EXAMINATION OF METABOLIC, HORMONAL, AND FRAILTY FACTORS AFFECTING MORTALITY IN ELECTIVE CARDIAC SURGERY

PhD thesis

Krisztina Tóth MD

Doctoral School of Theoretical and Translational Medicine

Semmelweis University

Supervisor: Andrea Székely, MD, PhD, med. habil, DSc, MTA

Official reviewers: János Tamás Varga MD, PhD, med. habil
Ákos Csomós MD, PhD, med. habil

Head of the Complex Examination Committee:
Gyula Domján MD, PhD, MTA

Members of the Complex Examination Committee:
Barna Babik MD, PhD
Katalin Keltai MD, PhD
Edit Dósa MD, PhD

Budapest
2023

Table of Contents

List of Abbreviations

AHR	Adjusted Hazard Ratio
ASD	Atrial Septal Defect
BDI	Beck Depression Inventory
BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CONUT	Controlling Nutritional Status
COPD	Chronic Obstructive Pulmonary Disease
CRP	C Reactive Protein
GNRI	Geriatric Nutritional Risk Index
HR	Hazard Ratio
HS	Hungarostudy
IBW	Ideal Body Weight
ICU	Intensive Care Unit
IQR	Interquartile Range
MELD	Model for End-Stage Liver Disease
NYHA	New York Heart Association Functional Classification
PBW	Present Body Weight
PNI	Prognostic Nutritional Index
SD	Standard Deviation
STS	Society of Thoracic Surgeons
TIA	Transient Ischemic Attack
TSH	Thyroid Stimulating Hormone
T_3	3,5,3′-Triiodothyronine
T_4	3,5,3′,5′-Tetraiodothyronine; also known as thyroxine

1. Introduction

Accurate pre-operative risk stratification is an important step in optimizing the patient's condition and ensuring the best possible post-operative outcome. Several well-developed scoring systems to estimate outcomes after surgery (1). Cardiac surgery is associated with disruption of homeostasis, triggering systemic inflammatory responses in the body in a way that it increases the chance for complications during postoperative recovery (2). In clinical practice, assessment and possible intervention before cardiac surgery have become an important issue in aiding postoperative recovery. There is no consensus yet in the international literature about the perfect scoring system (3). Frailty can be approached from two aspects; that is, the phenotypic and the accumulation of deficits approach (summed up in an index). The phenotypic approach contains physical deficiencies as elements, namely unintentional weight loss, fatigue, slow gait, and weakness (4). A meta-analysis collected 19 observational studies in which 66 448 patients were assessed for frailty and concluded that frail patients had a 1.5 times greater risk for prolonged hospital stay and 3 times risk of mid-term mortality. There is still no agreement which frailty scoring system is the best to use. The 19 studies examined used different methods (Bespoke Frailty Score, Katz Index, Fried/Modified Fried, Clinical Frailty, etc.) (5). Factors contributing to frailty consist of cellular and systemic physiological changes, including reduced nutritional intake, sarcopenia, associated comorbidities, and low physical activity (6).

Reduced levels of thyroid hormones were associated with elevated vascular resistance, decreased cardiac output, and immune dysfunction (7, 8). In case of cardiac transplantation, preoperative endocrine hormone levels play an important role, they have a connection with postoperative outcomes (9, 10). Some studies have emphasized the relationship between coronary artery disease and low testosterone levels (11-13). It is unclear if prolactin level has any predictive value before cardiac surgery. Haring et al. during a ten-year follow-up found that prolactin was associated with higher all-cause and cardiovascular mortality (14). A low number of cases (27 men) were examined who had normal prolactin levels and untreated hypertension, and the study found that during the diurnal peaks in prolactin, reduced endothelial function can be a possible cause of elevated blood pressure (15). The Framingham Heart Study examined more than 3000 patients, and it has found that there was association between prolactin levels and cardiovascular risk (16). Landber et al. found that different prolactin levels were associated neither with markers of heart failure, nor with cardiovascular mortality (17).

Assessment of preoperative nutritional status and, if necessary, prehabilitation are routinely assessed in some types of surgery (for example, colorectal or upper gastrointestinal surgeries) using the ERAS protocol (18). The international literature has not yet agreed on a system for estimating preoperative nutritional status in cardiac surgery. Cardiac cachexia and malnutrition play an important role in mortality after cardiac surgery, with a mortality rate of 20-40% per year (19). Both chronic malnutrition and iatrogenic malnutrition caused by reduced oral intake during preoperative hospital stay and the fasting period immediately before the operation contributes to the nutritional status of the patient(20).

Markers often used to assess malnutrition are albumin levels (21), and BMI scores (22), although with limitations, as albumin can be influenced by liver function and patients can be malnourished even normal or high BMI scores (23). Elderly patients are more susceptible to malnutrition, leading to an increased risk of infections, longer hospital stay, and death (24, 25).

2. Objectives

The aim of our project was to investigate additional risk stratifications to the routinely used medical variables in case of elective cardiac surgery.

Higher surgical mortality, extended length of hospital and intensive care unit (ICU) stay, and discharge to secondary nursing care have been observed in patients with poor outcome (26). The impact of frailty was analyzed in critical care and acute cardiac settings by the Acute Cardiovascular Care Association (ACCA) and by the European Society of Cardiology (ESC) (27). There are two descriptions for frailty: the cumulative deficit and the phenotype model (5 items: low physical activity, reduced grip strength, unintended weight loss, slow gait speed, and self-reported fatigue). We have hypothesized, that higher frailty scores (Comprehensive Geriatric Assessment based Frailty, Modified Frailty Index-11) are associated with higher postoperative mortality in elective cardiac surgery patients and these assessments add to the traditional risk factors.

The relationship between thyroid hormones and the cardiovascular system (including heart rate, myocardial contraction, blood pressure, smooth muscle tone, inflammatory pathways, etc.) is well known (7). Both hypothyroidism (decreased heart rate and contraction, therefore lower stroke volume, oedema, hypertension, prolonged QT, etc.) and hyperthyroidism (increased heart rate and contraction, thereby higher cardiac output, atrial fibrillation, etc.) are associated with cardiovascular changes that increase morbidity. Patients with euthyroid sick syndrome have lower laboratory parameters, but they are not hypothyroid, as probably these parameters indicate a maladaptive or adaptive response (28). The review of Bianchi et al. suggests that testosterone has a favorable effect on the cardiovascular system and the low serum level has a role in cardiovascular mortality (29).On the other hand, few longitudinal studies found that decreased testosterone levels do not have a predictive value in further cardiovascular events (30, 31). The role of prolactin in preoperative risk stratification is still unclear, as some studies have shown an association, some proved that there is none. Our hypothesis was that off-range thyroid, prolactin, and testosterone levels are associated with postoperative mortality in elective cardiac surgery patients.

An accurate assessment of the nutritional status is essential component in frailty and therefore in the postoperative outcome. Nutritional scoring systems often used in different types of surgeries are Geriatric Nutritional Risk Index (GNRI), COntrolling NUTritional Status (CONUT), and Prognostic Nutritional Index (PNI). They can be easily calculated by using standard body weight and laboratory data, such as serum albumin, total cholesterol, and lymphocyte counts. We have hypothesized that lower (GNRI, PNI) or higher (CONUT) nutritional score is associated with postoperative mortality in elective cardiac surgery patients.

3. Methods

3.1 Frailty study

The study was conducted in the Department of Cardiac Surgery of the Heart and Vascular Centre, Semmelweis University. It was a prospective cohort investigation with an approval of the Regional Ethics Committee (SE-TuKEB 250/2013) and registered on ClinicalTrials.gov (NCT02224222). This study was part of a larger recruitment which included vascular and cardiac surgery patients. Eighty-five elective cardiac surgery patients were enrolled between September of 2014 and August of 2017. All participants understood and signed the informed consent. All instruments were created following the relevant guidelines and regulations (Declaration of Helsinki). The inclusion criteria were 1) age over 18 years and 2) elective cardiac surgery. Exclusion criteria were 1) pregnancy and 2) legal incapacity or limited ability to understand the procedures and ethical approval. In terms of cardiac condition there were no restrictions. Eight patients were unable to complete the questionnaire, six participants were excluded because of surgical cancellation, and two patients had transcatheter aortic valve implantation or heart transplantation. The more detailed methodological description can be found in our published article (32).

Mortality was the primary outcome. Last assessed on November 2, 2020. The 1-year; 2-year and overall mortality were examined. Study population was compared to the Hungarian population retrieved from the Hungarostudy (HS) database.

3.1.1 Data collection and scoring systems

Participants' clinically relevant factors, such as previous comorbidities, preoperative lab parameters (ion homeostasis, blood count, renal function, etc.), intraoperative items (length of operation, length of cross-clamp, amount of blood loss, etc.), and postoperative parameters (postoperative medication, length of ventilation, ICU stay, hospital stay, etc.) were collected and analyzed the definition of the Society of Thoracic Surgeons (STS) of postoperative complications (multi-system organ failure, sepsis, renal dialysis, ICU readmission, cardiac arrest, reoperation for bleeding, etc.) was followed (33). The New York Heart Association Functional Classification (NYHA) (34) and the logistic

European System for Cardiac Operative Risk Evaluation (EuroScore II) (1) were used as risk stratification. Perioperative risk assessments used in the different studies shown in Table 1.

3.2 Endocrine study

The Endocrine study was a prospective cohort investigation with an approval of the Regional Ethics Committee (SE-TuKEB 35287-2/2018/EKU) and registered on ClinicalTrials.gov (NCT03736499). Three hundred and six people were enrolled between July 2018 and June 2020. All participants understood and signed the informed consent. All instruments were made following the relevant guidelines and regulations (Declaration of Helsinki). The inclusion criteria were 1) age over 18 years and 2) elective cardiac surgery. Exclusion criteria were 1) pregnancy and 2) legal incapacity or limited ability to understand the procedures and ethical approval. In terms of cardiac condition there were no restrictions. Forty-six patients were excluded because there were no endocrine laboratory results available, in six cases surgery was delayed beyond the time frame of the study, and two participants had other type of surgery. Mortality was the primary outcome measure. The survival rate of the study participants was last assessed on February 16, 2021. The 30-day, 1-year, and overall mortality rates were examined. More detailed methodological description can be found elsewhere (35).

3.2.1 Data collection and scoring systems

Beside the variables collected in the first study such as clinically relevant factors, preoperative lab parameters, intraoperative and postoperative items, different types of nutritional scores, preoperative endocrine levels, and different types of frailty assessment were evaluated and added to the database in a prospective manner. Risk scores used in the different studies shown in Table 1.

Table 1. - **Perioperative risk assessments used in different studies**

Risk Scores	Studies
Comprehensive Geriatric Assessment based Frailty (CGA)	• Frailty study
Modified Comprehensive Geriatric Assessment based Frailty (mCGA)	• Endocrine study
Modified Frailty Index-11	• Endocrine study
Geriatric Nutritional Risk Index (GNRI)	• Frailty study • Endocrine study
Controlling Nutritional Status (CONUT)	• Endocrine study
Prognostic Nutritional Index (PNI)	• Endocrine study
Model for End-Stage Liver Disease-Na (MELD-Na)	• Endocrine study
Model for End-Stage Liver Disease-XI (MELD-XI)	• Frailty study

3.3. Frailty Score

Frailty score had no role in therapeutic decision-making in either the Frailty study or the Endocrine study. The scores were calculated only after all patients got involved in the studies. It was calculated at the time of preoperative assessment. The detailed scoring systems are shown in Table 2.

