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

PhD thesis book

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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.

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. A meta-analysis collected 19 observational studies in which 66 448 patients were assessed for frailty and the conclusions were that frail patients had a 1.5x greater risk for prolonged hospital stay and 3x risk of mid-term mortality. There is still no agreement which frailty scoring system is the best to use. Factors contributing to frailty consist of cellular and systemic physiological changes, including reduced nutritional intake, sarcopenia, associated comorbidities, and low physical activity.

Reduced levels of thyroid hormones were associated with elevated vascular resistance, decreased cardiac output, and immune dysfunction. Some studies have emphasized the relationship between coronary artery disease and low testosterone levels. It is unclear if prolactin level has any predictive value before cardiac surgery. The Framingham Heart Study examined more than 3000 patients, and it has found that there was association between prolactin levels and cardiovascular risk. Landber et al. found that different prolactin levels were associated neither with markers of heart failure, nor cardiovascular mortality.

The international literature has not yet agreed on a system for estimating preoperative nutritional status in cardiac surgery. 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. Elderly patients are more susceptible to malnutrition, leading to an increased risk of infections, longer hospital stays, and death.

2. Objectives

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

- 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, blood pressure, inflammatory pathways, etc.) is well known. Some studies suggest that the low testosterone levels, low prolactin levels are risk predictors, while others state that decreased levels of these hormones do not have a predictive value in further cardiovascular events.

- 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 an essential component in frailty and therefore in the postoperative outcome.

- We have hypothesized that a 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, SE-TuKEB 35287-2/2018/EKU) and registered on ClinicalTrials.gov (NCT02224222). 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 more patients had transcatheter aortic valve implantation or heart transplantation. Mortality was the primary outcome measured. Last assessed on November 2, 2020. The 1-year; 2-year and overall mortality were examined. Participants' clinically relevant factors, such as previous comorbidities, preoperative lab parameters (ion homeostasis, blood count etc.), intraoperative items (length of operation, amount of blood loss etc.), and postoperative parameters (postoperative medication, 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. Of the traditional risk stratifications the New York Heart Association Functional Classification (NYHA) and the logistic European System for Cardiac Operative Risk Evaluation (EuroScore II) were used.

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 had been 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. 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.

1. Table - **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
MELD-Na	• Endocrine study
MELD-XI	• Frailty study

3.4. Nutritional status

3.4.2. Geriatric Nutritional Risk Index (GNRI)

To investigate the nutritional status of the study population GNRI(22) score was calculated.

$$\textbf{GNRI} = 1.487 \times \text{ALB (g/L)} + 41.7 \times \text{PBW/IBW (kg)}$$

IBW = height2 (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. they were divided into 2 groups based on the GNRI scores were greater than or equal to 91 points (0) or less than 91 points (1) (reference this classification was used in the x studies.

3.4.3. Controlling Nutritional Status (CONUT)

The score (35) contains 3 components: lymphocyte count, serum albumin level and cholesterol level.

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

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

***Cholesterol (mg/dl): Cholesterin (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 group, they were merged to one group to avoid the statistical bias we merged the two groups in one.

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 (36) was greater than or equal to 48 we gave a score zero, while if it was less than 48 than score one was given.

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.

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.

3.3.3. Modified Frailty Index-11

We calculated the frailty score with the modified frailty index of the National Surgical Quality Improvement Program. 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).

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 (40-42)), prolactin (Abbott Laboratories, Ireland, 2006 (43)) and ARCHITECT 2nd Generation Testosterone system (Abbott Laboratories, Ireland, 2015 (44)) chemiluminescent microparticulate immunoassay]. The blood samples were frozen until all necessary samples were collected and then they were measured together. Hormone levels were not involved in the therapeutic decision.

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 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). In the case of cardiopulmonary bypass time between survival and deceased groups, there was no significant difference (median 96.2 vs. 119.3 min). 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).

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). The median follow-up time was median 623 days (IQR 575-699 days). The median operation time was

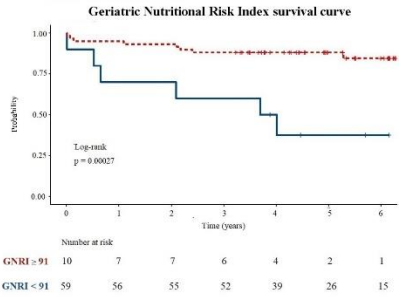
180.00 min (IQR 157.00-215.00 min), time spent in the ICU was 29 (IQR 22.00-71.63) hours. The median hospital stay was 10 days (IQR, 8.0-14.0 days). Those who died had longer cardiopulmonary bypass times (survivors 110.0 vs. deceased 80.0 min) and needed prolonged mechanical ventilation (survivors 10.25 hours vs. deceased 22.50 hours). 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 %.

4.3. Nutritional status

4.3.1. Geriatric Nutritional Risk Index

4.3.1.1. Frailty study

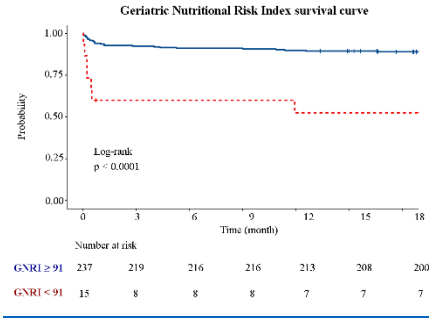
In the univariable Cox regression, GNRI points less than 91 were associated with higher risk of mortality (HR: 5.75, 95% CI: 1.98–16.66, p=0.001). In the multivariable model, GNRI was independently associated with higher risk for overall mortality after adjustment for EuroScore II and postoperative complications (AHR: 4.76, 95% CI: 1.52–14.92, P=0.007).



