Time course and relationship between plasma selenium concentrations, systemic inflammatory response, sepsis, and multiorgan failure

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Background. Selenium plays an important role in defence against acute illness. We investigated, in intensive care unit (ICU) patients, the time course of plasma selenium concentrations and their relationship to systemic inflammatory response syndrome (SIRS), organ dysfunction/failure, infection, and ICU outcome.

Methods. Plasma selenium and laboratory indices of organ dysfunction/failure, tissue inflammation, and infection were measured daily during the ICU stay in 60 consecutive ICU patients, 15 in each of four a priori defined subgroups: ICU controls (no SIRS); uncomplicated SIRS; severe SIRS; and severe sepsis/septic shock.

Results. Plasma selenium concentrations were below standard values for healthy subjects (74 μg litre⁻¹) in 55 patients (92%). Selenium concentrations decreased during the ICU stay in all groups, except controls, to a minimum value that was lower in patients with organ failure, particularly in those with infection. The minimum plasma selenium was inversely correlated to admission Acute Physiology and Chronic Health Evaluation II and Simplified Acute Physiology System II scores, indicators of inflammation, and the maximal degree of organ dysfunction/failure during the ICU stay. Plasma selenium was positively correlated with minimum platelet count, minimum plasma antithrombin activity, and protein C activity. In a receiver operator characteristic analysis, SAPS II score [area under the curve (AUC)=0.903] and minimum selenium concentration (AUC=0.867) were the strongest predictive factors for ICU mortality.

Conclusions. In critically ill surgical patients, plasma selenium concentrations are generally low with a greater decrease during the ICU stay in patients with organ failure, especially when attributed to infection. Lower plasma selenium concentrations are associated with more tissue damage, the presence of infection or organ dysfunction/failure, and increased ICU mortality.

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Selenium is an essential trace element with antioxidant and immunological functions. In humans, selenium is incorporated in an amino acid, selenocysteine, which is essential for the enzymatic functioning of selenoproteins, such as glutathione peroxidase (GPx), thioredoxin reductase, and iodine deiodinase.1,2 In Europe, selenium status, as determined by selenium concentrations in serum or plasma1 or by selenium intake,3 is not adequate for optimal GPx or immune function.1,2

Several studies have demonstrated impaired selenium kinetics in situations of acute oxidative stress in the intensive care unit (ICU).4–6 Forceville and colleagues5 observed low plasma selenium concentrations in ICU patients for more than 2 weeks and these concentrations correlated with outcome and organ failure.

†Declaration of interest. Dr Reinhart has received Speaker’s fees from Biosyn in the past 5 yr.
A meta-analysis by the Cochrane group failed to show any effect of selenium supplementation on outcome. However, a more recent meta-analysis showed that selenium supplementation was associated with a trend towards a lower mortality. Characterizing the relationship between plasma selenium concentrations and parameters of tissue inflammation/infection and organ dysfunction/failure may, thus, help in understanding the role of selenium in systemic inflammatory response syndrome (SIRS), sepsis, and multiple organ failure (MOF) and in identifying groups of patients who might benefit from selenium supplementation.

The aim of our study was, therefore, to investigate the time course of plasma selenium concentrations in critically ill patients and the relationship of selenium concentrations to the presence of SIRS, organ failure, infection, and ICU outcome.