3.3.1. Comprehensive Geriatric Assessment based Frailty (CGA)

We used previous medical history as recorded on the medical charts of the patients to obtain non-cardiac and cardiac history. Pre- and post-operative lab parameters were collected and analyzed. The scoring system was based on the CGA model with four main domains including medical history, functional limitations, cognition, and nutrition with a scoring range between 0–41 (32).

3.3.2. Psychosocial factors

The patients were asked to complete a questionnaire maximum 30 days before the surgery with the help of a trained nurse or medical student. The survey contained several psychosocial questionnaires [Geriatric Depression Scale (GDS), Beck Depression Inventory (BDI), Mini Mental State Examination (MMSE), Spielberger State-Trait Anxiety Inventory (STAI-S, STAI-T), Somatic Symptom Severity Scale (Patient Health Questionnaire 15 (PHQ15)), Caldwell Social Support Dimension Scale (CSSDS), Athens Insomnia Scale Inventory] and a short form of the Hungarostudy 2013 survey. Detailed description of the surveys can be found elsewhere (36).

3.3.3. Modified Frailty Index-11

We calculated the frailty score with the modified frailty index of the American College of Surgeons (ACS) National Surgical Quality Improvement Program (37). It has three main domains, that is, comorbidities, cognitive impairment, and functional impairment. The functional impairment was based on the GCA, nurses were asked two yes or no questions: Does the patient need help with moving and does the patient need help with grooming? If the answer was yes to one of them 1 point was given, and the maximum point was 2. The scores were divided into five equal groups (35).

Table 2. – **Assessment of different types of frailty scoring systems**

Modified Frailty Index 11		**Modified Comprehensive Geriatric Assessment based Frailty**		**Comprehensive Geriatric Assessment based Frailty**	
Medical comorbidities	Congestive heart failure (within 30 days of surgery)	**Cardiovascular**	Angina	**Cardiovascular**	Angina
	Diabetes mellitus (insulin dependent or noninsulin dependent)		Atrial fibrillation or flutter		Atrial fibrillation or flutter
	History of angina 1 month before surgery		Congestive heart failure		Congestive heart failure
	Cerebrovascular accident or stroke with neurologic deficit		Coronary artery disease		Coronary artery disease (based on cardiac catheterization)
			Diabetes mellitus (insulin dependent or noninsulin dependent)		Diabetes (history or use of insulin or oral hypoglycaemic drugs)
			Hypertension		Hypertension (history, blood pressure ≥140/90Hgmm, or use of antihypertensive drugs)
			Myocardial infarction		Myocardial infarction

Modified Frailty Index 11		Modified Comprehensive Geriatric Assessment based Frailty		Comprehensive Geriatric Assessment based Frailty	
Medical comorbidities	Chronic obstructive pulmonary disease	**Cardiovascular**	Peripheral vascular disease	**Cardiovascular**	Peripheral vascular disease
			Stroke or transient ischemic attack		Stroke or transient ischemic attack
		Noncardiovascular	Arthritis	**Noncardiovascular**	Anxiety
			Asthma		Arthritis
	Current pneumonia		Chronic kidney disease (Glomerular Filtration Rate<60 ml/min)		Asthma
					Cancer diagnosed within 5 years or metastatic cancer
					Chronic kidney disease (estimated Glomerular Filtration Rate <60 ml/min)
	Hypertension		Falls in the past year		Chronic obstructive pulmonary disease
					Depression (medical history or 5-item Geriatric Depression Scale score ≥2)
	History of myocardial infarction 6 months before operation		Sensory impairment		Degenerative spine disease (sciatica or spinal stenosis)
					Sensory impairment (hearing or vision impairment)
	Previous percutaneous coronary intervention or cardiac surgery				Fall in the past year
		Premedication	5 or more medicines taken	**Premedication**	5 or more medicines taken

Modified Frailty Index 11		Modified Comprehensive Geriatric Assessment based Frailty		Comprehensive Geriatric Assessment based Frailty	
Medical comorbidities		**Nutrition**	Serum albumin <3.50 g/dL	**Mini-Mental State Examination score**	27-30 points 24-26 points 21-23 points <21 points
	History of revascularization or amputation for peripheral vascular disease		Body mass index <21 kg/m²	**Nutrition**	Serum albumin <3.5 g/L
					Body mass index <21 kg/m^2
					Unintentional weight loss > 4.5 kg in the past year
		Rosow-Breslau	Unable to walk a flight of stairs	**Nagi items**	Difficulty pulling or pushing large objects (e.g., living room chair)
Functional and cognitive impairment	Dependent functional health status (total or partial) at time of surgery				Difficulty with lifting or carrying 4.5 kg (e.g., heavy bag of groceries)
			Unable to do heavy work around the house		Unable to walk up or down a flight of stairs
			Unable to do heavy work around the house	**Rosow-Breslau**	Unable to do heavy work around the house
					Unable to walk a flight of stairs Unable to do heavy work around the house

3.4. Nutritional status

3.4.1. Model for End-Stage Liver Disease (MELD)

In order to accurately assess nutritional status, the current state of the liver was quantitatively measured. We calculated the MELD-Na and MELD-XI scores (38), which is the international normalized ratio (INR) excluded Model for End-Stage Liver Disease (MELD). MELD = [0.975 · ln (serum creatinine (mg/dl)) + 0.378 · ln (serum bilirubin (mg/dl)) +1.120 · ln (INR)+ 0.643] · 10). In order to avoid negative scores, items below 1 are taken as 1. The following formulas were used:

$$\boldsymbol{MELD-Na} = MELD - Na\left(\frac{mmol}{l}\right) - (0.025 \cdot MELD \cdot (140 - \mathrm{Na}\left(\frac{mmol}{l}\right)) + 140$$

$$\textbf{MELD-XI} = 5.1 \cdot \ln\left(total\ bilirubin\left(\frac{mg}{dl}\right)\right) + 11.76 \cdot \ln\left(creatinine\ \left(\frac{mg}{dl}\right)\right)$$

3.4.2. Geriatric Nutritional Risk Index (GNRI)

To investigate the nutritional status of the study population GNRI(25) score was calculated.

GNRI = 1.487 · ALB (g/L) + 41.7 · PBW/IBW (kg)

IBW = height^2 (m) · 22
PBW = present body weight
IBW = ideal body weight

If the serum albumin levels were not available, we used the 65 percentage of the total protein level. Continuous variables were divided into two groups based on the GNRI scores. If the score was greater than or equal to 91 points, it was assigned the value of 0, and if the score was less than 91 points, it was assigned the value 1. This classification was used in both the Frailty and Endocrine studies.

3.4.3. Controlling Nutritional Status (CONUT)

The CONUT score (39) contains 3 components: lymphocyte count, serum albumin level, and cholesterol level (Table 2.).

Table 3. **- Controlling Nutritional Status (CONUT)**

**Total lymphocyte (count/mm3): (White blood cells(G/L) · 1000) · (Lymphocyte (%)·0.01)*

***Cholesterol (mg/dl): Cholesterol (mmol/l) ·38.6*

Normal	Light	Moderate	Severe
serum albumin 3.5-4.5 (g/dL) ***1 point***	serum albumin 3.0-3.49 (g/dL) ***2 points***	serum albumin 2.5-2.9 (g/dL) ***4 points***	serum albumin <2.5 (g/dL) ***6 points***
total lymphocyte ≥1600 (count/mm3)* ***0 point***	total lymphocyte 1200–1599 (count/mm3) ***1 point***	total lymphocyte 800–1199 (count/mm3) ***2 points***	total lymphocyte <800 (count/mm3) ***3 points***
cholesterol >180 (mg/dl)** ***0 point***	cholesterol 140–180 (mg/dl) ***1 point***	cholesterol 100–139 (mg/dl) ***2 points***	cholesterol <100 (mg/dl) ***3 points***
Total points			
0-1	***2-4***	***5-8***	***9-12***

A few participants were categorized into the moderate and severe groups and they were merged into one group to avoid statistical bias.

3.4.4. Prognostic Nutritional Index (PNI)

PNI was calculated by the following formula:

$$\boldsymbol{PNI} = 10.00 \cdot serum\ albumin\left(\frac{g}{dL}\right) + 0.005 \cdot total\ lymphocyte\ \left(\frac{count}{mm3}\right)$$

If the PNI score (40) was greater than or equal to 48, we gave the score zero, while if it was less than 48, the score one was given.

3.5. Endocrine levels

Preoperative TSH (thyroid stimulating hormone), fT4 (thyroxine), fT3 (triiodothyronine), testosterone, and prolactin were collected and analyzed [with ARCHITECT TSH, Free T4, Free T3 (Abbott Laboratories, Ireland, 2015 (41-43)), prolactin (Abbott Laboratories, Ireland, 2006 (44)) and ARCHITECT 2nd Generation Testosterone system (Abbott Laboratories, Ireland, 2015 (45)) chemiluminescent microparticulate immunoassay]. The blood samples were frozen until all necessary samples were collected and were then measured together. Hormone levels were not involved in the therapeutic decision. Testosterone and prolactin levels were examined both for the whole population and by sex (Table 4.).

Table 1. - **Endocrine hormone levels grouped based on the blood levels**

	TSH (U/ml)	T3 (pmol/l)	T4 (pmol/l)	Testosterone (ng/ml)		Prolactin (U/ml)	
				Men	*Women*	*Men*	*Women*
Low	<0.29	<2.39	<11.99	<2.49	<0.09	<52.99	<39.90
Normal	0.30-4.20	2.40-6.30	12.00-22.00	2.50-9.50	0.10-0.90	53.00-360.00	40.00-560.00
Elevated	≥2.41	≥6.31	≥22.10	≥9.51	≥0.91	≥360.10	≥560.10

3.6. Statistical analysis

SPSS Version 22.0.(IBM Corp. Released 2013. IBM SPSS Statistics for Windows, NY, USA) statistical software was used to analyze the enrolled participants' data. Means and standard deviations (SD) for normally distributed data and medians and interquartile ranges (IQR, 25th to 75th percentiles) for nonnormally distributed data were used. The Kolmogorov-Smirnov test and the Shapiro-Wilk test were used to determine the type of distribution. Categorical variables were presented as numbers (n) and percentages. Chi-square-test was applied to investigate the categorical variables. Fischer's exact analysis was performed in case a categorical value contained fewer than 5 items. Mann-Whitney U test was used for continuous variables. In case of nutritional, frailty scores, and endocrine values, categorical variables were generated from continuous scales with cut-off values based on international literature. Correlation between items were investigated by Pearson's correlation. Follow-up time was calculated from the day of surgery until death or the last query. Cox regression (univariable and multivariable) was performed to analyze the endpoints. The confidence intervals were 95%. For the survival analysis Breslow tests and log-rank test with Kaplan–Meier analysis were applied. The Kaplan-Meier curves were made by using the jamovi project (2021, jamovi (Version 1.6) [Computer Software]). P values less than 0.05 were considered statistically significant.

