

**SHORT THESIS FOR THE DEGREE OF DOCTOR OF
PHILOSOPHY (PhD)**

**Current Questions on Cardiac Surgical Risk
Stratification**

by György Koszta, MD

Supervisor: Béla Fülesdi, MD, DSc



UNIVERSITY OF DEBRECEN
DOCTORAL SCHOOL OF NEUROSCIENCES
DEBRECEN, 2014

Current Questions on Cardiac Surgical Risk Stratification

By

György Koszta, MD

Supervisor: Béla Fülesdi, MD, PhD, DSc

Doctoral School of Neurosciences, University of Debrecen

Head of the Examination Committee: Miklós Antal, MD, PhD, DSc

Members of the Examination Committee: János Magyar, MD, PhD,
DSC

Zoltán Vokó, MD, PhD, DSc

The Examination takes place at Department of Anatomy, Histology and Embryology,
Faculty of Medicine, University of Debrecen, on 26th of January 2015,
at 11 a.m.

Head of the Defense Committee: Miklós Antal, MD, DSc

Reviewers: István Édes, MD, PhD, DSc
Barna Babik, MD, PhD

Members of the Defense Committee: János Magyar, MD, PhD, DSc
Zoltán Vokó, MD, PhD, DSc

The PhD Defense takes place at the Lecture Hall of Bldg. A,
Department of Internal Medicine, Faculty of Medicine, University of
Debrecen, on 26th of January 2015, at 1 p.m.

Introduction

Risk stratification is an important question when a medical intervention is planned. It becomes even more significant when this intervention affects vital organ systems, technically difficult and expensive. All the above mentioned criteria are present in case of cardiac surgery.

Cardiac surgical risk stratification is in the focus of this PhD thesis. Our studies can be grouped into two major categories:

1. Validation of the renewed cardiac surgical prognostic function's performance among cardiac surgical patients.
2. Exploration of selenium concentration in the blood as a risk predictor in connection with postoperative outcome parameters.

Place of cardiac surgical risk stratification in practice

The practical value of cardiac surgical risk stratification can be described as follows:

1. Description of the risk through the patient-doctor interviews. From an ethical point of view it has paramount importance. It should be based on up-to-date scientific facts.
2. Supporting the decision making when two or more therapeutic options are available. There are several less invasive methods for the management of the problems that previously could only be treated with a cardiac operation. These are catheter-based methods which usually give palliative solutions, they are more expensive but their short-term outcome is better.
3. It offers an objective comparison of the results within or between cardiac surgical centers.

4. There are several factors which are not specified in cardiac surgical risk models. Their relative weight among the other risk factors can be a question in both everyday practice and clinical research. Oxidative stress is known to increase throughout the whole perioperative period. Selenium as a trace element plays a role in the protection against oxidative stress. The selenium concentration in the blood is not part of any risk stratification system, therefore its place as an independent risk factor is not fully described.

Aims

Our primary aim was to validate the renewed cardiac surgical prognostic function of EuroSCORE II in Hungary, because it is presumed that the properties of that patient population in which this function will be used may be different from the one that served as the derivation dataset. The Cardiac Surgical Centre of the University of Debrecen contributed data for the recalibration of EuroSCORE II, but Central and Eastern European regions were under-represented in the derivation dataset.

The selenium status is connected in many ways to the development of cardiac diseases, because it is linked to the most important cardiac risk factors (elevated lipid levels, type-2 diabetes mellitus), and the resulted pathological changes such as coronary disease, and myocardial dysfunction. The surgical treatment of these cardiac diseases often requires extracorporeal circulation which is responsible for the frequent systemic inflammatory response and increased oxidative stress. Selenium plays an important role in the protection against oxidative stress, but the importance of the low selenium status as an independent risk factor is not fully understood. It is not specified in EuroSCORE II and its connection with other risk predictors is not completely characterised. We intended to examine these above mentioned unanswered questions.