**Methods**

The study was approved by the Ethics Committee of Friedrich Schiller University hospital, and informed consent was obtained on admission to the ICU from all patients or their next-of-kin. Fifteen consecutive patients were included in each of four a priori defined subgroups: (i) ICU controls (no SIRS group) included patients with no evidence of SIRS, organ failure, or infection throughout the ICU stay; (ii) the uncomplicated SIRS group included patients fulfilling SIRS criteria without any underlying infection or associated organ failure in the ICU; (iii) the severe SIRS group included patients with established SIRS with accompanying organ failure with no evidence of underlying infection; and (iv) patients with a diagnosis of severe sepsis/septic shock. A total of 60 patients admitted to the 50-bed surgical ICU were, therefore, included in the study. Patients were included in the corresponding group on the first day after operation. If SIRS, severe SIRS, or severe sepsis developed later during the ICU stay, patients were reclassified into the corresponding group until the predefined number of patients in each group was reached. Exclusion criteria were: patients aged less than 18, advanced malignancy or other conditions with shortened life expectancy (<4 weeks), pregnancy, readmission after previous inclusion in the study, and patients in whom decisions to withhold or withdraw life-sustaining treatments were taken within the first 24 h of ICU admission.

SIRS, severe sepsis, and septic shock were defined according to the ACCP/SCCM consensus conference criteria. Infection was defined on the basis of clinical history, clinical symptoms, physical examination, and laboratory findings, suggesting the presence of infection (a known or strongly suspected source of infection with positive bacterial culture for a pathogen or presence of gross pus in a closed space) that justified administration of antimicrobial prophylaxis. Microbiologically documented infection was defined as infection supported by positive cultures of blood or body fluid from a site of suspected infection. Clinically documented infection was defined as the presence of gross pus or an abscess (anatomical or by imagery and histological evidence), but no microbiological confirmation as cultures remained sterile because of ongoing antibiotic therapy. Central nervous system failure was defined as disturbed consciousness, irritability, disorientation, or delirium without evidence of drug-induced manifestations; thrombocytopenia as platelet count <100 × 10^3 μl^-1 or >30% decline within 24 h without evidence of blood loss as an aetiological factor; respiratory failure as P_{A_{O_2}} <10 kPa in room air, P_{A_{O_2}}/F_{I_{O_2}} <33 kPa; cardiovascular failure as systolic blood pressure <90 mm Hg or mean arterial pressure <70 mm Hg for at least 1 h, despite adequate fluid resuscitation; renal failure as urinary output <0.5 ml kg^-1 h^-1 for at least 1 h in the absence of hypovolaemia or a two-fold increase in serum creatinine; and metabolic acidosis as base excess <−5 mEq litre^-1 or a plasma lactate concentration 1.5 times above the reference value.

The Acute Physiology and Chronic Health Evaluation (APACHE) II and the Simplified Acute Physiology System (SAPS II) scores were obtained within 24 h of admission. The sequential organ failure assessment (SOFA) score was calculated daily. The maximum SOFA score (SOFA_max) was defined as the highest SOFA score reached during the ICU stay. Data recorded on admission included age, sex, referring facility, primary and secondary admission diagnoses, associated co-morbidities, and surgical procedures preceding admission. The presence of SIRS criteria, organ failure, and infection was recorded daily together with the laboratory indices of organ dysfunction/failure (including platelet count, serum total bilirubin, serum creatinine, and serum lactate concentration), and markers of tissue inflammation and infection (including total leucocyte count, C-reactive protein (CRP), and procalcitonin (PCT)). In the case of clinically suspected infection, blood cultures were obtained together with specimens from all relevant sites (bronchial aspirates, urine, catheter tip, and pleural and ascitic fluids) for microbiological studies.

Blood samples were collected daily at 6 a.m.; routine indicators of organ dysfunction/failure were measured using automated measures in our laboratories. Lactate concentrations in arterial samples were measured using an automated blood gas analyser (ABL700 Radiometer, Copenhagen, Denmark). PCT was measured using an immuno-luminometric assay (LUMTest PCT, Brahms Diagnostica, Berlin, Germany) on a Berilux Analyzer 250 (Behring Diagnostics, Marburg, Germany), CRP was measured using a nephelometric assay (Dade-Behring), and interleukin-6 (IL-6) concentrations were measured with a commercial ELISA (Technoclone, Heidelberg, Germany; R&D systems, Hamburg, Germany). Protein C and antithrombin activities were determined chromogenically by the Coamatic®-Test (Chromogenix, Mölndal, Sweden).
Selenium concentrations in sepsis

Serum was separated 2–3 h after collection and stored at −80°C for the later determination of plasma selenium concentrations. Plasma selenium was measured by electrothermal atomic absorption spectrometry using a spectrometer equipped with a Zeeman effect background correction (5100 PC, Perkin-Elmer, Paris, France). Plasma selenium measurements were performed by staff in the laboratories of Biosyn Arzneimittel GmbH (Fellbach, Germany) blinded to the patient’s condition and clinical course, group assignment, and outcome.