The statistical analyses of the two projects differed in two aspects. In the first project PSMATCHING3 extension from R statistical software was also used to make a propensity matching between our cardiac population and the Hungarian patient cohort. Pairs were created from the Hungarostudy representative group and the elective cardiac population. The pairing was based on sex, age, place of residence, and legal status. The balance on baseline covariates were evaluated by using absolute standardized differences between the surgery and control groups. Acceptable standardized bias was a value less than 0.25. The differences in social state and psychological attitude were investigated by comparing the identical questions between the pairs. We compared our data (frailty study) with the healthy population of Hungarostudy 2013 (free access, face to face nationally representative household surveys, every 10 years, in Hungary, n=2000) to measure psychosocial background and health-related quality of life. Propensity score matching method was used on the identical questions. The comparison was made based on sex, residence, age, and employment state.

In the second project, the Cox regression categorical covariates method was used to analyze the differences between groups. The reference category was the first group. In the final multivariate model, a bootstrap method was performed to calculate the degree of over-optimism. The estimation was repeated on 1000 bootstrapped replicates. In the final model the covariates were fitted for each bootstrap sample. The covariates of the final multivariable models were fitted by applying the coefficients and were used to generate the C-indices.

4. Results

4.1. Descriptive data

4.1.1. Frailty study

We examined 69 patients who underwent elective cardiac surgery. The mean age was 65.33 (standard deviation (SD) ±9.83) years, and 63.8% (n=35) of the study population was male. The median EuroScore II was 1.56 (1.00–2.58). The detailed demographical data can be found in Table 1. of paper (32). The median follow-up time was 1,656 days, interquartile range (IQR 1,336-2,081 days). The median operation time was 180.0 min (IQR 153.50-213.75 min). The median hospital stay was 10.0 days (IQR, 8.0–14.0 days), and the median postoperative time spent in the ICU was 48.0 hours (IQR, 24.0– 72.0 hours). Regarding cardiopulmonary bypass time between survival and deceased groups, there was no significant difference (median 96.2 vs. 119.3 min). For detailed information on the types of surgery and their distribution, see Table 5. Six patients (8.9%) had postoperative complication [infection n=2 (2.9%), major bleeding requiring rethoracotomy n=1 (1.4%), multi-organ failure n=1 (1.4%), major thrombotic event n=2 (2.9%)].

We found significantly lower albumin levels in the deceased group. Both sodium level and GFR were lower in the deceased group. There was no significant difference in case of MELD-IX scores between survival and deceased groups.

Regarding chronic medication, use of Calcium channel blockers (p=0.057) and ACE-inhibitors tended to be higher in the deceased group compared to survivors.

4.1.2. Endocrine study

We examined 252 patients who underwent elective cardiac surgery, and 66.3% of them was male. The mean age was 64.2 years (SD ±11.1 years). The median EuroScore II was 1.71 (1.06-3.02). Detailed demographical data are shown in paper (32), Table 2 (35). The median follow-up time was 623 days (IQR 575-699 days). The median operation time was 180.00 min (IQR 157.00-215.00 min), time spent in the ICU was 29 (IQR 22.00-71.63) hours. The median hospital stay was 10 days (IQR, 8.0-14.0 days). Those who died had longer cardiopulmonary bypass times (survivors median 110.0 vs. deceased median 80.0 min) and needed prolonged mechanical ventilation (survivors median 10.25 hours vs. deceased median 22.50 hours)

Types of surgery are shown in Table 5. Fifty-nine patients had some postoperative complications (23.4%) [multi-organ failure n=3 (1.2%), infection n=18 (7.1%), need for permanent pacemaker n=15 (5.9%), bleeding requiring rethoracotomy n=11 (4.4%), ICU readmission n=3 (1.2%), other n=9 (3.6%) (cardiac tamponade, neurological disorder, etc.].

We found significantly lower albumin levels in the deceased group compared to those who survived. Hemoglobin levels were significantly lower (survival median 140.0 (g/l) (128.0-148.0) vs. deceased median 116.5 (g/l) (110.0-143.0) p=0.032) and CRP levels were statistically higher in the deceased group but not in a clinically relevant amount (survival median 2.2 (mg/l) (0.9-4.9) vs. deceased median 4.8 (mg/l) (1.3-13.3) p=0.021). Investigating chronic medications, the use of ACE-inhibitors (p=0.023) and Calcium channel blockers (p=0.017) were significantly higher in the survivor group.

Examining the first postoperative 72 hours, the vasoactive-inotropic support in the first postoperative 72 hours was significantly higher in the deceased group compared to the survived population.

Table 2. - **Distribution of different types of surgeries**

[a] CABG - coronary artery bypass grafting

[b] ASD - Atrial septal defect

	Frailty study		**Endocrine study**	
Type of surgery	**N**	**%**	**N**	**%**
Isolated CABG[a]	25	36	86	34
CABG+valve	2	3	14	6
Isolated valve	25	36	106	42
Combined valve	5	7	2	1
Valve +aortic	7	10	30	12
Other (ASD[b], myxoma)	5	7	14	6
	69		252	

4.2. Mortality

4.2.1. Frailty study

Fourteen patients (20.3%) died during the median 1,656 days (IQR 1,336-2,081 days) follow up. The number of in-hospital death was 2. Thirty-day mortality and one year mortality were n=3 (4.3%) and n=5 (7.2%), respectively. Second-year mortality was 2.9% (n=2). The detailed causes of 30-day-mortality are shown in Table 6.

4.2.2. Endocrine study

Thirty-three patients died during the median 623 days (IQR 575-699 days) follow-up. Thirty-day mortality was 7.5 % and the one-year mortality was 11.9 %. The detailed causes of death in the first 30 days can be found in Table 6.

Table 3. - **Cause of death in the first 30 days**

*%- looking at the whole population

Variables	**Frailty study**		**Endocrine study**	
	N	**%***	**N**	**%**
Multi-organ failure	2	2.30	5	1.98
Circulatory failure	1	01.45	4	1.59
Sepsis	-	-	6	2.38
Acute myocardial infarction	-	-	1	0.39
Bleeding, rethoracothomy	-	-	3	1.19

4.3. Nutritional status

4.3.1. Geriatric Nutritional Risk Index

4.3.1.1. Frailty study

In the frailty study, the GNRI adjusted for BMI was significant, independent predictor of overall mortality (AHR: 12.19, 95% CI: 2.81–52.85, P=0.001). In the univariable Cox regression, GNRI points less than 91 were associated with higher risk of mortality (HR: 5.75, 95% CI: 1.98–16.66, p=0.001). In the multivariable model, GNRI was independently associated with higher risk for overall mortality after adjustment for EuroScore II and postoperative complications (AHR: 4.76, 95% CI: 1.52–14.92, P=0.007). The results are plotted on a Kaplan-Meier survival curve (Figure 1.). We also examined the relationship of GNRI with MELD-IX and BMI. In case of overall mortality, GNRI remained a risk factor after adjustment to MELD-IX (AHR: 6.17, 95% CI: 2.10–18.13, p=0.001) and after adjustment to BMI (AHR: 12.19, 95% CI: 2.81–52.85, p=0.001).

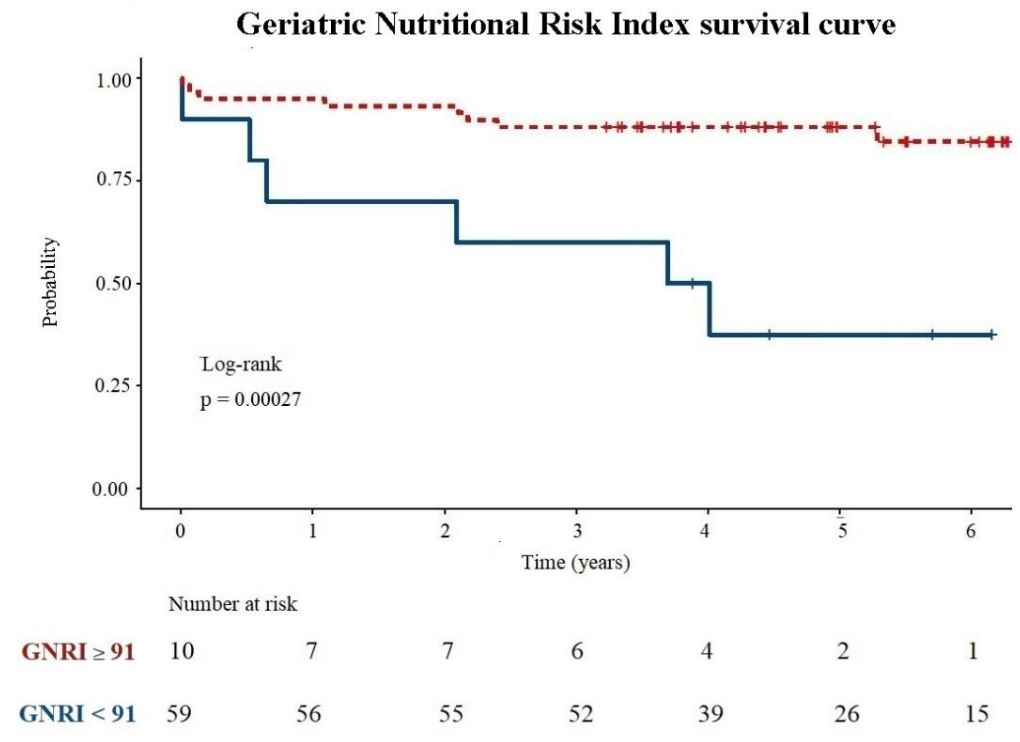

Figure 1. - **Kaplan-Meier survival based on the GNRI score** (red line: GNRI ≥91; blue line: GNRI <91). The picture above shows a log-rank test in a Kaplan-Meier curve. Follow-up time is given in years. GNRI, Geriatric Nutritional Risk Index (32)

4.3.1.2. Endocrine study

Univariate Cox regression showed that if the patients had with a GNRI less the 91 points, they had a higher risk for mortality (HR:5.97; 95% CI:2.58-13.79, p<0.001). Adjusted for EuroScore II and postoperative complications, GNRI scores were independently associated with mortality (AHR:4.384;95%CI:1.866-10.303, p=0.001). The results are plotted on a Kaplan-Meier survival curve (Figure 2.). We also observed correlation between the GNRI and MELD-Na scores (R: -0.509 p<0.001). In the multivariable Cox regression model, GNRI was found to be an independent predictor (HR:4.07; 95% CI:1.28-12.99, p=0.018). The c-index of multivariate models was 0.773 for GNRI.

