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ORIGINAL ARTICLE

Lower whole blood selenium level is associated with higher operative risk and mortality following cardiac surgery

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Abstract
Purpose The authors intended to test their hypothesis that a low blood selenium level is associated with higher mortality, morbidity, and increased inflammatory response following cardiac surgery.
Methods A single-center clinical survey was conducted on 197 consecutive patients undergoing on-pump operation in Debrecen, Hungary. Blood samples for whole blood selenium analysis were taken immediately before the surgery. Their risk profiles were evaluated according to the EuroSCORE. The outcome parameters were as follows: 30-day mortality, incidence of systemic inflammatory response syndrome, and cardiac and renal dysfunction. The main laboratory outcome variables were the postoperative concentrations of C-reactive protein and cardiac troponin I.
Results The mean blood selenium level was significantly lower in non-survivors 102.2 ± 19.5 μg/L compared with survivors 111.1 ± 16.9 μg/L ($p = 0.047$), and the mean age, EuroSCORE values, and troponin concentrations were significantly higher in the non-survivors. To exclude these potential confounders a logistic regression model was fitted to our data, with mortality as the outcome and the EuroSCORE, the degree of troponin elevation, and selenium concentration as explanatory variables. This model revealed that a lower selenium level was a minor but apparently existing risk factor for postoperative mortality.
Conclusion Further examinations are required to clarify the question that remained unanswered in this study: the role of low selenium in the causality chain leading to higher postoperative mortality.

Keywords Selenium · Cardiac surgery · Mortality · Risk factors

Introduction

Selenium plays an important role in the defense against increased oxidative stress. Investigators have suggested that the requirement for this trace element is increased in the postoperative period owing to increased oxidative stress, or because of losses through drains or dialysis or through wounds [1, 2]. In accordance with this theory, recent perioperative studies have demonstrated that selenium concentrations decrease in the early postoperative period [3]. Nonetheless, the extent to which whole blood selenium concentration and perioperative complications and mortality are associated with each other remains unknown.

Reduced selenium intake is a risk factor for mortality in several diseases and pathological conditions, including lung and prostate cancer and coronary heart disease [4]. Additionally, a low selenium level is a marker of adverse outcome in sepsis and the prognosis may be improved by selenium supplementation [5, 6]. However, the results of studies on the effectiveness of selenium supplementation in critically ill patients are conflicting [6–9]. Although dose–response analyses have shown that a 50 % increase in selenium levels is associated with a 24 % reduction in

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coronary artery disease risk [10], placebo-controlled studies proved only a moderate risk reduction in the coronary artery disease mortality rate [10, 11]. As suggested by experimental data, increased oxidative stress may play a role in ischemia–reperfusion injury, where the myocardium itself is the most profoundly affected organ. However, it is extremely difficult to demonstrate this phenomenon in clinical studies [12].

On the basis of the previously mentioned data it is not impossible that selenium supplementation may be beneficial in cardiac surgical and other patients who are exposed to increased oxidative stress. However, the investigation of selenium concentration as a risk predictor seems to be necessary prior to supplementation studies in this field. In the present study we tested our hypothesis that low whole blood selenium concentration in cardiac surgical patients is associated with higher mortality, increased inflammatory response, and more frequent organ dysfunction in the postoperative period. Cardiac surgical patients are usually free from baseline infections. Their health status is evaluated in detail before the surgery. Their operative risk equivalent to the probability of an adverse outcome can be expressed numerically using clinical scoring systems. Cardiac surgical procedures are associated with profound physiological changes affecting the immunological and endocrine systems when extracorporeal circulation is used. For this reason cardiac surgery itself and the immediate postoperative period provide ideal conditions for the investigation of the clinical consequences of increased oxidative stress.

Patients, materials, and methods

We conducted a prospective, single-center clinical survey of 197 consecutive patients at the Cardiac Surgical Department of the University of Debrecen, Hungary, during a 15-month study period. Exclusion criteria were active infections prior to surgery, aortic dissection and scheduled pulmonary embolectomy, and off-pump surgery. Preoperative lack of infection was confirmed clinically (general physical examination; otorhinolaryngological, gynecological, and urological consultations; and dental examination) and by screening preoperative C-reactive protein (CRP) levels.

Risk predictors

We collected the elements of the postoperative mortality risk predictor profile according to the logistic EuroSCORE risk stratification system described elsewhere in detail [13]. 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 our analysis.