Methods

Validation of EuroSCORE II in Debrecen

The recruitment of the validation cohort started on 1 November, 2010 and ended on 31 January, 2013 in a single cardiac surgical centre, shortly after data collection for EuroSCORE II ended. All the patients who underwent major cardiac surgical procedures (CABG, AVR, MVR, mitral valve repair, ascending aorta replacement or repair, atrial septal defect closure, atrial myxoma excision, or a combination of these) were enrolled and followed up to the 30th postoperative day. All the patients enrolled into this validation study signed an informed consent form in which they agreed to the use of the data in connection with their disease, their treatment and outcomes for scientific and publication purposes. The only outcome parameter was hospital mortality within this period.

For the calculation of the logistic EuroSCORE and EuroSCORE II p-values, online tools were used which can be found at www.euroscore.org.

The basic parameter of the prognostic performance of the old and new EuroSCORE was the O:E ratio.

Calibration of the scores was evaluated using the Hosmer-Lemeshow test. The expected mortalities in the deciles of the predicted risk were calculated on the basis of both models by averaging the individual p-values and comparing them with the observed mortality in each decile. The difference between the observed and the expected mortality was considered to be statistically significant if the HL-test result was <0.05 . In order to demonstrate the goodness-of-fit visually, calibration curves were created by using a smoothing method. These curves are the results of a local polynomial regression where the Epanechnikov kernel function was used with a bandwidth of 0.05.

The discriminative power of the risk stratification models was analysed by using the receiver operation characteristics (ROC) method. The area under the ROC curves and their 95 % confidence intervals were calculated and compared.

Another general measure of discriminative power was the Brier score (BS). The frequency of patients with individual $BS \geq 0.25$ is also reported.

Cardiac surgical subgroups were created according to the weight of intervention option (isolated coronary, single non-coronary, two procedures, three procedures) and on the basis of the procedural urgency (elective, urgent, emergent, salvage), and the same calibration and accuracy parameters were calculated, but only in connection with EuroSCORE II. If the size of a certain group was too small, the HL-test was modified: individual risks were sorted into five of three groups rather than into deciles in order to gain appropriate statistical power in each subgroup.

Evaluation of whole blood selenium in the perioperative period of cardiac surgery

Patients and methods

In order to prove the proposed hypothesis that the lower selenium level is associated with increased mortality and inflammatory response, a prospective, single-centre clinical survey was conducted on 197 consecutive patients at the Cardiac Surgical Department of the University of Debrecen in Hungary during a 15-month study period. Active infections prior to surgery, aortic dissection and scheduled pulmonary embolectomy, off-pump surgery were exclusion criteria.

Preoperative lack of infection was confirmed clinically (general physical examination, ENT, gynecological, urological consultations, dental examination) and with screening the preoperative CRP levels.

Risk predictors: elements of postoperative mortality risk predictor profile were collected according to the logistic EuroSCORE risk stratification. Additionally, other morbidity predictors that are not specified in the EuroSCORE, such as diabetes mellitus, body mass index, and serum albumin levels were also included in the analysis.

Assessment of the selenium level

Blood samples for whole blood selenium measurement were taken in the operating theatre immediately after the insertion of the central venous line. The samples were stored at -30 degree C until laboratory analysis. Whole blood selenium levels were measured by atomic absorption spectrometry in the laboratories of Byosin Arzneimittel GmbH (Fellbach, Germany). The laboratory team was unaware of the patients' previous history, health status, and the surgery planned. As blood samples for selenium were collected and analyzed later, the care provider team was unaware of the selenium level of the patients throughout the whole postoperative period. Diagnostic and therapeutic decisions were made entirely on the basis of the clinical routine.

Outcome parameters

The primary clinical outcome parameter was 30 days mortality after surgery. The predefined secondary outcome parameters were as follows:

- (1) Severe systemic inflammatory response syndrome (SIRS) on the first two postoperative days,
- (2) Infectious complications and severe sepsis throughout the in-hospital period,
- (3) Clinically most relevant postoperative organ dysfunctions, such as low output syndrome, postoperative atrial fibrillation, renal dysfunction necessitating renal replacement therapy.
- (4) Postoperative laboratory markers of inflammation: C-reactive protein (CRP), procalcitonine (PCT), Interleukin-6 (IL-6) and the degree of myocardial cell injury expressed with the release of cardiac Troponin-I (cTnI).