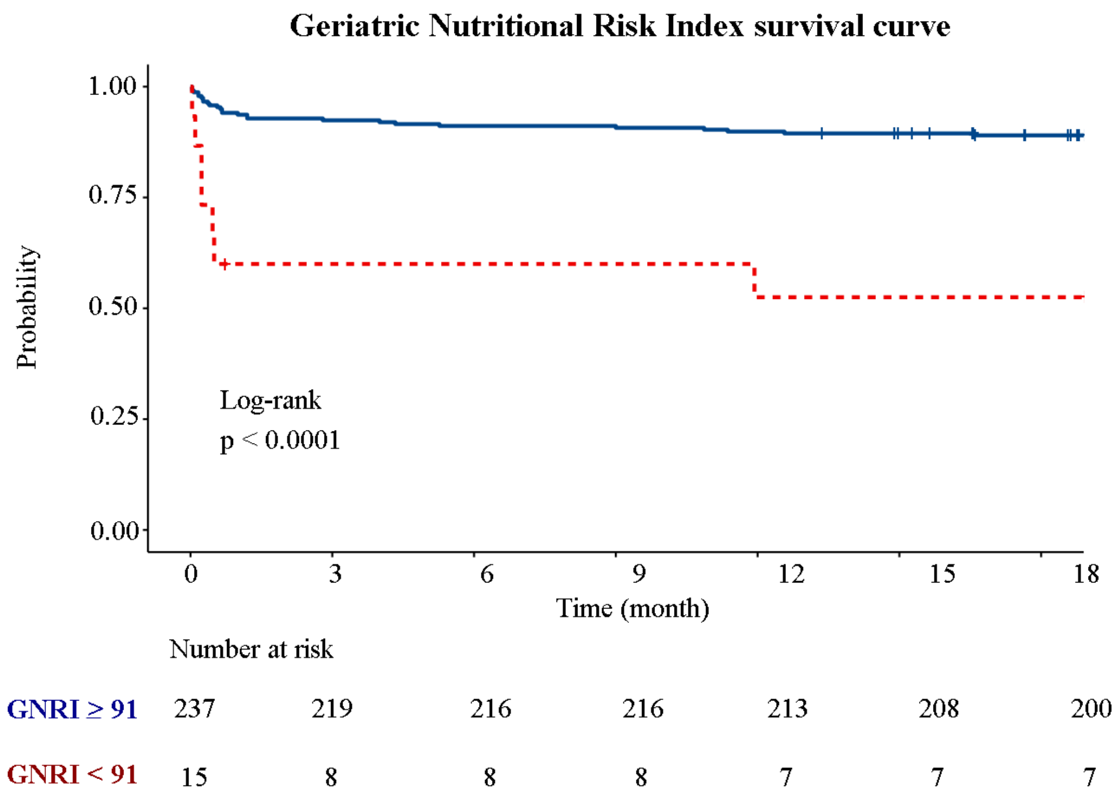

Figure 2. - **Geriatric Nutritional Risk Index survival curve**. Kaplan–Meier curves show the relationship between GNRI (Geriatric Nutritional Risk Index) and mortality. Blue line: GNRI ≥ 91 points; red line: GNRI<91 points. The figure shows that patients in the group with scores below the cut-off value lower scoring group had worse survival (35)

4.3.2. CGA-based Nutritional Score

4.3.2.1. Frailty study

CGA-based nutritional score and albumin had no correlation with BMI. Univariate Cox regression of CGA base nutritional score showed higher mortality risk in case of both 1-year mortality (HR: 6.74, 95% CI: 1.30–34.81, p=0.023) and 2-year mortality (HR: 5.37, 95% CI: 1.10–26.08, p=0.037).

4.3.2.2. Endocrine study

Univariate Cox regression showed no significant result neither in overall mortality (HR: 1.71, 95% CI: 0.82–3.59, p=0.152), nor in 30-day mortality (HR: 0.51, 95% CI: 0.8–3.28, P=0.478) or in 1-year mortality (HR: 1.01, 95% CI: 0.35-2.91, p=0.978).

4.3.3. Prognostic Nutritional Index

Examining the 252 patients in the Endocrine study, it was found that a PNI score less than 48 was associated with a higher risk for total mortality (HR:3.95; 95% CI:1.99-7.82, p<0.001). In multivariate Cox regression, PNI score less than 48 adjusted for MELD-Na was associated with overall mortality (HR:3.54;95% CI:1.72-7.32, p=0.001). In multivariate Cox regression, PNI < 48 points was associated with higher overall mortality (AHR:3.465; 95%CI:1.735-6.918, p<0.001) after adjustment for postoperative complications and EuroScore II. The c-index of multivariate models was 0.736 for PNI. The results are plotted on a Kaplan-Meier survival curve (Figure 3.).

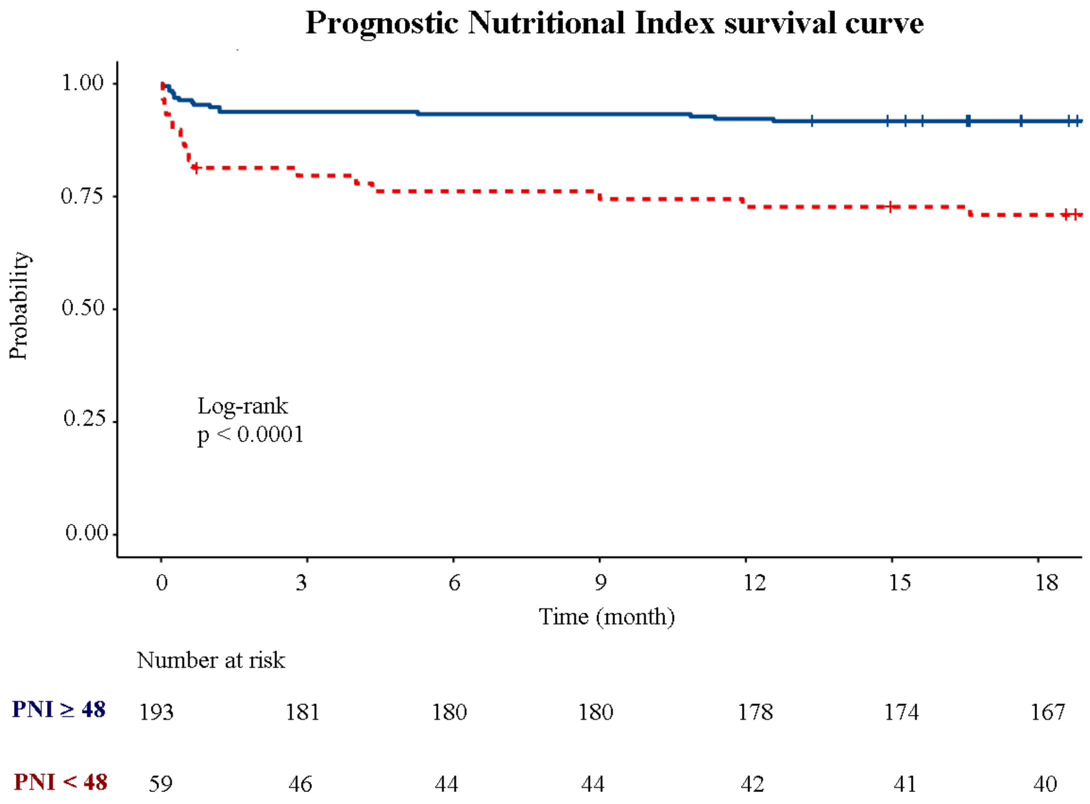

Figure 3. - **Prognostic Nutritional Index survival curve.** Kaplan–Meier curves show the relationship between PNI (prognostic nutritional index) and mortality. Blue line: PNI ≥ 48 points; red line: PNI < 48 points. The figure shows that patients in the group with scores below the cut-off value had worse survival (35)

4.3.4. Controlling Nutritional Status

Applying the 4-group model of the CONUT score, the groups with higher CONUT points (HR:1.81; 95% CI:1.13-2.89, p=0.013) were associated with a higher risk for overall mortality. In the 3-group model the higher CONUT scores were associated with higher overall mortality risk (HR:1.82; 95% CI:1.10-3.03, p=0.021). In the multivariate Cox regression model, the CONUT 3-group model was not associated with 30-day mortality (AHR:1.22; 95%CI:0.65-2.29 p=0.519) and 1-year mortality (AHR:1.45; 95% CI:0.86-2.47 p=0.166), after adjustment for EuroScore II and postoperative complications. In the same multivariable model, CONUT 3-group model was associated with higher risk of overall mortality (AHR:1.736; 95%CI:1.736-2.866 p=0.031). The c-index of multivariate models was 0.672 for CONUT. The results are plotted on a Kaplan-Meier survival curve (Figure 4.).

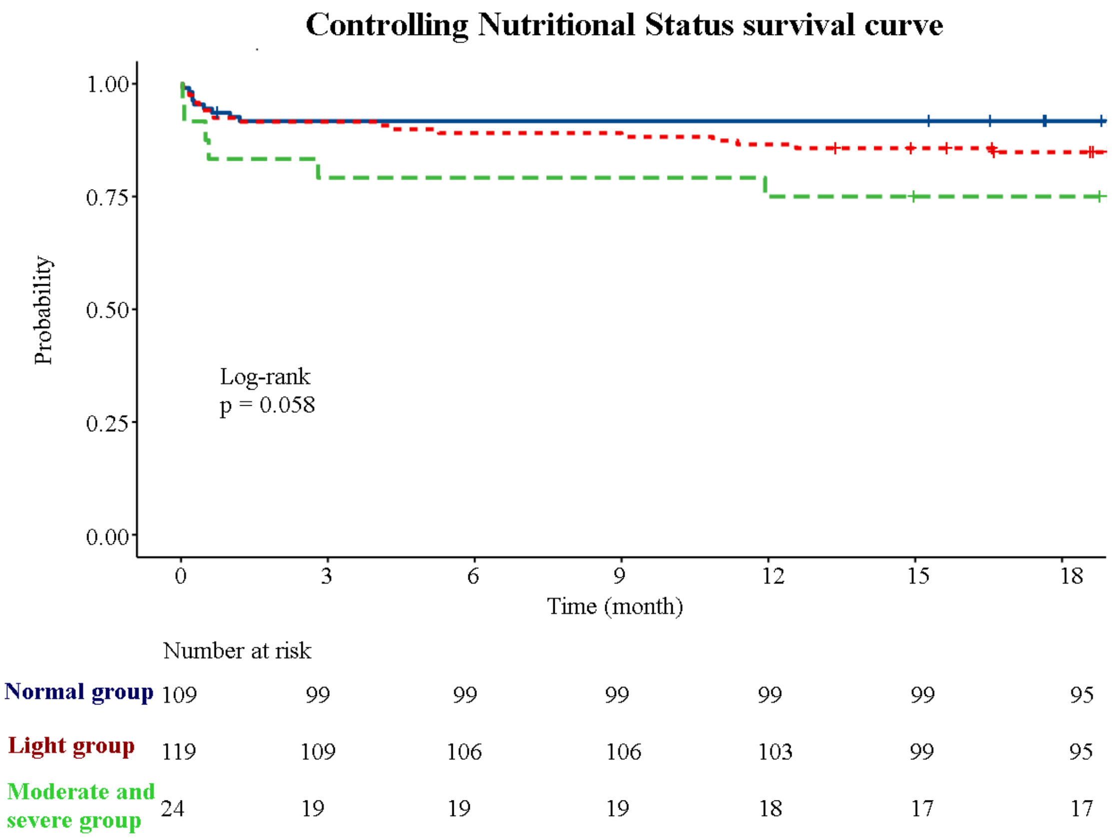

Figure 4. - **Controlling Nutritional Status survival curve**. Kaplan–Meier curves show the relationship between CONUT (controlling nutritional status) and mortality. Blue line: normal group (CONUT 0-1 point); red line: light group (2-4 points); green line: moderate and severe groups (5-12 points). The figure shows that patients in the moderate and severe group tended to have worse survival (35)

4.4. Frailty

4.4.1 CGA-based Frailty Score

4.4.1.1. Frailty study

The CGA-based frailty assessment did not show significant association with overall mortality. The items of CGA (Cardio, Nagi, MMSE, etc.) were separately investigated with mortality. The mortality risk increased by 42% if the patient had a higher Noncardiovascular score (AHR: 1.42, 95% CI: 1.03–1.96, P=0.029). In multivariate COX-regression, Noncardiovascular score showed significantly higher risk for overall mortality (AHR: 1.44, 95% CI: 1.02–2.04, P=0.036) after adjustment to EuroScore II and postoperative complications.