Patients without SIRS and those with uncomplicated SIRS received balanced oral meals with no additional supplements. Patients in the severe SIRS and severe sepsis/septic shock groups received artificial enteral (n=29) or parenteral (n=1) nutritional support. Enteral formulas in our institution provide 100 µg of selenium per day (Sondalis Iso®, Nestlé Nutrition, UK) using a continuous perfusion through gastric or duodenal (three patients because of gastric reflux >500 day⁻¹) feeding tubes. Our target caloric intake was 25 kcal kg⁻¹ ml h⁻¹ (ideal body weight) per day and this was achieved in 2–3 days in all patients. The minimal infusion rate in the 29 patients fed enterally was 21 ml h⁻¹ (500 ml of Sondalis Iso⁰ day⁻¹, equivalent to 25 µg of selenium per day), mostly during the first day, and the median amount administered over the ICU stay was 1500 ml (inter-quartile range: 500–2000). Additional micronutrient supplements included two vials of electrolytes and multi-trace elements (Inzolen HK®, Dr F. Koeler Chemie, Alsbach-Haenlein, Germany) each containing 3.1 mg of Zn, 1.8 mg of Cu, and 0.99 mg of Mn, one vial of multivitamins (Cernevit®, Baxter AG, Volketswil, Switzerland) containing 3.5 mg of thiamine, 11.2 IU of vitamin E, and 500 mg of vitamin C. The patient fed parenterally received a multi-trace element supplementation (Tracitrans Plus AMP, Fresenius Kabi, Bad Homburg v.d.H., Germany) containing 105 µg of selenium in the form of sodium selenite.

Statistical analysis

Data were analysed using SPSS 12.0 for windows (SPSS Inc., Chicago, IL, USA). Kolmogorov–Smirnov test was used to verify the normality of distribution of continuous variables. Non-parametric tests were used for non-normally distributed variables. Differences between groups were assessed using analysis of variance (ANOVA; with subsequent pairwise comparisons using Student’s t-test) or a Kruskal–Wallis test (with subsequent pairwise comparisons using a Mann–Whitney U-test) as appropriate. The Wilcoxon test was used to compare baseline and subsequent selenium concentrations. Correlations between variables were investigated by Pearson’s or Spearman-rho tests as appropriate and the corresponding R² was calculated. The predictive value of plasma selenium concentrations on ICU outcome was calculated using a receiver operator characteristic (ROC) curve and the area under the curve (AUC) was computed. P<0.05 was considered significant. Data are presented as mean (sd) unless otherwise indicated.

Results

Sixty patients were enrolled in the study (40 males and 20 females, mean age 63 years). Patients were mostly admitted after cardiac surgery (all on-pump; n=47, 78%). Seven patients were referred from other facilities and did not undergo any surgical procedure in the 48 h preceding ICU admission because of respiratory failure (n=2), septic shock (n=2), deterioration in the level of consciousness (n=1), seizures (n=1), and congestive heart failure (n=1). The median (IQR) ICU length of stay (LOS) was 4 (2–8) days and the overall ICU mortality was 15% (n=9) (Table 1).