SIRS and severe SIRS were diagnosed on the basis of the ACCP/SCCM Consensus Guideline.

Postoperative acute renal failure was diagnosed according to the RIFLE criteria: (1) serum creatinine level above 350 $\mu\text{mol/L}$, or (2) three times higher

than the preoperative value, or (3) urine output lower than 0.3 ml/kg/hour for more than 24 hours, or anuria lasting more than 12 hours.

Statistical methods

The normality of the continuous data was tested with the Shapiro-Wilk and Shapiro-Francia-test. The equality of the variances was examined with the F-test. The mean values of the continuous parameters were compared with unpaired T-tests. Mann-Whitney rank-sum tests were used if the variances differed significantly ($p < 0.05$). The relationship between the whole blood selenium levels and the continuous variables were assessed with pairwise correlation analysis, the R-square values, and their significance was reported. Logistic regression models were fitted upon our data using the observed mortality as dependent variable to receive an explicit expression of the blood selenium concentrations' relative merit in the outcome. The basic model was the logistic EuroSCORE itself, in Model 1 the additional independent variable (besides the logistic EuroSCORE p-value) was the blood selenium concentration. The postoperative troponin I concentration and the EuroSCORE p-value were involved in Model 2. In Model 3 all three above mentioned variables were used as explanatory variables. The performance of these models was compared in ROC analysis. We considered the result of the statistical tests significant when $p < 0.05$.

Results

Results of the EuroSCORE II validation study in Debrecen

General description

A total of 2287 patients were included in the analysis, 1491 males and 796 females. Females were significantly older than males (61.7 ± 10.1 years vs. 64.4 ± 9.8 years, $p < 0.01$) and had a higher risk according to both scores.

Logistic EuroSCORE probabilities were 0.0727 ± 0.1037 for males vs. 0.0982 ± 0.1380 for females, $p < 0.001$. EuroSCORE II probabilities were 0.0397 ± 0.0619 for males vs. 0.0553 ± 0.0901 for females, $p < 0.001$.

Single coronary operations were performed in 1038 cases (45.4 %), the majority of which were on-pump procedures. Aortic valve replacement (AVR) was the most frequent non-coronary intervention.

The expected mortality of 8.18 % (95% CI: 7.7-8.6 %) as calculated by the logistic EuroSCORE, was significantly higher than the 4.5% (95% CI: 4.2% -4.8%) mortality predicted by EuroSCORE II, $p < 0.01$. 123 persons (5.4 %) died within 30 days following cardiac surgery.

The logistic EuroSCORE indicated higher risks in the majority of the cases. The EuroSCORE II p-values were higher in only 244 Individuals, 109 of whom died.

Comparison of calibrations for the logistic EuroSCORE and EuroSCORE II

The logistic EuroSCORE predicted a significantly higher ($p < 0.001$) mortality than we observed. The overall O:E ratio was 0.66. This means that the old EuroSCORE indicates 1.5-times higher-than-real mortality, which was rather variable among the different risk categories.

The H-L test also revealed a significant deviation in expected and observed mortality ($p = 0.0084$) when EuroSCORE II was used for the outcome prediction, but in this case the observed mortality was slightly higher than the expected one (O:E ratio = 1.19. Up to the 40% expected mortality rate the calibration was almost perfect. Above this level the function significantly underestimated the risk.

Discriminative power of the logistic EuroSCORE and EuroSCORE II

The results showed an AUC of 0.8177 (95 % CI: 0.7786-0.8569) for EuroSCORE II, which is slightly higher than the AUC (0.8017, 95 % CI: 0.7596-0.8438) of the logistic EuroSCORE, the difference not being significant ($p=0.1930$).