The functional items, such as MMSE (p=0.486), Rosow-Breslau (p=0.280), and Nagi (p=0.820) were not related to overall mortality.

4.4.1.2. Endocrine study

Univariate Cox regression showed no significant association with overall mortality (p=0.568). We examined the scores divided into 3 and 5 groups. Neither the 3-group CGA-based frailty score, nor the 5-group version showed any significant association with 30-day, 1-year, or overall mortality. The CGA items Cardio, Noncardiovascular, and Rosow scores were not associated with mortality.

Table 4. – **Univariate Cox regression of CGA-based scores**

	Frailty Study					Endocrine Study			
Follow-up	Scores	Exp (B)	95.0% CI for Exp(B)		Sig.	Exp (B)	95.0% CI for Exp(B)		Sig.
			Lower	Upper			Lower	Upper	
30-day mortality	Frailty	0.83	0.52	1.32	0.443	0.91	0.77	1.08	0.291
	Noncardiovascular	0.85	0.34	2.10	0.731	0.68	0.35	1.31	0.254
	Cardio	1.16	0.48	2.80	0.741	0.89	0.71	1.12	0.338

	Rosow-Breslau	0.38	0.05	2.60	0.326	1.15	0.64	2.07	0.619
1-year mortality	Frailty	1.11	0.86	1.44	0.413	1.00	0.87	1.15	0.961
	Noncardiovascular	1.16	0.71	0.90	0.530	0.94	0.58	1.53	0.830
	Cardio	1.19	0.67	2.11	0.540	0.97	0.80	1.17	0.770
	Rosow-Breslau	0.93	0.27	3.16	0.917	1.34	0.80	2.23	0.256
Overall mortality	Frailty	1.16	0.96	1.41	0.105	1.04	0.90	1.19	0.568
	Noncardiovascular	1.42	1.03	1.96	0.029	1.01	0.65	1.58	0.936
	Cardio	0.94	0.61	1.44	0.777	0.98	0.82	1.18	0.903
	Rosow-Breslau	1.67	0.68	4.06	0.259	1.35	0.83	2.20	0.223

4.4.2. Modified Frailty Score-11

In the Endocrine study, the modified Frailty Score-11 was not connected to 30-day mortality (p=0.149), 1 year mortality (p=0.754), or total mortality (p=0.882).

4.4.3. Hungarostudy

Our frailty study of 69 cardiac surgery patients was compared with the Hungarostudy (HS) group. Using propensity score matching analysis, 63 pairs were created. In the cardiac population, financial difficulties or smoking habits appeared less frequently than in the HS group-based control population. The CSSDS's comparison indicates that the HS cohort received more social support outside of the families than the study population.

4.5. Endocrine status

Endocrine status was only observed in our endocrine investigation. Preoperative hormone levels as continuous variables showed no statistically significant difference between the deceased and the survivors. We have found that chronic amiodarone medication was associated with higher T4 levels (still in the normal range) compared to the T4 levels of patients without this medication (p=0.02). Among those who needed vasoactive-inotropic support, the preoperative T3 was less compared to those without support (p=0.016). While those who needed mechanical ventilation more than 24 hours had a lower T3 level compared to those who did not need it (p<0.001). The length of operation was associated with T3 level (R: -0.151 p= 0.031) and length of stay in the ICU with T4 level (R: 0.173 p=0.006). Frailty and nutritional scores were not correlated with thyroid hormones. Hormone levels did not correlate with BMI.

4.5.1. Comparison of endocrine status of men and women

Men were younger, had lower EuroScore II values and higher median BMIs than women. Between the two sexes prolactin levels did not differ, T4 was significantly lower in women. Men had higher GNRI values (median 122.10 vs. median 116.42 p=0.022). Prolactin levels in women (R: -0.234, p=0.032) while in men testosterone level (R: -0.219, p=0.004) had a negative correlation with GNRI. There was no difference in frailty scores.

5. Discussion

We found in the Frailty study that in case of elective cardiac surgery patients, the CGA-based nutritional status and Noncardiovascular items have an association with higher mortality even after adjustment for postoperative complications and EuroScore II. However, the CGA-based other domains (cardiac, functional status, etc.) and the CGA frailty score were not associated with mortality. Based on these findings, CGA-based Noncardiovascular and nutritional scores could be used as a mortality prediction tool before elective cardiac surgeries. GNRI is an independent predictor for 2 years and overall mortality after adjustment for MELD, BMI, or EuroScore II.

We found in the Endocrine study that preoperative serum TSH, T3, T4, testosterone, and prolactin levels were not associated with mortality. We only found a weak correlation between the preoperative T4 serum levels and postoperative time spent in the ICU, and between serum T3 levels and the operation time. Lower PNI and lower GNRI scores were associated with 30-day, 1-year, and overall mortality. Women's prolactin levels and men's testosterone levels had a negative correlation with GNRI. In our study, the preoperative endocrine hormone levels were not associated with mortality or other examined nutritional domains.

In perioperative patient management nutritional status plays a crucial role. Decrease in activity, physical function, and energy consumption can lead to progression of malnutrition (25, 46). In patients with comorbidities, such as COPD, chronic renal failure and cirrhosis tend to have a weaker nutritional status because of the physiological mechanisms of the diseases. The Nutri-Day Study investigated the role of glucose, lactate, and citrate macronutrients in CVVHD with TSC-RCA patients. They found that if the patients did not have increased blood lactate or glucose levels, the macronutrients did not have any relevant effect on bioenergetic loss or uptake. However, if the patients had elevated blood levels, a significant caloric loss was observed (47). Hepatic dysfunction has a significant role in nutritional status, both because of its cardiovascular effects and because of its altered synthesis capacity. Cirrhotic patients have a higher 30-day mortality after cardiac surgery (25). A good predictor for this is the MELD score, which is nowadays part of routine screening before transplantation (48).

In the routine preoperative management, the mostly used predictors are BMI and serum albumin levels. BMI is a fast and easy-to use score, but it has well known limitations, as even with a normal BMI patients can be malnourished. Low albumin levels (<3.5 g/dL) in cardiac surgery patients were linked with higher mortality risk (53, 54).

Calculation of nutritional status can be easily performed using the routine laboratory parameters. Early identification of a malnutrition provides the opportunity for preoperative intervention, dietary advice, feeding, or even the possibility of parenteral nutrition.

In most recent international literature, the nutritional risk scores frequently in different settings are GNRI (25), PNI (40) and CONUT (39). We aim to apply the scores to our elective cardiac surgery patients and examine their association with mortality. Regarding GNRI, a score lower than 91 points was considered to indicate that the patient is malnourished (49). Ogawa et al. found in cardiac surgery settings that if the patient had low GNRI points, it led to delayed or no rehabilitation (50). Other studies reported in transcatheter aortic valve replacement populations (51) that decreased GNRI had an association with higher mid-term mortality and that during the complicated postoperative time decreased GNRI played an important role (49, 52). In the Frailty study, GNRI and albumin levels were associated with higher mortality. We investigated the relationship between hepatic dysfunction and nutritional status by using MELD and GNRI scores. We found that lower GNRI was associated with increased mortality independently.

Several studies examined the relationship between total lymphocyte count, serum albumin levels, total cholesterol levels, and nutritional status. These articles agreed that lower albumin and cholesterol have an association with weaker nutritional status (53, 54). In case of total lymphocyte count, the international literature is controversial, as some studies (55, 56) suggest that low lymphocytes count is associated with malnutrition, while some (57, 58) do not find relationship with aging and the presence of comorbidities causing physiological changes that can have an impact on the immune system and thus on the number of lymphocytes (56, 59). People with heart failure and physiological compensators like hypoperfusion and low cardiac output can lead to inflammatory and neurohormonal responses (60). Patients with cardiac diseases often have symptoms such as oedema that may affect the digestive system, causing malabsorption (61). As can be observed in the international literature, the CONUT and PNI scores are mostly applied in cancer patients (62-66).

In the Endocrine study we examined three types of nutritional scores and all were associated with overall mortality. These findings support the importance of perioperative nutritional status management. The calculation of the scores is fast and easy to implement and only the routine pre-operative patient examination and laboratory results are required. It would be a good next step to make perioperative nutritional status management part of the daily anesthetic ambulatory examination and to investigate which therapeutic interventions could optimize patients' nutritional status before elective cardiac surgery.

The concept of frailty has become more widespread in the last decades. Two main approaches are known, namely the deficit accumulation and the phenotypic approaches. The deficit model is based on a Canadian study (67) which contained 70 different items. Over time, different studies have reduced this number to different levels (37, 68). The phenotypic model contains five main domains (self-reported fatigue, low physical activity, unintended weight loss, slow gait speed, and reduced grip strength) (69).

A meta-analysis of observational studies of cardiac surgery patients (6 multicenter, 13 single center) examined the different types of frailty assessments. The mostly used assessments in the studies were Fried/Modified Fried (25%), Bespoke Frailty Score (17%), Deficit Index (17%), Katz Index (8%), and Clinical Frailty Score (8%). Frail patients were older, had more comorbidities, and were more often women. Frail and prefrail statuses were both investigated, and they were connected to higher operative mortality and reduced long-term survival (frail $p<0.001$, prefrail $p<0.001$)(5). While in another meta-analysis including 31,343 participants showed that frail and pre-frail statuses were associated with cardiovascular disease. Six prospective studies reported that during a median of 4.4 years (range 1- 11.4 years) follow up, the risk of cardiovascular death was three times higher in the frail group (70).

The CGA-based frailty model uses a complex, multi-component method which contains psychological, functional, and cognitive parts. Because of its complexity, it can be divided into smaller domains which can be used separately (71). The International Conference of Frailty and Sarcopenia Research in 2019 proposed a simpler starting point system, leading to a more complex CGA point system in case the first screening suggests further testing of frailty (72). In our Frailty study, the domains used for daily self-sufficiency (Nagi score and Rosow-Breslau score) were not significant predictors of mortality. In our Endocrine study, the Rosow-Breslau score was not significant either. The Noncardiovascular score could be a potential tool to summarize conditions such as sensory impairment or anxiety not included in the routinely applied risk stratifications, for example, the EuroScore II and the ASA. We got inconsistent results in case of the Noncardiovascular score, because in the Frailty study we found that in case of a higher Noncardiovascular score, the overall mortality was also higher. However, in the Endocrine study we did not find any significant results. Nevertheless, there is a greater difference in follow-up time between the two studies (Frailty study median 1,656 days vs. Endocrine study median 623 days). The MMSE domain could not be considered a mortality predictor in the Frailty study and this finding is in contrast to the results of our previous vascular study (36). The explanation could be that the vascular and cardiac patients behave differently and their cognitive and physical statuses were also different. However, the frailty score calculated in both cardiac and vascular patients were predictive for mortality (73). A big drawback of CGA-based frailty calculation is that it takes a lot of time to be accurately recorded. The CGA-based Frailty scoring system was not significantly associated with mortality, neither in the Frailty study, or in the Endocrine study.