The surgical procedures were categorized into 3 groups: isolated coronary bypass grafting, heart valve surgery, and combined operations. The patients were sorted into the combined group if more than one heart valve was affected by the surgery or if valvular and coronary procedures were performed together. Owing to the complexity of an ascending aortic operation patients with this procedure were also sorted into the combined group. An individual was placed in the "Redo" category if there were one or more previous cardiac operations in the past history of the patient.

Assessment of selenium level

Blood samples for whole blood selenium measurement were taken immediately after insertion of the central venous line in the operating theater. The samples were stored at −30 °C until the laboratory analysis. Whole blood selenium levels were measured by atomic absorption spectrometry in the laboratories of Byosin Arzneimittel (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 levels of the patients throughout the whole postoperative period. Diagnostic and therapeutic decisions were made entirely on the basis of the clinical routine.

The oxygenator and the tubing system of the extracorporeal circuit were primed with 1400 mL lactated Ringer's solution. Crystalloid cardioplegic solution (1000 mL) was administered after the aortic cross-clamping. None of the patients required deep hypothermic circulatory arrest and only mild hypothermia was applied (goal rectal temperature 34 °C). The mean flow on the cardiopulmonary bypass (CPB) was 2.5–3.0 L/min/m^2. The baseline fluid intake was the standard 1 mL/kg/h during the first 12 h after the surgery.

Outcome parameters

The *primary* clinical outcome parameter was the 30-day 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 dysfunction, such as low cardiac output syndrome, postoperative

atrial fibrillation, and renal dysfunction necessitating renal replacement therapy.

(4) Postoperative laboratory markers of inflammation: CRP, procalcitonin (PCT), interleukin-6 (IL-6), and degree of myocardial cell injury expressed by the release of cardiac troponin-I (cTnI).

SIRS and severe SIRS were diagnosed on the basis of the ACCP/SCCM consensus guideline [14].

Postoperative acute renal failure was diagnosed according to the RIFLE criteria [15]: (1) serum creatinine level above 350 μmol/L, or (2) three times higher than the preoperative value, or (3) urine output lower than 0.3 mL/kg/h for more than 24 h, or anuria lasting more than 12 h.

Ethics

The study was approved by the Medical Ethics Committee of the University of Debrecen (H-4032, Debrecen, Nagyerdei krt. 98., Chairman: József Szentmiklósy M.D., Ph.D.) under registration number as follows DEOEC RKEB/KEB Nr. 3092A-2010. All patients provided written informed consent.

Statistical methods

Data were collected, stored, and processed with the help of the STATA10 (StataCorp, Texas, USA) statistical package. The normality of the continuous data was tested with the Shapiro–Wilk test and the Shapiro–Francia test. The equality of 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 ($p < 0.05$). Quartiles of the blood selenium concentration were created and the distribution of frequencies in the selenium quartiles was tested with the non-parametric Kruskal–Wallis rank test. The relationships between the whole blood selenium levels and the continuous variables were assessed with Spearman's rank correlation analysis, and the Spearman's rho values and their significance were reported.

Logistic regression models were fitted to our data, using the observed mortality as a dependent variable to obtain an explicit expression of the relative weight of the blood selenium concentration in the outcome. We used three logistic regression models in addition to the basic model. 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 of the above-mentioned variables were used as explanatory variables. The performance of these models was compared in receiver operating characteristic (ROC) analysis. We considered the results of the statistical tests significant when $p < 0.05$.

Results

We enrolled 197 patients, 71 females and 126 males, in the study. Their mean age was 63.6 ± 9.6 years. The sum of the EuroSCORE was 13.65, which corresponded to a 6.93 % expected mortality. The baseline characteristics of the cohort are summarized in Tables 1 and 2.

Whole blood selenium level

Figure 1 is a histogram of the measured whole blood selenium concentrations, showing that the data were normally distributed.