The Brier score for EuroSCORE II was 0.0447, which is also insignificantly lower than the logistic EuroSCORE's Brier score of 0.0457 ($p=0.775$).

The Brier score was equal or higher than 0.25 in the case of 119 patients (5.2 %) when EuroSCORE II was used for outcome prediction. It was 126 (5.5 %) with the logistic EuroSCORE. This means that the frequency of inaccurate predictions given by the old logistic EuroSCORE was only insignificantly higher than that experienced with the new EuroSCORE ($p=0.6521$).

Analysis of cardiac surgical subgroups

Further analyses were performed on the surgical subgroups created according to the “weight of intervention” categories defined by EuroSCORE II. The result of the Hosmer-Lemeshow test revealed a good calibration for EuroSCORE II in the single coronary operation group ($p=0.5789$). The new EuroSCORE slightly over-predicted the risk (O:E ratio=0.75). Its accuracy was also excellent with an AUC of 0.8118 (95 % CI: 0.7132-0.9105).

The calibration in the “other than isolated coronary” group showed less perfect goodness-of-fit with an HL-test p-value of 0.0084. The ROC AUC was also smaller: 0.7873 (95 % CI: 0.7401 - 0.8345). This group includes extremely diverse interventions and patients (see Table 2) that can be divided into three further subgroups according to the complexity of the intervention.

In the “single non-coronary” group the HL-test indicated poor calibration. Observed mortality was 1.77 times higher than expected mortality. In the two combined operation groups the accuracy of EuroSCORE II diminished with the increasing complexity of the procedure, and the calibrations were also unsatisfactory. However, the deviations were smaller compared with the single non-coronary procedures.

The Brier score was lowest in the isolated CABG group: 0.0195 with the lowest frequency (2.1%) of the patients with higher than 0.25. The BS increased with the complexity of the intervention and reached a rather high level of 0.1225 among those patients who underwent the most complex operations, indicating that the risk prediction was ambiguous in 13.2 % of the patients in this group.

Analysis of the procedural urgency subgroups

The O:E ratio of the elective procedures was 1.1 with no significant deviation between observed and expected mortality (HL-test $p=0.1396$). Both the ROC analysis and the BS revealed good discriminative power and accuracy in this subgroup.

In the urgent operation group, the O:E ratio of 1.045 showed only a small difference, and the result of the HL-test was not significant ($p=0.0921$). The ROC AUC reached only the acceptable level; however, the Brier scores were equal or higher than 0.25 in only 6.6 % of the patients, which is slightly higher than this ratio in the whole cohort.

With very high ratios of ambiguous predictions neither the calibration nor the accuracy proved to be satisfactory in the emergency and the salvage groups. A discrepancy was found between the result of ROC analysis and the Brier score in the emergency group, where the ROC AUC was as high as 0.7708, but the mean BS was 0.1945 with a ratio of 27.27 % for $BS \geq 0.25$.

Low selenium level as a cardiac surgical risk factor

197 patients, 71 females and 126 males, were enrolled in the research. Their mean age was 63.6 ± 9.6 years. The sum of the EuroSCORE was 13.65, which corresponds to a 6.93% expected mortality. The whole blood selenium level data were normally distributed.

Relationship between categorical risk predictors and whole blood selenium levels:

Selenium concentrations were significantly lower in patients with pulmonary hypertension (systolic pulmonary artery pressure higher than 60 mmHg), in those who required emergency surgery due to unstable angina, and in patients who suffered from myocardial infarction within 90 days prior to the operation.

The logistic EuroSCORE value, which is the predictable likelihood of death within 30 days following cardiac surgery, showed a relatively weak inverse correlation with the selenium level (R²: -0.2155, p<0.01). The calculated preoperative glomerular filtration rate (GRF) showed a weak positive correlation with the selenium level (R²: 0.2340, p<0.01) similarly with the body mass index and the preoperative albumin levels (R²: 0.2585, p<0.01 and R²:0.3437, p<0.01 respectively).

