perioperative routine risk assessment.

In Study A, after an extended analysis, a significant relationship was identified between the patients' preoperative cognitive dysfunction and worse long-term mortality. Thus, the following conclusions were drawn.

A/1. Based on our findings, cognitive mapping should be applied to estimate the postoperative mortality risk more accurately in the future. The presence of the mildest cognitive impairment in the preoperative period potentially represents a risk factor for increased mid- and long-term mortality after vascular surgery.

A/2. The MMSE was used to assess cognitive impairment with modified cut-off values to obtain a more sensitive estimate. Sadly, we are just past the two-year COVID lockdown period, which included infrequent check-ups and a lack of face-to-face connections. Patients with low MMSE scores can disappear from health care, as they will not ask for an appointment with the doctors.

A/3. During the analysis of socioeconomic characteristics, the vascular surgery group reported significantly higher social support than the general control group (based on the Hungarostudy cohort), as measured using the Caldwell Social Support Dimension Scale.

The subanalysis of the vascular surgical patient cohort showed that (B/1.) chronic, preoperative opioid derivate use may have a negative impact on postoperative mortality. The increasing number of patients who regularly use opioid derivatives (either medicinally or illicitly) further emphasizes the importance of the current findings. In accordance with previous findings in the literature on the negative effect on mortality, an impact on the incidence and severity of depression symptoms and cognitive impairment was also demonstrated (B/2.). While these problems led to the strengthening of guidelines and prescriptions in the United States and in a couple of European countries, general practitioners in Hungary will prescribe opioid derivates very easily without considering the enormous side effects and cognitive decline in these cases. A multimodal, modern approach and pain clinics would help in the management of chronic pain therapy. Recently, several medications and therapies have been developed to replace opioids.

There was an urgent need for a comprehensive approach, and thus, a comprehensive frailty index was created. To develop this scoring system, we reviewed the literature and registered our indicators, and common points were identified. Variables were categorized and ranked into 4 domains. Finally, we can draw the following conclusions:

C/1. A comprehensive frailty index could be a useful and reliable method for estimating long-term mortality among vascular and cardiac surgery patients.

This extensive approach to frailty is necessary to correctly describe patients' preprocedural risk to securing optimal care and follow-up for the patients, thus increasing the quality-adjusted life years. Using a comprehensive frailty index in parallel with traditional risk estimation methods could be more accurate for calculating the patients' preoperative risk and prognosis, especially their risk of long-term mortality.

DOI:10.14753/SE.2024.2930

7. Summary

The purpose of my research work was to investigate risk factors in preoperative settings. Among vascular and cardiac surgical patients, various factors were examined and evaluated as potential risk factors for mortality. During the process, the focus was on those factors that had not received much interest at the time in the perioperative routine risk assessment. These factors are related to frailty syndrome, which is a lesser-known clinical condition that is associated with postprocedural mortality, morbidity, and quality of life.

During my research work that is summarized in this thesis, the effect of mild cognitive impairment on long-term mortality was identified in the vascular surgical patient cohort. The Mini Mental State Examination with modified cut-off values can be used detect clinically significant cognitive dysfunction. Preoperative chronic opioid derivative administration could also be a predictor of long-term mortality in these patients. Chronic opioid use is related to a higher rate of depression, anxiety, and loss of cognitive performance.

The comprehensive frailty approach showed a useful method to estimate cardiac and vascular surgical patients' preoperative frailty status. For this purpose, a multidomain frailty index was created using widespread indicators for different aspects. However, comprehensive frailty mapping could be a time-consuming process, and its usefulness for estimating long-term mortality was proven in our cohort.

Our findings could be useful during preprocedural risk stratification, thereby making risk assessment more precise. A more accurate estimation can help to identify patients who need rehabilitation. Furthermore, this precision can lead to correct choices regarding the optimal treatment for our patients, especially in difficult cases.

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10. Acknowledgements

First of all, I would like to announce my special thanks to my supervisor, Professor Dr. Andrea Székely, without whom this Ph.D. thesis could not have been completed. I received guidance, encouragement, as well as continuous support from her during my studies, and I could turn to her for any advice whenever I needed. She always has new ideas which are motivating us during our work.

I am grateful to the Head of the Department, Professor Dr. Béla Merkely, for providing us the possibility to accomplish our work.

I would also like to say thanks my Ph.D. associates, Dr. Ádám Nagy, Dr. Krisztina Tóth, Dr. Ágnes Sándor, Dr. Balázs Szécsi and Dr. Csaba Eke who were helpful colleagues during our research.

My appreciation also goes to the Student's Scientific Association member Dr. Rita Szentgróti, who did their job with great enthusiasm.

My sincere thanks go all to the nurses and doctors working at the Cardiovascular Surgical Intensive Care Unit and Heart Transplant Intensive Care Unit of Heart and Vascular Center, Semmelweis University.

And finally, I am very grateful to my family for all the support and patience they have shown me during my PhD studies.