Relationship between age, gender, and selenium level

The mean selenium level in the 71 female participants was 106.4 ± 16.1 μg/L, which was significantly lower than the mean selenium concentration (113 ± 17.4 μg/L) in the males ($p = 0.01$). A relatively strong correlation was found between age and the whole blood selenium level (Table 2), with a calculated Spearman's rho value of −0.342 ($p < 0.01$). Age–whole blood selenium scatter plots, separately for females and males, together with the fitted lines of the age–whole blood selenium relationship, are depicted in Fig. 2. Equations describing the age–blood selenium relationship were established based on the results of linear regression. Equations describing the expectable blood selenium level, in μg/L, were as follows:

$$\text{for males}: \mathrm{Se}\,(\mu g/L) = 145 - 0.52 \times \text{ age (years)},$$

$$\text{for females}: \mathrm{Se}\,(\mu g/L) = 144 - 0.57 \times \text{ age (years)}.$$

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 owing to unstable angina, and in patients who had suffered from myocardial infarction within 90 days prior to the operation. The presence of other risk predictors did not show a statistically proven association with the selenium status (Table 1). A tendency was observed for an accumulation of patients with specific risk predictors in the first selenium quartile, but the Kruskal–Wallis test did not show significant frequency differences in case of any specific risk predictors, except for chronic atrial fibrillation.

Table 1 Association between risk predictors and whole blood selenium concentration

Risk predictor	Status	*n* (%)	Se (μg/L)	*p*	Frequencies in Selenium quartiles				
			Mean (SD)		1st	2nd	3rd	4th	*p*
Sex	Female	71 (36)	106.4 (16.1)		25	16	17	13	
	Male	126 (64)	113.0 (17.4)	0.01	25	33	32	36	ns
Operation type	CABG	89 (45)	111.6 (15.2)		18	25	23	23	
	Heart valve	49 (25)	110.0 (20.2)		16	11	9	13	
	Combined	59 (30)	109.7 (17.5)	ns	16	13	17	13	ns
Redo surgery	Yes	15 (7.6)	110.1 (16.0)		3	4	4	4	
	No	182 (92.4)	110.7 (17.3)	ns	47	45	45	45	ns
Diabetes mellitus	Yes	53 (27)	108.8 (18.8)		16	11	12	14	
	No	144 (73)	111.3 (16.6)	ns	34	38	37	35	ns
COPD	Yes	35 (18)	111.2 (13.3)		7	10	7	11	
	No	172 (82)	110.5 (17.9)	ns	43	39	42	38	ns
Pulmonary hypertension	Yes	14 (7)	102.2 (21.8)		7	2	1	4	
	No	183 (93)	111.3 (16.7)	0.0470	43	47	48	45	ns
Unstable angina	Yes	12 (6)	101.2 (9.7)		6	4	2	0	
	No	185 (94)	111.2 (17.4)	0.0267	44	45	47	49	0.0749
LV ejection fraction	<30 %	10 (5)	103.5 (14.5)		5	2	1	2	
	30–50 %	48 (24)	110.1 (19.1)		15	9	12	12	
	>50 %	139 (71)	111.3 (16.7)	ns	30	38	36	35	0.0749
MI within 90 days	Yes	9 (4.6)	101.2 (13.6)		5	2	1	1	
	No	188 (95.4)	111.1 (17.2)	0.0467	45	57	48	48	ns
Chronic atrial fibrillation	Yes	15 (7.6)	105.1 (23.7)		7	2	0	6	
	No	182 (92.4)	111.1 (16.5)	ns	43	47	49	43	0.0261
Peripheral vascular disease	Yes	64 (32.5)	111.4 (18.6)		15	17	13	19	
	No	133 (67.5)	110.2 (16.5)	ns	35	32	36	30	ns
Prior cerebrovascular accident	Yes	20 (10.2)	105.8 (17.1)		5	8	4	3	
	No	177 (89.8)	111.2 (17.7)	ns	45	41	45	46	ns
Emergency surgery	Yes	8 (4)	100.0 (7.2)		4	3	1	0	
	No	189 (96)	111.1 (17.4)	0.0302	46	46	48	49	ns

Intervals of the selenium quartiles: 1st, 60.6–99.5 μg/L; 2nd, 99.8–109.8 μg/L; 3rd, 110.2–119.1 μg/L; 4th, 119.7–156.9 μg/L

CABG coronary artery bypass grafting, *COPD* chronic obstructive pulmonary disease, *LV* left ventricle, *MI* myocardial infarction, *SD* standard deviation, *ns* not significant

Table 2 Results of Spearman's rank correlation analysis of continuous baseline variables and whole blood selenium concentration

Parameter	Mean	SD	Spearman's rho	*p*
Age (years)	63.60	9.6	−0.3420	<0.01
BMI (kg/m^2)	29.4	12.1	0.2736	<0.01
Preoperative albumin (g/L)	41.7	4.8	0.3531	<0.01
EuroSCORE (%)	6.9	8.7	−0.3118	<0.01
Preoperative GFR (L/min/1.73 m^2)	76.2	30.7	0.1713	<0.0161