Age, gender, and selenium relationship

The mean selenium level of the 71 female participants was 106.4 ± 16.1 µg/L which is statistically significantly lower than the mean selenium concentration (113 ± 17.4 µg/L) of the males, p=0.01. A relatively strong correlation was found between the age and the whole blood selenium level with the calculated R-squared value of -0.325 (p<0.01).

Mortality, morbidity and selenium

The overall 30-day mortality of the cohort was 5.58% (n=11). The whole blood selenium level was lower (102.2 ± 19.5 µg/L) for non-survivors compared to that of survivors (111.1 ± 16.9 µg/L), this difference was statistically significant (p=0.047). The patients who developed low cardiac output syndrome and atrial fibrillation in the postoperative period had

significantly lower whole blood selenium concentration. Differences are apparent, but insignificant in cases of early postoperative SIRS and acute kidney injury. However it must be noted that the patients with the above mentioned complications were also older and had higher operative risk indicated by the logistic EuroSCORE. We were unable to demonstrate statistically significant differences in the mean selenium level of the patients with and without infectious complications including the postoperative sepsis and sternal wound infection.

Laboratory parameter, inflammatory and myocardial cell injury markers

The postoperative serum albumin concentration showed the strongest correlation with the selenium level ($R^2: 0.3423$, $p < 0.01$).

The CRP concentration on the first postoperative day correlated inversely with the selenium ($R^2: -0.2747$, $p < 0.01$), but neither the postoperative interleukin-6 nor the procalcitonine concentration showed statistically significant correlation with the selenium status. The more frequent renal injury among the patients with lower blood selenium are reflected by the correlation of the selenium level and the lowest postoperative GFR values ($R^2: 0.1728$, $p = 0.0152$) too.

Multivariate regression analysis

Logistic regression models were fitted upon our data. The 30-day mortality was the dependent variable in each of these models. The ROC area of the logistic EuroSCORE was 0.7399 (95 % CI: 0.5862-0.8913). Model 1 involving the logistic EuroSCORE p-value and the whole blood selenium concentration with the ROC area of 0.7913 (95% CI: 0.6884-0.8943) showed insignificantly ($p = 0.8590$) better performance in the outcome prediction than EuroSCORE alone. The EuroSCORE and the postoperative troponin I level were used as explanatory variables in Model 2. The ROC area was 0.8289

(95% CI: 0.6752-0.9827), however it was not significantly higher than EuroSCORE's ROC area ($p=0.2298$). Model 3 with three explanatory variables (selenium, EuroSCORE, troponin I) showed the highest ROC area: 0.9052 (95 % CI: 0.8340-0.9763), which was significantly higher than the ROC area of EuroSCORE ($p=0.0118$).

Discussions

Discussion of the EuroSCORE II validation study

Data collection for this validation study began after the completion of the recruitment phase of the EuroSCORE II project. Consequently, our results reflect the most current cardiac surgical outcomes. .

No major differences were detected in the composition of the risk predictors compared with the reported data in the original EuroSCORE publication. The mean age of our cohort was less than two years older and the ratio of female participants was slightly higher.

In accordance with other validation studies I have proved that the new EuroSCORE effectively and reliably predicted the risk for the majority of the patients who underwent the most frequent coronary bypass procedures, and proved to be satisfactory in general when the operation was performed electively. The O:E ratio of 0.75 indicated that EuroSCORE II tends to overestimate the real risk in coronary patients. However, it did not reach the level of statistical significance.

EuroSCORE II underestimated the real risk in those patients with higher than 0.6 EuroSCORE II p-values.

The second area of poor goodness-of-fit was that of the emergency and salvage procedures. The unsatisfactory calibration in the single non-coronary group is probably partially the consequence of the disproportionately higher ratio of emergency and salvage operations in this group. The other possible explanation is the older age of the patients who underwent aortic valve replacement. They were approximately five years older than the mean of the cohort.