The ICU control (no SIRS) group included 15 patients admitted after uncomplicated procedures, 12 after elective and 3 after emergency surgery (cardiac surgery in 14 patients and oropharyngeal surgery in 1 patient). Patients assigned to the SIRS group were all admitted after cardiac surgery, 10 elective and 5 emergency interventions, and developed SIRS criteria within 0–2 days of ICU admission. Fifteen patients who developed failure of one or more organs within 0–4 days from ICU admission in the presence of SIRS criteria were included in the severe SIRS group; 10 had undergone elective and 5 emergency cardiac surgery. The severe sepsis/septic shock group comprised 12 patients with septic shock and 3 patients with severe sepsis. The main sources of infection were the lung (n=7), the abdomen (n=4), the urinary tract, and surgical wounds (n=2), with documented microbiological evidence of

Table 1 Patient characteristics of the study group (n=60). Data are given as mean (sd) or absolute numbers unless specified otherwise. CABG, coronary artery bypass grafting. *Seven patients referred from other facilities (including one patient admitted after polytrauma) did not undergo any surgical procedure in the day preceding admission. Excluding seven patients with combined CABG/cardiac valve replacement procedures. †Including one patient who had combined valvular and vascular surgery. ‡Thoraco-abdominal oesophageal resection (n=1) and oropharyngeal surgery (n=2)

<table>
<thead>
<tr>
<th>Age (yr)</th>
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<tbody>
<tr>
<td>Sex, Male/Female</td>
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</tr>
<tr>
<td>SAPS II score</td>
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</tr>
<tr>
<td>APACHE II score</td>
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</tr>
<tr>
<td>Source of admission (%)</td>
<td></td>
</tr>
<tr>
<td>Operating room</td>
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</tr>
<tr>
<td>Emergency room</td>
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</tr>
<tr>
<td>Other ICU</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Other hospital</td>
<td>5 (8.3)</td>
</tr>
<tr>
<td>Type of intervention* (%)</td>
<td></td>
</tr>
<tr>
<td>Elective</td>
<td>35 (58.3)</td>
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<tr>
<td>Emergency</td>
<td>18 (30)</td>
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<tr>
<td>Surgical procedure* (%)</td>
<td></td>
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<tr>
<td>CABG</td>
<td>38 (63.3)</td>
</tr>
<tr>
<td>Cardiac valve replacement†</td>
<td>9 (15)</td>
</tr>
<tr>
<td>Vascular surgery‡</td>
<td>4 (6.7)</td>
</tr>
<tr>
<td>Others*</td>
<td>3 (5)</td>
</tr>
<tr>
<td>ICU LOS, days, median [IQR] (range)</td>
<td>4 [2–8] (2–34)</td>
</tr>
<tr>
<td>ICU mortality (%)</td>
<td>9 (15)</td>
</tr>
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</table>
infection in nine patients. Age and APACHE II, SAPS II, and SOFA scores were significantly different among the study groups (Table 2). The APACHE II score was similar and the SAPS II score was lower in patients with SIRS compared with those without SIRS.

At inclusion, 55 patients (92%) had plasma selenium concentrations less than the standard value for healthy subjects (i.e. 74 μg litre\(^{-1}\)). Patients with SIRS had higher plasma selenium concentrations at admission compared with patients without SIRS and those with severe SIRS. However, the minimum, maximum, and mean values during the ICU stay were similar in patients with and without SIRS in the absence of organ failure or infection. Patients with severe sepsis/septic shock had the lowest plasma selenium concentrations at study inclusion [43.5 (34.3) μg litre\(^{-1}\)] (Table 2). Age correlated neither to the initial nor to the minimum selenium concentrations. In patients with severe sepsis/septic shock, initial and minimum plasma selenium concentrations were similar in those who were referred from other facilities (\(n=6\)) and in other patients [49.9 (23.7) μg litre\(^{-1}\) vs 39.3 (14.4) μg litre\(^{-1}\) and 21 (7.9) μg litre\(^{-1}\) vs 24.3 (9.3) μg litre\(^{-1}\), respectively].