SD standard deviation, *BMI* body mass index, *GFR* glomerular filtration rate

Table 2 summarizes the relationship between whole blood selenium levels and the continuous preoperative parameters. The logistic EuroSCORE value, which is the predictable likelihood of death within 30 days following cardiac surgery, showed an inverse correlation with the selenium level (Spearman's rho −0.3118, $p < 0.01$). The calculated preoperative glomerular filtration rate (GFR) showed a weak positive correlation with the selenium level (Spearman's rho 0.1713, $p < 0.0161$) as did the body mass index and the preoperative albumin level (Spearman's rho 0.2736, $p < 0.01$ and Spearman's rho 0.3531, $p < 0.01$, respectively).

Mortality, morbidity, and selenium level

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) in non-survivors compared with that in survivors (111.1 ± 16.9 μg/L), and this difference was statistically significant ($p = 0.047$). Six of the non-surviving patients were in the first selenium quartile. The patients who developed low cardiac output syndrome and those who developed atrial fibrillation in the postoperative period had significantly lower whole blood selenium concentrations than patients without these characteristics. Differences in mean selenium concentrations were apparent, but not significant, in patients with early postoperative SIRS and those with acute kidney injury (Table 3).

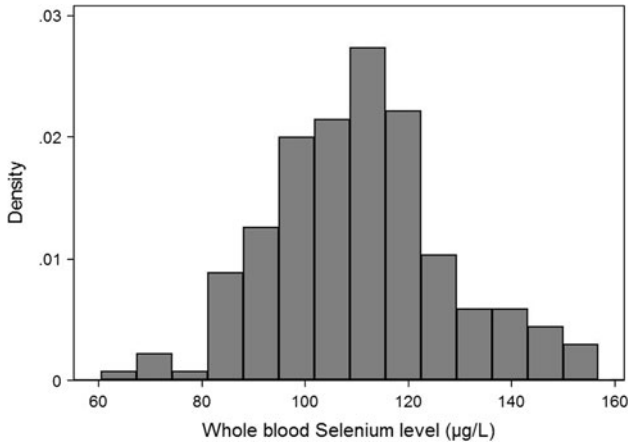

Fig. 1 Histogram of the whole blood selenium in the cohort

However, it must be noted that the patients with the abovementioned complications were also older than those without complications, and had a higher operative risk, as indicated by the logistic EuroSCORE. Their extracorporeal circulation and aortic cross-clamping times were significantly longer than those in the complication free group. These differences may be clinically important among the non-survivors and among those who developed early postoperative SIRS. A similar relationship to that of extracorporeal circulation and aortic cross clamping times was demonstrated by assessing the degree of postoperative troponin-I elevation (Table 4). We were unable to demonstrate any statistically significant differences in the mean selenium level between patients with and without infectious complications (including postoperative sepsis and sternal wound infection).

Laboratory parameters and inflammatory and myocardial cell injury markers (Table 5)

The mean preoperative CRP concentration in the studied cohort was 7.24 ± 3.93 mg/L. There was no significant difference in this laboratory parameter between the survivors (7.05 ± 3.45 mg/L) and the non-survivors (7.71 ± 4.91 mg/L).

The CRP concentration on the first postoperative day was inversely correlated with the selenium level (Spearman's rho −0.2499, $p < 0.01$), but neither the postoperative IL-6 nor the postoperative PCT concentrations showed a statistically significant correlation with selenium status. Also, the greater frequency of renal injury among the