The incidence of patients with a BS equal or higher than 0.25 was also calculated. I interpret this ratio as a marker of uncertainty of prediction. It was fairly low: 2.1 % among the coronary patients and 3.3 % in the elective procedures. However, results showed that more than 10% of the patients received uninformative or even misleading forecasts regarding the probability of death within the postoperative 30 days when non-elective procedures were needed. This ratio was more than one-quarter among patients who underwent emergency operations, and only a little lower than half in salvage operations. The ROC area reached lowest level in the salvage operations. However, it must be noted here that the low number of patients in this cohort prevents us from drawing profound conclusions. These findings are in keeping with the results of the recently published study by Grant et al on the performance of the new EuroSCORE among emergency patients. Besides inadequate accuracy, Grant et al have found an almost perfect O:E ratio in this group. However, EuroSCORE II overestimated the probability of mortality among the high-risk patients conversely compares with our own results.

The question may thus be raised as to whether these findings in the non-elective subgroups are due to the poor calibration of EuroSCORE II or whether other local and healthcare-related factors must also be taken into account?

When searching for an answer to the first part of the question, some practical aspects must be mentioned. EuroSCORE II gave inaccurate predictions when emergency operations were needed. This is understandable in situations where incomplete information collection may contribute to the more difficult prediction of the expectable outcome. It is also likely that the acutely deteriorated physiology results in more complex and multiple ways of the interactions among the risk factors. Unfortunately, interactions were not defined in EuroSCORE II. In addition to older age, those determinants that may most extensively modify the effect of other risk predictors probably account for the different degrees of urgency. Careful evaluation of the results provided by other studies may help exposing the local factors that otherwise cannot be distinguished from inadequate calibration.

A perfectly calibrated preoperative risk stratification model may well be a theoretical illusion, because it ab ovo lacks the information of several not-

included, “minor” factors as well as the effect of intraoperative and postoperative events, which may additively modify the outcome. These individual or healthcare related factors may be systematic or sporadic. The former—if they have a negative impact on the patients' outcome—should be revealed and corrected during continuous quality control.

The effect of the intraoperative and early postoperative factors may be reflected most practically in the course of the postoperative parameters and biomarkers such as cardiac troponines.

The frequent recalibration of the prognostic functions may help keep track of the better results in association with the fast development of cardiac surgery and other clinical areas in the recent years. It is very likely that the ratio of high-risk patients will increase in the future. The treatment of these elderly patients will become more complex and expensive, while the results will not be too much better. The solution for this problem may be the more frequent use of catheter-based techniques. Since these methods usually offer palliative solutions only and their costs are higher compared with traditional operations, and the selection of the patients for these new methods is not fully solved, the cardiac surgical risk stratification will become increasingly important.

Significance of low blood selenium in the perioperative period of cardiac surgery

In this study we prospectively assessed the association between preoperative whole blood selenium levels and different outcome parameters, such as mortality, postoperative complications, and laboratory markers in patients undergoing cardiac surgical operations. It is known that selenium deficiency is a risk factor for coronary heart disease and associated with chronic circulatory failure. These conditions occur quite frequently among cardiac surgical patients. Recently published studies found that a major operation itself and the extracorporeal circulation may result in increased oxidative stress and suggested selenium supplementation.

Data in the present study reflect Central European values. The blood selenium concentration shows significant geographical variations. The

population mean values are between 60 and 110 µg/L, which depends mainly on the quality of the soil which is the major source of subsistence.

The normal value for whole blood selenium concentration was 123.86 ± 19.14 µg/L in a previous survey performed on 96 healthy Hungarian individuals. According to recent data a daily intake of selenium that achieves a serum concentration of 80-95 µg/L maximizes the activity of seleno-enzymes. As the concentration of selenium in plasma is about 80% of that in the whole blood this corresponds with a total blood selenium of 100-120 µg/l. Selenium is connected to the albumin in the blood, so it is not surprising that the selenium concentration is relatively strongly correlated with the serum albumin concentration.