Ehlert et al. (74) used a 11-item, while Arya et al. (37) used a 13-item modified frailty scoring system based on the NSQIP (American College of Surgeons (ACS) National Surgical Quality Improvement Program) database, which investigated vascular surgery patients. Our modified frailty score-11 had low sensitivity for mortality in elective cardiac surgery patients. This type of frailty assessment was not used in cardiac surgery patients. To explain the reasons behind the different findings in cardiac and vascular surgery populations, further investigations are needed, but we can assume that both cardiac and vascular surgery patients commonly have the same precipitating factors, such as hypertension, atherosclerosis, and diabetes, while probably there could be differences in cognitive function and the rate of TIA, stroke (75).

It is important to take into consideration that frailty is a dynamic status, and both the improvement and impairment of physical and cognitive conditions could be expected. In this study our goal was to recognize the impaired patients in a quick, simple, reproducible and easy way that can be applied in clinical practice. The frailty scoring systems we examined were not associated with mortality, although the extensive international literature (5, 76) states that the usefulness of the frailty scoring systems is important, but that a perfect version applicable to cardiac surgery population has not yet been found. Moreover, it is vital to take further steps after the identification of frail patients and work with allied professionals (e.g., dietician, physiotherapist, neurologist) in order to improve the patient's condition before elective cardiac surgery.

In the Frailty study we compared the cardiac surgery population with the healthy Hungarian population. In different clinical situations the social assistance plays an important role (77, 78). Those patients on the waiting list of surgeries who have higher social support have a higher likelihood to participate in rehabilitation (77). The Caldwell Social Support Dimension Scale measures the patient's different interpersonal relationships. The survey also investigates how much a person can rely on those around them. We found that the control, healthy HS group had better social support outside of their families than our cardiac surgery group, which can play an important role in postoperative rehabilitation.

The physiological effects of thyroid hormones on the body are well known. In case of nontreated hyperthyroidism clinicians can expect increased heart rate, cardiac contractility, and decreased systemic vascular resistance, causing increased cardiac output. While a hypothyroid patient can show signs of increased vascular resistance, low cardiac output, and immune dysfunction.

The most common abnormality is the euthyroid sick syndrome, which occurs in 70% of hospitalized patients. In this condition patients have a low serum T3 level, but it is not clear if it is an adaptive or maladaptive response (7, 28). In a retrospective study patients treated in ICU had an increased mortality rate if they had a low T3 level. However, the samples were taken after ICU admission, therefore, the hormonal levels at this point in time may indicate a stress response to the primary disease (79). This result is similar to the findings of our previous study in transplanted patients. Twenty to thirty percentage of patients with regular use of amiodarone and decompensated end-stage heart failure had some kind of change in the serum thyroid level (9). Additionally, our previous study showed no association between T3 levels and mortality or other adverse postoperative events in patients undergoing heart transplantation. It could be explained by the stress response following heart transplantation, which caused a uniquely strong T3 depression regardless of the later patient outcome. Some studies examined T3 supplement therapy in cardiac surgery. T3 was administered when aortic cross clamp was removed during the operation. The authors stated that it reduced the need of inotropic therapy, improved hemodynamic status in the postoperative period, but it had no effect on the length of hospital stay or on mortality (80, 81). In our prospective Endocrine study, the thyroid serum levels had no association with mortality but low T3 was associated with prolonged mechanical ventilation (82), although in the cardiac surgery population the incidence of pathological low or high thyroid serum levels was low. The thyroid levels did not associate with nutritional status.

Testosterone takes part in cardiac remodeling and low testosterone serum level may be associated with coronary artery disease (8, 11). There are several studies on the relationship between testosterone levels and the cardiovascular system. Corona et al. screened 70 studies and Araujo et. al examined 18 studies, and both meta-analyses found that low testosterone level is associated with cardiovascular morbidity and mortality (83, 84). Furthermore, other studies found that patients with coronary artery disease had lower testosterone levels than healthy controls (85, 86). In our findings, the changes in testosterone levels were not associated with mortality. Coronary artery disease was not more frequent in men in the elective cardiac surgery population.

The Nurses Health Study investigated more than 800 postmenopausal women and found that prolactin levels have an association with self-reported hypertension (87), while other studies suggested that there is a relationship between lower prolactin levels and increased cardiovascular risks (14, 16). Another community-based investigation found no relationship between prolactin levels and BMI (88). We found no association between changes in prolactin levels and mortality or BMI. When investigating women separately, prolactin levels and GNRI were correlated.

Limitations of the studies

Both of our research studies (Frailty study and Endocrine study) were conducted in a single center. In the Frailty study our population was relatively small. Filling the survey took an extended period of time, which made the enrollment difficult.

In the Frailty study we have tried to differentiate between our former studies about anxiety and depression, the frailty items and the HS epidemiological survey. In patients undergoing elective cardiac surgery we wanted to examine the feasibility of comprehensive frailty items. Then we have applied our recent former experiences and requested our patients to complete both psychosocial and frailty questionnaires. Finally, a comparison was made between our cardiac study population and the Hungarian survey population. Tendencies play important role in sociological and psychological topics.

In the Endocrine study a post hoc power analysis was executed for the primary and secondary outcomes. The given sample size had sufficient power for predicting mortality with the help of clinical predictors. The study was underpowered in case of T3, T4, testosterone, and prolactin. Relatively few cases occurred in the low and high hormone level groups. During the last part of patients' enrollment, the SARS-CoV epidemic started in our country. Data about COVID infections and vaccinations were not collected, so we do not have information whether this had any influence on the participants' condition during the follow-up period. The lockdown may have partly taken a role in the high mortality rate, as this unusual situation leads to lack of vigilance and rehabilitation.

6. Conclusions

In the Frailty study we have found that the Noncardiovascular score and the Nutritional score based on CGA were associated with overall mortality after adjustment for postoperative complications and EuroScore II. Low GNRI score was an independent predictor in case of mortality in elective cardiac surgery patients. This CGA-based frailty formula did not correlate well with mortality in cardiovascular patients.

In the Endocrine study we have found that thyroid, prolactin, and testosterone hormones are probably not predicting factors for mortality in elective cardiac surgery patients, but further larger studies may be needed to make a firm conclusion. Neither the modified frailty 11 score, nor the modified CGA-based formula is a proper tool for cardiovascular patients' frailty assessment. Nutritional status should be assessed before surgery to identify those at risk and for clinicians to have the chance to intervene in time.

Routine pre-operative laboratory monitoring of thyroid hormones, prolactin, and testosterone serum levels are not recommended. However, in high-risk cardiac surgery patients, e.g., before heart transplantation, it is still recommended. The use of these frailty score systems (mFI-11, mCGA, CGA) is not recommended as a routine preoperative screening. Further investigation is suggested to establish frailty accurately and easily. It is recommended that one of the nutritional scores (GNRI, PNI, CONUT) be integrated into routine preoperative risk assessment, which can be used either in anesthesia or in surgical ambulatory care when a surgical diagnosis is made. If the scores suggest malnutrition, further actions are needed.

7. Summary

This thesis aimed to investigate the possible risk factors and available tools for risk assessment in patients undergoing elective cardiac surgery. The risk factors were observed in two separate cardiac populations.

In total we examined 321 patients (n=69 vs. n=252) who underwent an elective cardiac surgery. In the Frailty study the mean age was 65.43 years (SD 9.81 years). During the median 1,656 days (IQR 1,336–2,081 days) follow up time, 14 (20.3%) cardiac surgery patients died. In the Endocrine study the mean age was 64.23 years (SD 11.07 years). There were 13 deceased patients (13.01%) at the end of the follow-up time (median 623 days (IQR 575-699 days)).

1) The CGA-based frailty assessment score was not associated with the postoperative mortality in elective cardiac surgery patients.

2) The modified frailty index 11 was not a postoperative mortality predictor in elective cardiac surgery patients.

3) Thyroid hormones, prolactin, and testosterone were examined both as continuous variables and as variables grouped based on low, normal, and high levels and were not significantly associated with overall mortality. The study was underpowered regarding T3, T4, testosterone and prolactin. Relatively few cases occurred in the groups with low and high hormone levels. We could not draw a firm conclusion.

4) GNRI points lower than 91 also showed a relationship with increased postoperative mortality in elective cardiac surgery patients.

5) PNI of less than 48 points is a good mortality predictor in elective cardiac surgery patients.

6) Higher CONUT score is an indicator of higher mortality risk in elective cardiac surgery patients.

All in all, the nutritional scores are easy and fast to calculate and give the clinicians a perspective about the real nutritional status of the patient.

8. References

1. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, et al. EuroSCORE II. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2012;41(4):734-44; discussion 44-5.
2. Hill A, Arora RC, Engelman DT, Stoppe C. Preoperative Treatment of Malnutrition and Sarcopenia in Cardiac Surgery: New Frontiers. Critical care clinics. 2020;36(4):593-616.
3. Wleklik M, Czapla M, Denfeld Q, Przybylski R, Reczuch K, Uchmanowicz I. The how and why of assessing frailty syndrome in cardiac surgery. Advances in clinical and experimental medicine : official organ Wroclaw Medical University. 2022;31(10):1061-4.
4. Emmert DA, Arcario MJ, Maranhao B, Reidy AB. Frailty and cardiac surgery: to operate or not? Current opinion in anaesthesiology. 2022;35(1):53-9.
5. Lee JA, Yanagawa B, An KR, Arora RC, Verma S, Friedrich JO. Frailty and pre-frailty in cardiac surgery: a systematic review and meta-analysis of 66,448 patients. Journal of cardiothoracic surgery. 2021;16(1):184.
6. Junius-Walker U, Onder G, Soleymani D, Wiese B, Albaina O, Bernabei R, et al. The essence of frailty: A systematic review and qualitative synthesis on frailty concepts and definitions. European journal of internal medicine. 2018;56:3-10.
7. Razvi S, Jabbar A, Pingitore A, Danzi S, Biondi B, Klein I, et al. Thyroid Hormones and Cardiovascular Function and Diseases. Journal of the American College of Cardiology. 2018;71(16):1781-96.
8. McIver B, Gorman CA. Euthyroid sick syndrome: an overview. Thyroid : official journal of the American Thyroid Association. 1997;7(1):125-32.
9. Nagy Á, Holndonner-Kirst E, Eke C, Szécsi B, Szabó A, Plamondon MJ, et al. Perioperative Low Tetraiodothyronine Levels and Adverse Outcomes After Heart Transplantation: A Retrospective, Observational Study. Journal of cardiothoracic and vascular anesthesia. 2020;34(10):2648-54.
10. Nagy Á, Szécsi B, Eke C, Szabó A, Mihály S, Fazekas L, et al. Endocrine Management and Hormone Replacement Therapy in Cardiac Donor Management: A Retrospective Observational Study. Transplantation proceedings. 2021;53(10):2807-15.