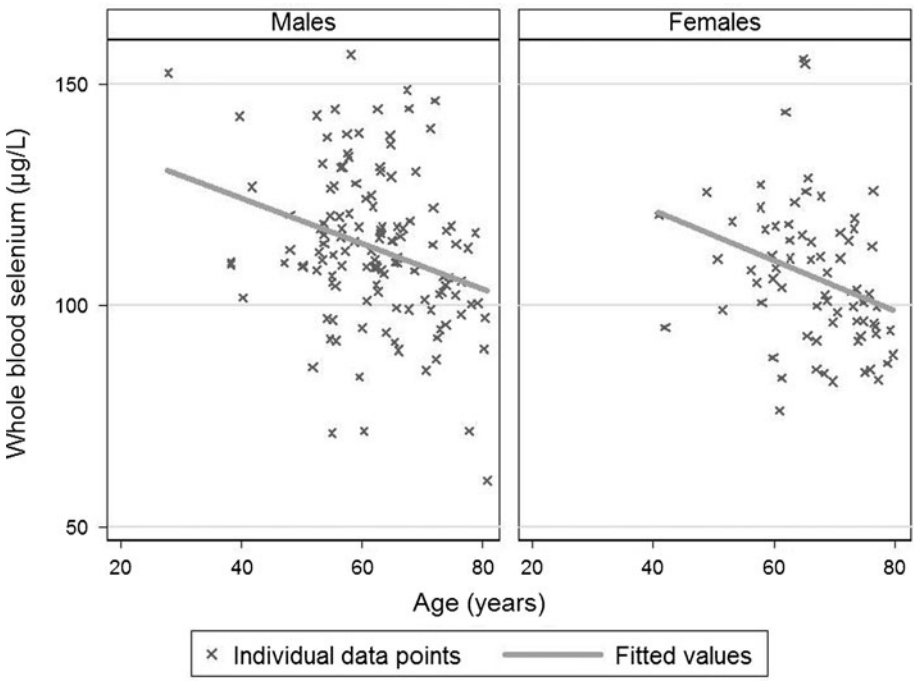

Fig. 2 Scatter plots and fitted lines of the age–whole blood selenium relationship, shown separately in males and females

Table 3 Association between categorical outcome parameters and whole blood selenium concentration

Outcome parameter	Status	*n* (%)	Se (μg/L)	*p*	Frequencies in selenium quartiles				
			Mean (SD)		1st	2nd	3rd	4th	*p*
Mortality	Yes	11 (5.6)	102.2 (19.5)		6	2	1	2	
	No	186 (94.4)	111.1 (16.9)	0.0470	44	47	48	47	0.1409
SIRS	Yes	26 (13.2)	105.6 (17.1)		10	7	4	5	
	No	171 (86.8)	111.4 (17.2)	0.0558	40	42	45	44	0.3182
LOS	Yes	52 (26.4)	106,6 (16.3)		19	11	13	9	
	No	145 (73.6)	112.1 (17.3)	0.0252	31	38	36	40	0.1413
a-Fib	Yes	60 (30.5)	106,4 (18.8)		23	10	14	13	
	No	137 (69.5)	112.5 (16.2)	0.0105	27	39	35	36	0.0378
AKI	Yes	14 (7.1)	103.9 (19.9)		6	3	2	3	
	No	183 (92.9)	111.1 (16.9)	0.0636	44	46	47	46	0.4534
Sepsis	Yes	17 (8.6)	107.4 (21.8)		6	5	1	5	
	No	180 (91.4)	110.9 (16.7)	ns	44	44	48	44	0.2948
Wound infection	Yes	12 (6.1)	110.4 (18.1)		4	2	3	3	
	No	185 (93.9)	110.6 (17.2)	ns	46	47	46	46	0.8823

Intervals of the selenium quartiles: 1st, 60.6–99.5 μg/L; 2nd, 99.8–109.8 μg/L; 3rd, 110.2–119.1 μg/L; 4th, 119.7–156.9 μg/L

SIRS systemic inflammatory response syndrome, *LOS* low cardiac output syndrome, *a-FIB* atrial fibrillation, *AKI* acute kidney injury, *SD* standard deviation

patients with lower blood selenium was reflected by the correlation of the selenium level and the lowest postoperative GFR value (Spearman's rho 0.1722, $p = 0.0155$). The serum albumin concentration on the 7th postoperative day showed a strong correlation with the selenium level (Spearman's rho 0.3505, $p < 0.01$).

Multivariate regression analysis

The beta values and the odds ratios of the explanatory variables of the three different logistic models are summarized in Table 6. 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 whole blood selenium level, with an ROC area of 0.7913 (95 % CI 0.6884–0.8943), showed a non-significant ($p = 0.8590$) better performance in the outcome prediction than the EuroSCORE alone. The EuroSCORE and 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 the 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), and thiswas significantly higher than the ROC area of the EuroSCORE ($p = 0.0118$). The ROC curves of the above three models are depicted in Fig. 3.