During the ICU stay, there was a significant decrease in plasma selenium concentrations in all groups, except for patients without SIRS (Table 2). The minimum value reached was lower in patients with severe SIRS and lowest in those with severe sepsis/septic shock. Patients without SIRS exhibited an increase in plasma selenium concentrations compared with baseline values over the 1–3 days of follow-up. However, in patients with SIRS, plasma selenium concentrations decreased in all but one patient over the ICU stay. Likewise, a decrease in plasma selenium concentrations was observed in patients with severe SIRS and those with severe sepsis/septic shock, reaching a nadir by 3–4 days after study inclusion (Fig. 1).

Daily plasma selenium concentrations correlated positively with serum albumin concentrations (\(R^2=0.16\), \(P<0.01\)). The selenium/albumin ratio paralleled plasma selenium concentrations over the study period.

Total leucocyte count and serum PCT concentrations were significantly higher in patients with SIRS, organ failure, or infection than in those without SIRS (Table 3). The maximum leucocyte count, serum CRP, and serum PCT were also significantly higher in patients with SIRS, organ failure, and sepsis. Serum IL-6 concentrations increased over the ICU stay in patients with severe sepsis/septic shock to maximum concentrations greater than those recorded for patients with severe SIRS [634 (387) pg ml\(^{-1}\), \(P<0.01\)], despite similar concentrations at inclusion.

The minimum plasma selenium concentration was inversely correlated (Fig. 2) to the maximum leucocyte count (\(R^2=0.22\), \(P<0.01\)), the maximum serum CRP (\(R^2=0.28\), \(P<0.01\)), the maximum serum PCT (\(R^2=0.3\), \(P<0.01\)), and the maximum serum IL-6 (\(R^2=0.42\), \(P<0.01\)).

SOFA score was lower at study inclusion in patients with SIRS compared with those without SIRS; higher SOFA scores were observed in patients with severe SIRS and patients with severe sepsis/septic shock compared with those without organ failure (Table 2). The minimum plasma selenium concentration was inversely correlated to the maximal degree of organ dysfunction/failure during the ICU stay as assessed by the maximum SOFA score (\(R^2=0.42\), \(P<0.01\)). Laboratory determinants of organ function were similar between patients with and without SIRS in the absence of organ failure (Table 3). Protein C activity was similar at inclusion but decreased to a minimum value that was lower in patients with severe sepsis/septic shock than in those with severe SIRS [28 (12) vs 44 (12)%, \(P<0.05\)].

The minimum plasma selenium concentration inversely correlated to the maximum serum lactate concentration (\(R^2=0.38\), \(P<0.01\)), the maximum total serum bilirubin (\(R^2=0.18\), \(P<0.01\)), and the maximum serum creatinine (\(R^2=0.27\), \(P<0.01\)). Positive correlations were present between plasma selenium concentrations and the minimum platelet count (\(R^2=0.31\), \(P<0.01\), the minimum

### Table 2 Severity/organ dysfunction scores and plasma selenium concentrations according to the presence of SIRS. Data are given as mean (so) [range]. *P<0.05 (ANOVA), †P<0.05 compared with no SIRS, ‡P<0.01 compared with SIRS, §P<0.05 compared with SIRS, ¶P<0.01 compared with severe SIRS, ‼P<0.05 (Kruskal–Wallis test)