1. Figure - **Kaplan-Meier survival based on the GNRI score** (red: GNRI ≥91; blue: 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 (29)

4.3.1.2. Endocrine study

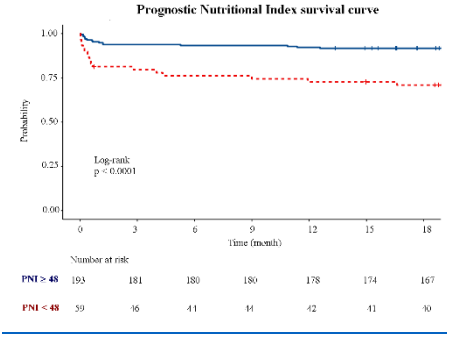
Univariate Cox regression showed that if the patient had a GNRI less the 91 points, they had a higher risk for mortality (HR:5.97; 95% CI:2.58-13.79, p<0.001). Adjusted for EuroScore II and postoperative complications, GNRI scores were independently associated with mortality (AHR:4.384;95%CI:1.866-10.303, p=0.001).



2. Figure - **Geriatric Nutritional Risk Index survival curve**. Kaplan–Meier curves show the relationship between the GNRI (Geriatric Nutritional Risk Index) and mortality. Blue line - GNRI ≥ 91 points; red line - GNRI<91 points. The figure shows that patients in the lower scoring group had worse survival (32)

4.3.3. Prognostic Nutritional Index

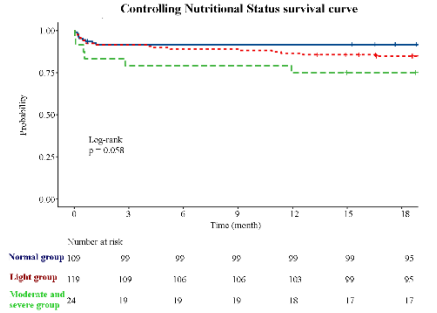
Examining the 252 patients in the endocrine study, a PNI score less than 48 was associated with a higher risk for total mortality (HR:3.95; 95% CI:1.99-7.82, p<0.001). In multivariate Cox regression, a PNI < 48 points was associated with higher overall mortality (AHR:3.465; 95%CI:1.735-6.918, p<0.001) after adjustment for postoperative complications and EuroScore II.



3. Figure - **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 lower scoring group had worse survival (32)

4.3.4. Controlling Nutritional Status

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). After adjustment for EuroScore II and postoperative complications, CONUT 3-group model was associated with higher risk of overall mortality (AHR:1.736; 95%CI:1.736-2.866 p=0.031).



4. Figure - **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 group (5-12 points). The figure shows that patients in the lower scoring group tended to have worse survival (32)

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 a 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.

4.4.2. Modified Frailty Score-11

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

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) than those 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). Operation time was associated with T3 level (R: -0.151 p= 0.031) and length of staying in the ICU with T4 level (R: 0.173 p=0.006). Frailty and nutritional scores were not correlated with thyroid hormones.

3. Table - ***Preoperative labor parameters in relation to survivors and deceased***

Variables		Survivors (n=219)				Deceased (n=33)				
		N	%	Median	IQR	N	%	Median	IQR	p value
TSH [a] (μU/ml)				1.5	(0.9-2.4)			1.3	(0.8-2.1)	0.316
FT3 [b] (pmol/l)				4.7	(3.9-5.3)			4.3	(3.4-5.3)	0.311
FT4 [c] (pmol/l)				17.2	(15.6-19.2)			17.8	(15.3-20.8)	0.378
Prolactin (μU/ml)				213.7	(162.1-295.3)			245.6	(181.4-359.3)	0.265
Testosterone (ng/ml)				1.9	(0.3-3.8)			1.5	(0.3-3.5)	0.999
TSH	low	19	8.6			6	17.6			0.231
	normal	187	85.3			25	73.5			
	high	13	5.9			2	5.8			
T3	low	7	3.2			1	2.9			0.535
	normal	204	93.1			32	94.1			
	high	8	3.6			0	0.0			
T4	low	5	2.2			1	2.9			0.780
	normal	195	89.0			28	82.3			
	high	19	8.6			4	11.7			

5. 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 in cardiac surgery. 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 surgical ambulatory care when a surgical diagnosis is made. If the scores suggest malnutrition, further actions are needed.

6.1. Bibliography of the candidate's publications (sumIF:4.819)

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6.2. Not related to the dissertation **(sumIF:9.519)**

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- **Tóth K,** Pilia E, Landoni, Oreggia D, Giacomarra S, Losiggio R, Yavorovskiy A, Likhvantsev V, Székely A, Covello RD and the Melatonin Group (2023) Melatonin as adjuvant treatment in COVID-19 patients. A meta-analysis of randomized and propensity matched studies. Signa Vitae 2023 DOI: 10.22514/sv.2023.076

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