Discussion

Selenium is an important trace element that is involved in defense mechanisms against oxidative stress through selenoproteins, most of which are antioxidant enzymes [16, 17]. The incorporation of selenium into selenocysteine is an essential step in creating a redox-active center of glutathione peroxidase (GPx) and other enzymes. Systemic inflammatory response syndrome, sepsis, multiple organ dysfunction syndrome, and major trauma are characterized by increased oxidative stress, where the formation of reactive oxygen species (ROS) exceeds the capacity of the pathways responsible for their elimination. Beyond direct cell membrane damage, ROS initiate the synthesis of several cytokines with metabolic effect. These pathophysiological changes altering the function of organ systems result in increased morbidity and mortality [18].

In the present 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. There are several reasons why we conducted this investigation in this cohort. First, patients undergoing cardiac surgery represent a relatively homogeneous cohort, with very similar preoperative risk factor profiles. Additionally, complete exclusion of any inflammatory source is usually performed prior to surgery in all patients, and their general health condition and the expected outcome can be expressed

Table 4 Association between postoperative complications and major outcome predictors

Outcome parameter	Status	*n* (%)	Age (years)	*p*	EuroSCORE (%)	*p*	cTnI (μg/L)	*p*	ECC time (min)		AX time (min)	
			Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	*p*	Min (SD)	*p*
Mortality	Yes	11 (5.6)	69 (2.0)		16.88 (18.85)		24.55 (30.11)		120 (44)		82 (24)	
	No	186 (94.4)	63.3 (0.7)	0.0271	6.34 (7.46)	<0.01	2.68 (7.10)	<0.01*	78 (32)	<0.01	53 (26)	<0.01
SIRS	Yes	26 (13.2)	66.8 (7.5)		16.46 (17.12)		14.32 (22.28)		112 (40)		73 (30)	
	No	171 (86.8)	63.1 (9.8)	0.0355	5.48 (5.39)	<0.01	2.31 (6.70)	<0.01*	75 (30)	<0.01	52 (25)	<0.01
LOS	Yes	52 (26.4)	67.2 (7.7)		12.03 (13.22)		9.45 (4.86)		98 (38)		66 (28)	
	No	145 (73.6)	62.3 (9.9)	<0.01*	5.10 (5.42)	<0.01	1.91 (18.64)	<0.01*	73 (30)	<0.01	50 (25)	<0.01
a-Fib	Yes	60 (30.5)	67 (7.4)		10.74 (12.76)		6.18 (15.48)		87 (40)		58 (30)	
	No	137 (69.5)	61.6 (9.9)	<0.01*	5.26 (5.51)	<0.01	2.90 (7.10)	ns*	77 (30)	ns	53 (25)	ns
AKI	Yes	14 (7.1)	67.8 (5.9)		13.96 (15.64)		13.23 (8.43)		105 (44)		73 (27)	
	No	183 (92.9)	63.3 (9.8)	ns*	6.34 (7.62)	<0.01	3.18 (26.39)	ns*	78 (32)	0.0170	53 (26)	<0.01
Sepsis	Yes	17 (8.6)	66 (7.4)		13.12 (15.60)		11.84 (24.94)		99 (41)		68 (28)	
	No	180 (91.4)	63.3 (9.8)	ns	6.34 (7.62)	0.0381	3.15 (8.25)	ns*	78 (33)	<0.01	53 (27)	0.0141
Wound infection	Yes	12 (6.1)	64.1 (7.2)		6.29 (8.90)		5.23 (10.96)		93 (31)		57 (25)	
	No	185 (93.9)	63.5 (9.8)	ns	6.97 (6.10)	ns	3.81 (10.23)	ns*	79 (34)	ns	54 (27)	ns

SIRS systemic inflammatory response syndrome, *LOS* Low cardiac output syndrome, *a-FIB* atrial fibrillation, *AKI* acute kidney injury, *cTnI* cardiac troponin I, *ECC* extracorporeal circulation, *AX* aortic cross-clamping, *SD* standard deviation

Asterisks were used to indicate if non-parametric statistical test were used when calculating the *p*-value

Table 5 Results of Spearman's rank correlation analysis of the continuous outcome variables and the whole blood selenium concentration

Parameter	Mean	SD	Spearman's rho	*p*
Postoperative CRP (mg/L)	119.6	70.7	−0.2499	<0.01
Postoperative PCT (μg/L)	2.1	4.5	−0.0172	ns
Postoperative IL-6 (μg/L)	137.1	107.1	−0.0437	ns
Postoperative albumin (g/L)	34.4	6.7	0.3505	<0.01
Postoperative min GFR (L/min/1.73 m^2)	60.2	26.3	0.1722	0.0155
Postoperative cTnI (μg/L)	3.9	10.9	0.0257	ns