11. Marsh JD, Lehmann MH, Ritchie RH, Gwathmey JK, Green GE, Schiebinger RJ. Androgen receptors mediate hypertrophy in cardiac myocytes. Circulation. 1998;98(3):256-61.
12. Nettleship J, Jones R, Channer K, Jones T. Testosterone and coronary artery disease. Frontiers of hormone research. 2009;37:91-107.
13. Kloner RA, Carson C, 3rd, Dobs A, Kopecky S, Mohler ER, 3rd. Testosterone and Cardiovascular Disease. Journal of the American College of Cardiology. 2016;67(5):545-57.
14. Haring R, Friedrich N, Völzke H, Vasan RS, Felix SB, Dörr M, et al. Positive association of serum prolactin concentrations with all-cause and cardiovascular mortality. European heart journal. 2014;35(18):1215-21.
15. Stamatelopoulos KS, Georgiopoulos GA, Sfikakis PP, Kollias G, Manios E, Mantzou E, et al. Pilot study of circulating prolactin levels and endothelial function in men with hypertension. American journal of hypertension. 2011;24(5):569-73.
16. Therkelsen KE, Abraham TM, Pedley A, Massaro JM, Sutherland P, Hoffmann U, et al. Association Between Prolactin and Incidence of Cardiovascular Risk Factors in the Framingham Heart Study. Journal of the American Heart Association. 2016;5(2).
17. Landberg E, Dahlström U, Alehagen U. Serum prolactin and macroprolactin in heart failure: no relation to established laboratory or clinical parameters. Annals of clinical biochemistry. 2011;48(Pt 1):51-6.
18. Gustafsson UO, Scott MJ, Hubner M, Nygren J, Demartines N, Francis N, et al. Guidelines for Perioperative Care in Elective Colorectal Surgery: Enhanced Recovery After Surgery (ERAS(®)) Society Recommendations: 2018. World J Surg. 2019;43(3):659-95.
19. Hill A, Nesterova E, Lomivorotov V, Efremov S, Goetzenich A, Benstoem C, et al. Current Evidence about Nutrition Support in Cardiac Surgery Patients-What Do We Know? Nutrients. 2018;10(5).
20. von Haehling S, Anker MS, Anker SD. Prevalence and clinical impact of cachexia in chronic illness in Europe, USA, and Japan: facts and numbers update 2016. Journal of cachexia, sarcopenia and muscle. 2016;7(5):507-9.
21. Koifman E, Magalhaes MA, Ben-Dor I, Kiramijyan S, Escarcega RO, Fang C, et al. Impact of pre-procedural serum albumin levels on outcome of patients undergoing

transcatheter aortic valve replacement. The American journal of cardiology. 2015;115(9):1260-4.

22. Koifman E, Kiramijyan S, Negi SI, Didier R, Escarcega RO, Minha S, et al. Body mass index association with survival in severe aortic stenosis patients undergoing transcatheter aortic valve replacement. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2016;88(1):118-24.

23. Gavriilidou NN, Pihlsgård M, Elmståhl S. High degree of BMI misclassification of malnutrition among Swedish elderly population: Age-adjusted height estimation using knee height and demispan. European journal of clinical nutrition. 2015;69(5):565-71.

24. Huang BT, Peng Y, Liu W, Zhang C, Chai H, Huang FY, et al. Nutritional State Predicts All-Cause Death Independent of Comorbidities in Geriatric Patients with Coronary Artery Disease. The journal of nutrition, health & aging. 2016;20(2):199-204.

25. Unosawa S, Taoka M, Osaka S, Yuji D, Kitazumi Y, Suzuki K, et al. Is malnutrition associated with postoperative complications after cardiac surgery? Journal of cardiac surgery. 2019;34(10):908-12.

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

27. Richter D, Guasti L, Walker D, Lambrinou E, Lionis C, Abreu A, et al. Frailty in cardiology: definition, assessment and clinical implications for general cardiology. A consensus document of the Council for Cardiology Practice (CCP), Association for Acute Cardio Vascular Care (ACVC), Association of Cardiovascular Nursing and Allied Professions (ACNAP), European Association of Preventive Cardiology (EAPC), European Heart Rhythm Association (EHRA), Council on Valvular Heart Diseases (VHD), Council on Hypertension (CHT), Council of Cardio-Oncology (CCO), Working Group (WG) Aorta and Peripheral Vascular Diseases, WG e-Cardiology, WG Thrombosis, of the European Society of Cardiology, European Primary Care Cardiology Society (EPCCS). European journal of preventive cardiology. 2022;29(1):216-27.

28. Ranasinghe AM, Bonser RS. Thyroid hormone in cardiac surgery. Vascular pharmacology. 2010;52(3):131-7.

29. Bianchi V, Mezzani A. Androgens and cardiac diseases. Monaldi archives for chest disease = Archivio Monaldi per le malattie del torace. 2013;80(4):161-9.
30. Alexandersen P, Haarbo J, Christiansen C. The relationship of natural androgens to coronary heart disease in males: a review. Atherosclerosis. 1996;125(1):1-13.
31. Feldman HA, Johannes CB, Araujo AB, Mohr BA, Longcope C, McKinlay JB. Low dehydroepiandrosterone and ischemic heart disease in middle-aged men: prospective results from the Massachusetts Male Aging Study. American journal of epidemiology. 2001;153(1):79-89.
32. Tóth K, Szabó A, Nagy Á, Szabó D, Szécsi B, Eke C, et al. Preoperative nutritional state is associated with mid- and long-term mortality after cardiac surgery. Annals of palliative medicine. 2021;10(11):11333-47.
33. Reddy HG, Shih T, Englesbe MJ, Shannon FL, Theurer PF, Herbert MA, et al. Analyzing "failure to rescue": is this an opportunity for outcome improvement in cardiac surgery? Ann Thorac Surg. 2013;95(6):1976-81; discussion 81.
34. Caraballo C, Desai NR, Mulder H, Alhanti B, Wilson FP, Fiuzat M, et al. Clinical Implications of the New York Heart Association Classification. Journal of the American Heart Association. 2019;8(23):e014240.
35. Tóth K, Szabó A, Menyhárd J, Benke K, Radovits T, Pólos M, et al. Poor Preoperative Nutritional Status, but Not Hormone Levels, Are Associated With Mortality After Cardiac Surgery. Journal of cardiothoracic and vascular anesthesia. 2022;36(8 Pt B):3074-83.
36. Szabó A, Tóth K, Nagy Á, Domokos D, Czobor N, Eke C, et al. The effect of cognitive dysfunction on mid- and long-term mortality after vascular surgery. BMC Geriatr. 2021;21(1):46.
37. Arya S, Kim SI, Duwayri Y, Brewster LP, Veeraswamy R, Salam A, et al. Frailty increases the risk of 30-day mortality, morbidity, and failure to rescue after elective abdominal aortic aneurysm repair independent of age and comorbidities. Journal of vascular surgery. 2015;61(2):324-31.
38. Liao S, Lu X, Cheang I, Zhu X, Yin T, Yao W, et al. Prognostic value of the modified model for end-stage liver disease (MELD) score including albumin in acute heart failure. BMC cardiovascular disorders. 2021;21(1):128.

39. De Ulíbarri JI, González-Madroño A, de Villar NG, González P, González B, Mancha A, et al. CONUT: a tool for controlling nutritional status. First validation in a hospital population. 2005;20(1):38-45.
40. Iwakami N, Nagai T, Furukawa TA, Sugano Y, Honda S, Okada A, et al. Prognostic value of malnutrition assessed by Controlling Nutritional Status score for long-term mortality in patients with acute heart failure. International journal of cardiology. 2017;230:529-36.
41. Laboratories A. TSH, 7K62, G6-2266/ R06, B7K62H. 2015.
42. Laboratories A. Free T3, 7K63, G68141R03, B7K6WH. 2015.
43. Laboratories A. Free T4, 7K65, G68166R03, B7K6FH. 2015.
44. Laboratories A. Prolactin, 7K76, B7K76H, 56-5214/R1. 2006.
45. Laboratories A. 2nd Generation Testosterone, 2P13, G5-6077/R01, B2P1WH. 2015.
46. Luo H, Yang H, Huang B, Yuan D, Zhu J, Zhao J. Geriatric Nutritional Risk Index (GNRI) Independently Predicts Amputation Inchronic Criticallimb Ischemia (CLI). PloS one. 2016;11(3):e0152111.
47. Wechselberger S, Compton F, Schilling J. Impact of Continuous Veno-Venous HemoDiALYsis with Regional Citrate Anticoagulation on Non-NUTRItional Calorie Balance in Patients on the ICU-The NUTRI-DAY Study. Nutrients. 2022;15(1).
48. Harjola VP, Mullens W, Banaszewski M, Bauersachs J, Brunner-La Rocca HP, Chioncel O, et al. Organ dysfunction, injury and failure in acute heart failure: from pathophysiology to diagnosis and management. A review on behalf of the Acute Heart Failure Committee of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). European journal of heart failure. 2017;19(7):821-36.
49. Bouillanne O, Morineau G, Dupont C, Coulombel I, Vincent JP, Nicolis I, et al. Geriatric Nutritional Risk Index: a new index for evaluating at-risk elderly medical patients. The American journal of clinical nutrition. 2005;82(4):777-83.
50. Ogawa M, Izawa KP, Satomi-Kobayashi S, Kitamura A, Ono R, Sakai Y, et al. Poor preoperative nutritional status is an important predictor of the retardation of rehabilitation after cardiac surgery in elderly cardiac patients. Aging Clin Exp Res. 2017;29(2):283-90.

51. Shibata K, Yamamoto M, Kano S, Koyama Y, Shimura T, Kagase A, et al. Importance of Geriatric Nutritional Risk Index assessment in patients undergoing transcatheter aortic valve replacement. American heart journal. 2018;202:68-75.

52. Dent E, Hoogendijk EO, Visvanathan R, Wright ORL. Malnutrition Screening and Assessment in Hospitalised Older People: a Review. The journal of nutrition, health & aging. 2019;23(5):431-41.

53. Mueller C, Compher C, Ellen DM. A.S.P.E.N. clinical guidelines: Nutrition screening, assessment, and intervention in adults. JPEN Journal of parenteral and enteral nutrition. 2011;35(1):16-24.

54. Rocha NP, Fortes RC. Total lymphocyte count and serum albumin as predictors of nutritional risk in surgical patients. Arquivos brasileiros de cirurgia digestiva : ABCD = Brazilian archives of digestive surgery. 2015;28(3):193-6.

55. Fávaro-Moreira NC, Krausch-Hofmann S, Matthys C, Vereecken C, Vanhauwaert E, Declercq A, et al. Risk Factors for Malnutrition in Older Adults: A Systematic Review of the Literature Based on Longitudinal Data. Advances in nutrition (Bethesda, Md). 2016;7(3):507-22.

56. Kaya T, Açıkgöz SB, Yıldırım M, Nalbant A, Altaş AE, Cinemre H. Association between neutrophil-to-lymphocyte ratio and nutritional status in geriatric patients. Journal of clinical laboratory analysis. 2019;33(1):e22636.

57. Omran ML, Morley JE. Assessment of protein energy malnutrition in older persons, Part II: Laboratory evaluation. Nutrition (Burbank, Los Angeles County, Calif). 2000;16(2):131-40.

58. Bauer JM, Wirth R, Volkert D, Werner H, Sieber CC. [Malnutrition, sarcopenia and cachexia in the elderly: from pathophysiology to treatment. Conclusions of an international meeting of experts, sponsored by the BANSS Foundation]. Deutsche medizinische Wochenschrift (1946). 2008;133(7):305-10.