The age factor showed the second strongest correlation with blood selenium among the demographic and anthropometric variables. Statistically significant difference was found between men's and women's absolute blood selenium concentration too. If we accept that age is one of the major determinants of the selenium level, linear regression equations may be used for both men and women in order to describe the age-blood selenium concentration relationship. These equations were practically the same. Women were significantly older in this sample so the reported difference may be a statistical artifact caused by the higher age of the female participants in this study.

When assessing the association between the categorical preoperative parameters and whole blood selenium concentrations, We found that the presence of any risk predictor is associated with lower selenium level, however it reached the level of statistical significance only in case of an emergency operation due to unstable angina and recent myocardial infarction, as well as in case of pulmonary hypertension. This is in accordance with previous European studies showing an association between selenium levels and coronary heart disease and chronic heart failure. It is important to note that studies from the US could not prove this relationship. In our cohort, the association between selenium levels and worse cardiovascular status continued to exist in the postoperative phase as well: those with low selenium level more frequently showed low cardiac output syndrome and postoperative

atrial fibrillation. These conditions can be described with increased oxidative stress.

In a recently published study Stoppe and co-workers found that early lower postoperative whole blood selenium concentration is a predictive factor for the development of multiple organ failure following cardiac operations. Their hypothesis and the design of study were very similar to the present paper. They examined the perioperative data of 60 patients who underwent cardiac operations. The preoperative and immediate postoperative whole blood selenium levels were analyzed. The mean selenium concentration of their entire patient group was below the normal level of their geographical area (100-140 µg/L), even preoperatively, and a highly significant decrease was demonstrated in the concentration of selenium and other anti-oxidant trace elements (Cu, Zn). Patients who developed multiple organ failure later in the postoperative period showed spectacularly greater decrease in the trace element concentrations in the early postoperative period when they were relatively stable and complication free. Several mechanisms may be behind this trace element concentration decrease: such as redistribution, dilution, and depletion during oxygen species scavenging, however a clear explanation for this phenomenon is still lacking.

The design of the above mentioned study was very similar to my investigation but in the former an important question remained unanswered: the relative impact of the low antioxidant trace element status on the adverse outcome in context with other mortality and morbidity predictors. We have evaluated our Data in the present research was evaluated from this point of view as well.

In our study the primary outcome parameter was the within 30-day mortality following the cardiac operation. A statistically significant difference was found between the mean blood selenium concentration of the survivors and non-survivors. The age and the operative risk described by the logistic EuroSCORE were also higher among non-survivors. Assessing certain variables describing the postoperative morbidity (low cardiac output syndrome, postoperative atrial fibrillation, and acute kidney injury) similar age and EuroSCORE associations were observed. From these results it may be concluded that these complications are due to older age and higher operative risk of the affected participants.

In order to eliminate the effect of these confounders three different logistic regression models have been created involving the explanatory variables thought to be most predictive for the adverse outcome. These explanatory variables were the logistic EuroSCORE's p-value, the whole blood selenium, and the degree of postoperative troponin I release. The calculation of logistic EuroSCORE includes the age of the patients, thus age was not employed as independent variable. These variables were selected in three different ways. Only the model involving all three of these independent variables including the whole blood selenium concentration showed significantly better performance than EuroSCORE in ROC analysis ($p=0.0119$).

Selenium is a trace element of vital importance. As a co-factor of seleno-enzymes it plays a role in the protection against oxidative stress. It is incorporated as seleno-cystein into the active centre of glutathion-peroxidase. Common feature of SIRS, sepsis, multiple organ failure, and surgical trauma is the increased oxidative stress, when the generation of reactive oxygen metabolites exceeds the capacity of the pathways responsible for their elimination. These oxygen metabolites are responsible for cellular injury and initiate the secretion of further mediators and cytokines resulted in profound metabolic changes. These abnormalities will lead to increased mortality and morbidity. Currently we know very little about the selenium deficiency as a perioperative risk factor, because the measurement of blood selenium is not part of the everyday routine. On the basis of our results we conclude that the selenium status is not a negligible factor. Results of the present study indicate that the likelihood of severe selenium deficiency is increasing with the risk of surgery. The selenium concentration had very small beta-value in the regression analysis, therefore I claim it to be a minor risk factor. May it become more significant among the elderly patients with multiple co-existing diseases? This question can only be answered by randomised selenium substitution studies. Such future studies may help us answer another crucial question: whether a lower selenium level is only collateral to the more severe health status or whether it is a real event in the causality chain leading to higher mortality and morbidity.