CRP C-reactive protein, *PCT* procalcitonin, *IL-6* interleukin-6, *GFR* glomerular filtration rate, *cTnI* cardiac troponin I

quantitatively by the EuroSCORE risk stratification system [13]. Second, it has been proven that low selenium levels may be associated with an increased risk of coronary heart disease [10] and chronic heart failure [19], conditions that frequently occur in our patient group. Third, recently published studies have confirmed that surgery alone, but even more, the use of cardiopulmonary bypass (CPB), represents an increased oxidative stress situation [20] which, theoretically, may be prevented by selenium supplementation.

In the first part of our "Results" section we provided a description of preoperative whole blood selenium levels in our cohort. It is important to note that these figures represent Central European data. Selenium levels show large geographic variations, ranging from 60 to 110 μg/L, depending on the origin and quality of the soil the food supply comes from [3, 21–24].

The normal value for the whole blood selenium level was 123.86 ± 19.14 μg/L in a previous survey performed in 96 healthy Hungarian individuals [3]. 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 [25]. As the concentration of selenium in plasma is about 80 % of that in whole blood, this corresponds to a total blood selenium level of 100–120 μg/L. Selenium is connected to albumin in the blood so it is not surprising that the selenium concentration is correlated relatively strongly with the serum albumin concentration. In the present study, none of the investigated individuals demonstrated a pathologically low albumin concentration preoperatively (which might have been associated with a risk of adverse outcomes). An association between lower albumin and lower selenium concentrations was apparent on the 7th postoperative day; however, several other factors

Table 6 Logistic regression models describing the relative weight of whole blood selenium in the postoperative outcome following cardiac surgery

	EuroSCORE	Model 1	Model 2	Model 3
Constant	–	−0.7	−4.0	1.4
Selenium				
Beta	–	−0.026	–	−0.052
OR (95 % CI)	–	0.97 (0.94–1.01)	–	0.95 (0.90–0.99)
p	–	0.209	–	0.033
Troponin I				
Beta	–	–	0.07	0.077
OR (95 % CI)	–	–	1.1 (1–1.12)	1.1 (1.0–1.12)
p	–	–	<0.01	<0.01
EuroSCORE *p* value				
Beta	–	5.95	5.76	5.37
OR (95 % CI)	–	382.0 (5.4–26960)	317.0 (4.4–22886)	215.2 (2.1–22327)
p	–	0.006	<0.01	0.023
ROC area	0.7388	0.7913	0.8289	0.9052
R^2	–	0.1143	0.2736	0.3310

OR odds ratio, *ROC* receiver operating characteristics, *95 % CI* 95 % confidence interval

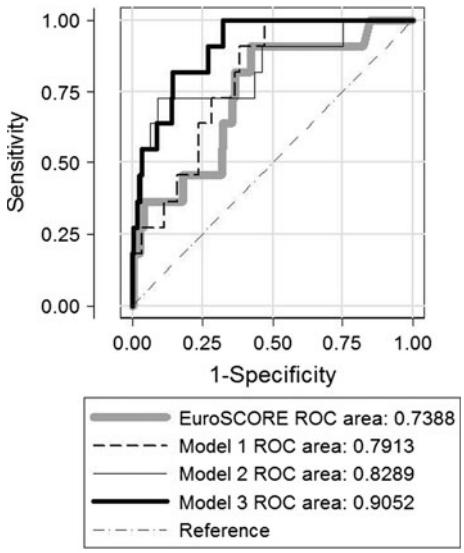

Fig. 3 Receiver operating characteristics (*ROC*) curves of the EuroSCORE and three logistic regression models

such as the effect of variable fluid retention may have been involved in this phenomenon.

Among the demographic and anthropometric variables we examined, age showed a strong correlation with the blood selenium level. Also, a statistically significant difference was found between the men's and women's absolute blood selenium concentrations. If we accept that age is one of the major determinants of the selenium level, linear regression equations can be created for both men and women in order to describe the age–whole blood selenium concentration relationship. We found that these equations were practically the same in men and women in our cohort. However, the women in this sample were significantly older than the men so the reported difference may be a statistical artifact caused by the higher age of the female participants in this study. Surprisingly, of the three inflammatory markers studied, only the postoperative CRP level showed a statistically significant, but actually weak, correlation with selenium.