59. Cohen S, Danzaki K, MacIver NJ. Nutritional effects on T-cell immunometabolism. European journal of immunology. 2017;47(2):225-35.

60. Mann DLJTroimitfh. Recent insights into the role of tumor necrosis factor in the failing heart. 2001:3-12.

61. von Haehling S, Lainscak M, Springer J, Anker SDJP, therapeutics. Cardiac cachexia: a systematic overview. 2009;121(3):227-52.

62. Peng L, Meng C, Li J, You C, Du Y, Xiong W, et al. The prognostic significance of controlling nutritional status (CONUT) score for surgically treated renal cell cancer and upper urinary tract urothelial cancer: a systematic review and meta-analysis. European journal of clinical nutrition. 2022;76(6):801-10.

63. Takagi K, Buettner S, Ijzermans JNM, Wijnhoven BPL. Systematic Review on the Controlling Nutritional Status (CONUT) Score in Patients Undergoing Esophagectomy for Esophageal Cancer. Anticancer research. 2020;40(10):5343-9.

64. Uemura S, Iwashita T, Ichikawa H, Iwasa Y, Mita N, Shiraki M, et al. Impact of Controlling nutritional status (CONUT) in patients with unresectable advanced pancreatic cancer receiving multi-agent chemotherapy: A single center, retrospective cohort study. Pancreatology : official journal of the International Association of Pancreatology (IAP) [et al]. 2022;22(2):304-10.

65. Cadwell JB, Afonso AM, Shahrokni A. Prognostic nutritional index (PNI), independent of frailty is associated with six-month postoperative mortality. Journal of geriatric oncology. 2020;11(5):880-4.

66. Chen L, Bai P, Kong X, Huang S, Wang Z, Wang X, et al. Prognostic Nutritional Index (PNI) in Patients With Breast Cancer Treated With Neoadjuvant Chemotherapy as a Useful Prognostic Indicator. Frontiers in cell and developmental biology. 2021;9:656741.

67. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. The journals of gerontology Series A, Biological sciences and medical sciences. 2007;62(7):722-7.

68. Panayi AC, Haug V, Kauke-Navarro M, Foroutanjazi S, Diehm YF, Pomahac B. The modified 5-item frailty index is a predictor of perioperative risk in head and neck microvascular reconstruction: An analysis of 3795 cases. American journal of otolaryngology. 2021;42(6):103121.

69. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. The journals of gerontology Series A, Biological sciences and medical sciences. 2001;56(3):M146-56.

70. Veronese N, Cereda E, Stubbs B, Solmi M, Luchini C, Manzato E, et al. Risk of cardiovascular disease morbidity and mortality in frail and pre-frail older adults: Results

from a meta-analysis and exploratory meta-regression analysis. Ageing research reviews. 2017;35:63-73.

71. Lee H, Lee E, Jang IY. Frailty and Comprehensive Geriatric Assessment. Journal of Korean medical science. 2020;35(3):e16.

72. Dent E, Morley JE, Cruz-Jentoft AJ, Woodhouse L, Rodríguez-Mañas L, Fried LP, et al. Physical Frailty: ICFSR International Clinical Practice Guidelines for Identification and Management. The journal of nutrition, health & aging. 2019;23(9):771-87.

73. Szabo A. SD, Toth K., Szecsi B., Szentgórti R., Nagy A, Eke Cs., Sandor A, Benke K., Merkely B, Gál J, Szekely A Comprehensive frailty assessment with multidimensional frailty domains as a predictor of mortality among vascular and cardiac surgical patients. Physiology International. 2023 in press.

74. Ehlert BA, Najafian A, Orion KC, Malas MB, Black JH, 3rd, Abularrage CJ. Validation of a modified Frailty Index to predict mortality in vascular surgery patients. Journal of vascular surgery. 2016;63(6):1595-601.e2.

75. Szabó A, Szabó D, Tóth K, Szécsi B, Szentgróti R, Nagy Á, et al. Comprehensive frailty assessment with multidimensional frailty domains as a predictor of mortality among vascular and cardiac surgical patients %J Physiology International. 2023.

76. Sepehri A, Beggs T, Hassan A, Rigatto C, Shaw-Daigle C, Tangri N, et al. The impact of frailty on outcomes after cardiac surgery: a systematic review. The Journal of thoracic and cardiovascular surgery. 2014;148(6):3110-7.

77. Pushkarev G, Kuznetsov V, Yaroslavskaya E, Bessonov I. Social support for patients with coronary artery disease after percutaneous coronary intervention. Journal of psychosomatic research. 2019;119:74-8.

78. Aliche JC, Ifeagwazi CM, Chukwuorji JC, Eze JE. Roles of Religious Commitment, Emotion Regulation and Social Support in Preoperative Anxiety. Journal of religion and health. 2020;59(2):905-19.

79. Shigihara S, Shirakabe A, Kobayashi N, Okazaki H, Matsushita M, Shibata Y, et al. Clinical Significance of Low-Triiodothyronine Syndrome in Patients Requiring Non-Surgical Intensive Care ― Triiodothyronine Is a Comprehensive Prognostic Marker for Critical Patients With Cardiovascular Disease ―. Circulation Reports. 2021;advpub.

80. Ranasinghe AM, Quinn DW, Pagano D, Edwards N, Faroqui M, Graham TR, et al. Glucose-insulin-potassium and tri-iodothyronine individually improve hemodynamic performance and are associated with reduced troponin I release after on-pump coronary artery bypass grafting. Circulation. 2006;114(1 Suppl):I245-50.

81. Mullis-Jansson SL, Argenziano M, Corwin S, Homma S, Weinberg AD, Williams M, et al. A randomized double-blind study of the effect of triiodothyronine on cardiac function and morbidity after coronary bypass surgery. The Journal of thoracic and cardiovascular surgery. 1999;117(6):1128-34.

82. Tóth K. SA, Menyhárd J., Merkely B., Gál J., Székely A. T3 levels but not testosterone and prolactin is associated with prolonged ventilation in elective cardiac surgery patients. Euroanaesthesia 2021; The European Anaesthesiology Congress, Abstracts Programme. 2021;39; 137 (7078).

83. Araujo AB, Dixon JM, Suarez EA, Murad MH, Guey LT, Wittert GA. Clinical review: Endogenous testosterone and mortality in men: a systematic review and meta-analysis. The Journal of clinical endocrinology and metabolism. 2011;96(10):3007-19.

84. Corona G, Rastrelli G, Monami M, Guay A, Buvat J, Sforza A, et al. Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. European journal of endocrinology. 2011;165(5):687-701.

85. Rosano GM, Sheiban I, Massaro R, Pagnotta P, Marazzi G, Vitale C, et al. Low testosterone levels are associated with coronary artery disease in male patients with angina. International journal of impotence research. 2007;19(2):176-82.

86. Wu FC, von Eckardstein A. Androgens and coronary artery disease. Endocrine reviews. 2003;24(2):183-217.

87. Zhang L, Curhan GC, Forman JP. Plasma prolactin level and risk of incident hypertension in postmenopausal women. Journal of hypertension. 2010;28(7):1400-5.

88. Friedrich N, Rosskopf D, Brabant G, Völzke H, Nauck M, Wallaschofski H. Associations of anthropometric parameters with serum TSH, prolactin, IGF-I, and testosterone levels: results of the study of health in Pomerania (SHIP). Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association. 2010;118(4):266-73.

9. Bibliography of the candidate's publications

9.1. RELATED TO DISSERTATION

- Tóth K, Szabó A, Nagy Á, Szabó D, Szécsi B, Eke C, Sándor Á, Susánszky É, Holndonner-Kirst E, Merkely B, Gál J, Székely A. (2021) Preoperative nutritional state is associated with mid- and long-term mortality after cardiac surgery. Ann Palliat Med, 10: 11333-11347.
- Tóth K, Szabó A, Menyhárd J, Benke K, Radovits T, Pólos M, Merkely B, Gál J, Székely A. (2022) Poor Preoperative Nutritional Status, but Not Hormone Levels, Are Associated With Mortality After Cardiac Surgery. J Cardiothorac Vasc Anesth, 36: 3074-3083.

9.2. NOT RELATED TO DISSERTATION

- Szabó A, Tóth K, Nagy Á, Domokos D, Czobor N, Eke C, Sándor Á, Merkely B, Susánszky É, Gál J, Székely A. (2021) The effect of cognitive dysfunction on mid- and long-term mortality after vascular surgery. BMC Geriatr, 21: 46.
- Szabo A; Szabo D; Toth K; Szecsi B; Sandor A; Szentgroti R; Parkanyi B ; Merkely, B ; Gal J; Szekely A. (2021) Effect of Preoperative Chronic Opioid Use on Mortality and Morbidity in Vascular Surgical Patients CUREUS 13 : 12 Paper: e20484 , 8 p.
- Tóth K. SA, Menyhárd J., Merkely B., Gál J., Székely A. (2021) T3 levels but not testosterone and prolactin is associated with prolonged ventilation in elective cardiac surgery patients. Euroanaesthesia 2021; The European Anaesthesiology Congress, Abstracts Programme, 39; 137
- Szabo A., Szabo D., Toth K., Szecsi B., Szentgórti R., Nagy A, Eke Cs., Sandor A, Benke K., Merkely B, Gál J, Szekely A (2023) Comprehensive frailty assessment with multidimensional frailty domains as a predictor of mortality among vascular and cardiac surgical patients. Physiology International 2023 in press
- Tóth K, Fresilli S, Paoli N, Maiucci G, Salvioni M, Kotani Y, Katzenschlager S, Weigand MA, Landoni G. (2023) D-dimer levels in non-COVID-19 ARDS and COVID-19 ARDS patients: A systematic review with meta-analysis. PLoS One, 18: e0277000.
- Covello RD, Pasin L, Fresilli S, Toth K, Damiani C, Hajjar LA, Zangrillo A, Landoni G. Meta-Analysis of Glucocorticoids for Covid-19 Patients Not Receiving Oxygen. (2023) NEJM Evidence DOI: 10.1056/EVIDoa2200283

10. Acknowledgements

I would like to thank my supervisor, Prof. Andrea Székely for all her help, for sharing her professional experience, for her critical reading of my manuscripts and her constructive criticism. Thank you for your help in the progress of my research and clinical career.

I am grateful for András Szabó MD, to help me get started in my science work when I was still a medical student and still helps me any time I have a question or get stuck in the working process.

I would like to thank my partner, Ádám Fáró, for patiently enduring my overtime and my complaints and for creating a stable background for me to carry out my thesis. I would like to thank my friend Csaba Eke MD, for suggesting to go work with Andrea Székely as a med student, supported me to start my PhD and is still supporting me with professional consultations.

I would like to thank my family and friends all the emotional support they gave me during my studies.

I appreciate the opportunity to conduct our studies in the Department of Cardiac Surgery of the Heart and Vascular Centre, Semmelweis University.

I am grateful to all the cardiac surgery patients who agreed to participate in our research between 2014 and 2020, helping us to advance our scientific knowledge and better understand preoperative risk factors and their assessments.

Finally, everyone deserves to be thanked, whom I do not have a chance to mention by name, but was involved on the road to my Ph.D.