Summary

We have proved EuroSCORE II to be more suitable for the outcome prediction of the cardiac surgical patients than its predecessor was.

However, EuroSCORE II is not optimally calibrated because it slightly overestimates the risk of coronary operations, while in the non-coronary group it predicts lower-than-real probability for the mortality within 30 days.

The inaccuracy of EuroSCORE increased with the complexity of the operations. In the high-risk categories the underestimation of the risk became more significant.

In non-elective operations both the calibration and the discriminative power were poorer compared with the elective operations.

EuroSCORE II in its current form appears to be suitable for the comparison of the results between different centres, but local recalibration may be useful to improve its performance.

We have demonstrated a potential clinical use of EuroSCORE II, when the significance of blood selenium as a cardiac surgical risk factor was studied. It makes the creation of homogenous patient groups unnecessary and, for this reason, the evaluation of minor risk factors becomes less cumbersome.

We have proved that the preoperative low blood selenium level's effect on mortality is small and possibly not independent from other risk predictors. The low selenium level was associated with recent myocardial infarction and pulmonary hypertension. Selenium substitution may only be effective among high risk patients. This information assists planning future studies in this field.



Register number: DEENKÉTK/258/2014.
Item number:
Subject: Ph.D. List of Publications

Candidate: György Koszta
Neptun ID: AL7KG8
MTMT ID: 10038450
Doctoral School: Doctoral School of Neurosciences

List of publications related to the dissertation

1. **Koszta, G.**, Sira, G., Szatmári, K., Farkas, E., Szerafin, T., Fülesdi, B.: Performance of EuroSCORE II in Hungary: A Single-centre Validation Study.
Heart Lung. Circ. Epub ahead of print (2014)
DOI: <http://dx.doi.org/10.1016/j.hlc.2014.04.005>
IF:1.172 (2013)
2. **Koszta, G.**, Kacska, Z., Szatmári, K., Szerafin, T., Fülesdi, B.: Lower whole blood selenium level is associated with higher operative risk and mortality following cardiac surgery.
J. Anesth. 26 (6), 812-821, 2012.
DOI: <http://dx.doi.org/10.1007/s00540-012-1454-y>
IF:0.867





List of other publications

3. **Kosztá G.**, Fülesdi B.: A szelén szerepe a cardiovascularis és intenzív kezelést igénylő betegségek létrejöttében és kezelésében.
Orv. Hetil. 154 (41), 1621-1627, 2013.
DOI: <http://dx.doi.org/10.1556/OH.2013.29727>

Total IF of journals (all publications): 2,039

Total IF of journals (publications related to the dissertation): 2,039

The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of Web of Science, Scopus and Journal Citation Report (Impact Factor) databases.

11 September, 2014



7. Acknowledgements

First of all I would like to say Thank You to my supervisor Dr. Béla Fülesdi who helped with his valuable advises in the preparation of the publications serving as the base of my Thesis.

Thanks to the colleagues in the Cardiac Surgical department, who helped with their precise work in the data collection.

Eszter Farkas MD and Per Arbrink MD were 6th year medical students in 2013/2014 academic year. They are practising doctors now. Their work was invaluable in the preparation of clinical data for statistical analysis.

Special Thanks to Dr. Olga Bársony for the linguistic correction of the manuscript of our articles, that speeded-up the publication process.

Last but not least I am grateful to my family for the loving background at home making my everyday practice possible.