When assessing the association between the categorical preoperative parameters and whole blood selenium concentrations, we found that the presence of any risk predictor was associated with a lower selenium level. However, the level of statistical significance was reached only for the risk predictors of urgent operations owing to unstable angina and recent myocardial infarction, as well as in patients with pulmonary hypertension. This finding is in accordance with previous European studies showing associations between selenium levels and coronary heart disease [10] as well as chronic heart failure [19]. It is important to note that studies from the United States did not confirm this relationship [4]. 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 levels more frequently presented with low cardiac output syndrome and postoperative atrial fibrillation. These conditions are partially characterized by increased oxidative stress.

In a recently published study, Stoppe et al. [26] found that lower early postoperative whole blood selenium concentration was a predictive factor for the development of multiple organ failure following cardiac operations. 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 in their entire patient group was below the normal level of their geographic area (100–140 μg/L) even preoperatively, and a highly significant decrease was demonstrated in the concentrations of selenium and other antioxidant trace elements (Cu, Zn). The patients who developed multiple organ failure later in the postoperative period, compared with those without such multiple organ failure, showed a spectacularly greater decrease in trace element concentrations in the early postoperative period when they were relatively stable and complication-free. Several mechanisms may be behind the fall in the concentrations of trace elements, such as redistribution, dilution, and depletion during oxygen species scavenging. However, a clear explanation for this phenomenon is still lacking.

To date we are not aware of any other clinical investigations concerned specifically with blood selenium concentration as a risk factor following cardiac surgery, except for the cited study by Stoppe et al. [26]. Their hypothesis and the design of their study were very similar to those of the present study. However, an important question was left unanswered in their study: the relative impact of the low antioxidant trace element status on adverse outcome in the context of other mortality and morbidity predictors. We have analyzed our data from this point of view. In our study the primary outcome parameter was the 30-day mortality following the cardiac operation and not the development of multiple organ failure. We evaluated the initial, preoperative blood selenium concentration, because this may be more relevant than the postoperative level as a risk predictor as it is not affected by intraoperative factors. Changes in the selenium concentration during CPB and the immediate postoperative period may be influenced by several, not fully understood mechanisms, making it very difficult to perform a correct analysis and draw valid conclusions. In the present study, we found a statistically significant difference between the mean blood selenium concentrations of the survivors and non-survivors. Also, age and the operative risk described by the logistic EuroSCORE were higher among non-survivors. Our assessment of certain variables describing postoperative morbidity (low cardiac output syndrome, postoperative atrial fibrillation, and acute kidney injury) revealed similar age and EuroSCORE associations with these variables. From these results it can be supposed that these complications were due to the older age and higher operative risk of the affected participants.

As we have seen above, the patients who died were not only older but also had a higher operative risk and greater cardiac troponin I release. In order to exclude the effect of these confounders, we created three different logistic regression models involving the explanatory variables thought to be the most predictive for an adverse outcome. These explanatory variables were the logistic EuroSCORE's p value, whole blood selenium level, and the degree of postoperative troponin I release. The calculation of the logistic EuroSCORE includes the age of the patients so we did not use age as an 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 the EuroSCORE in the ROC analysis ($p = 0.0119$). Very little practical data is available about the role of selenium deficiency as a risk factor for adverse outcome following cardiac surgery because checking the selenium concentration is not part of the preoperative routine and it will probably not be part of it in the future, either. However, we can be confident that selenium status is not a negligible factor. The new information confirmed in the present study is that the likelihood of selenium deficiency increases with the general operative risk. Evaluation of the beta values and the odds ratios revealed a very low influence of whole blood selenium on the outcome. The question of whether this minor effect may be more meaningful among elderly patients with several comorbidities can only be answered by randomized, controlled selenium supplementation studies performed in high-risk elderly patients scheduled for cardiac surgery. This topic is very close to the subject of selenium supplementation studies in septic patients. However, its concept differs basically from those studies. In contrast to the major selenium supplementation studies [27]—which usually failed to demonstrate any beneficial effect on mortality— randomized, controlled selenium supplementation studies performed in high-risk elderly patients scheduled for cardiac surgery would involve pre-emptive selenium supplementation in patients who are originally not critically ill, but in whom the likelihood of the postoperative deterioration of their status is very high.

Such future studies may help us to answer another interesting question, too; namely, 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.

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