<table>
<thead>
<tr>
<th></th>
<th>No SIRS</th>
<th>SIRS</th>
<th>Severe SIRS</th>
<th>Severe sepsis/septic shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age *</td>
<td>64 (8) [48–83]</td>
<td>56 (10) [25–66]</td>
<td>66 (9) [49–77]</td>
<td>65 (13) [32–85]</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>12/3</td>
<td>13/2</td>
<td>7/8</td>
<td>8/7</td>
</tr>
<tr>
<td>APACHE II score *</td>
<td>8.8 (2.1) [5–13]</td>
<td>8.8 (3.4) [0–14]</td>
<td>17.1 (5.5) [10–34]</td>
<td>21.6 (9.5) [0–42]</td>
</tr>
<tr>
<td>SAPS II score *</td>
<td>26.5 (8.6) [12–47]</td>
<td>20.1 (5.6) [12–32]</td>
<td>35.3 (6.2) [27–51]</td>
<td>45.6 (12.4) [26–68]</td>
</tr>
<tr>
<td>SOFA scores *</td>
<td>Initial 4.5 (2.5) [1–9]</td>
<td>3.7 (1.6) [1–6]</td>
<td>8.2 (2.6) [5–13]</td>
<td>10.7 (3.5) [5–16]</td>
</tr>
<tr>
<td></td>
<td>Max 4.5 (2.5) [1–9]</td>
<td>3.7 (1.6) [1–6]</td>
<td>9.5 (3.0) [5–15]</td>
<td>14.2 (3.0) [5–18]</td>
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<td></td>
<td>Mean 4.2 (2.4) [1–9]</td>
<td>3.5 (1.4) [1–5.5]</td>
<td>7.3 (2.4) [5–13]</td>
<td>10.8 (3.0) [2.9–14.3]</td>
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<td>Plasma selenium, μg litre(^{-1})</td>
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<tr>
<td>Initial* 48.2 (14.7) [28.9–81.0]</td>
<td>59.1 (11.4) [38.8–78.0]</td>
<td>48.6 (13.8) [28.2–74.0]</td>
<td>43.5 (34.3) [16.0–158.7]</td>
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<tr>
<td>Min* 48.2 (14.7) [28.9–81]</td>
<td>51.2 (12.9) [29.1–78]</td>
<td>37.6 (7.9) [19–50.3]</td>
<td>23 (8.7) [10.1–38.6]</td>
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<tr>
<td>Max 58.5 (13.1) [31.4–81.0]</td>
<td>59.9 (13.1) [38.8–90.0]</td>
<td>52.1 (13.5) [28.2–74.1]</td>
<td>56.3 (35.0) [28.9–158.7]</td>
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</tr>
<tr>
<td>Mean* 53.4 (12.8) [30.8–81]</td>
<td>55.5 (12.5) [38.5–84.1]</td>
<td>43.4 (8.4) [23.4–59.5]</td>
<td>37.3 (14.5) [20.3–78.6]</td>
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plasma antithrombin activity ($R^2=0.52$, $P<0.01$), and protein C activity ($R^2=0.21$, $P=0.01$).

The median (IQR) ICU LOS was 2 (2–3) days in patients with or without SIRS, 6 (4–8) days in patients with severe SIRS, and 13 (8–17) days in patients with severe sepsis/septic shock. Nine patients died in the ICU; one patient in the severe SIRS group died 3 days after emergency coronary artery bypass grafting with progressive cardiogenic shock and eight patients in the severe sepsis/septic shock group died as a consequence of sepsis-related MOF. Non-survivors had significantly lower initial and minimum plasma selenium concentrations than survivors (Fig. 3). APACHE II ($R^2=0.31$, $P<0.01$) and SAPS II ($R^2=0.29$, $P<0.01$) scores correlated inversely with the minimum selenium concentrations. In a ROC analysis for the prediction of ICU mortality (Table 4), SAPS II score and the minimum plasma selenium concentration were the most significant predictive factors. A cut-off point for minimum plasma selenium of 36 μg litre$^{-1}$ had 89% sensitivity, 71% specificity, 35% positive predictive value, and 95% negative predictive value (Fig. 4).

Discussion
In our study, plasma selenium concentrations were less than the standard value for healthy subjects in 92% of a selected group of critically ill patients admitted to a surgical ICU. This observation has been reported previously in various groups of critically ill patients.$^4$–$^6$ The aetiology of low plasma selenium concentrations is probably multifactorial, including reduced intake, reduced binding proteins due to increased utilization and redistribution, initiation of the acute phase response with increased demands, haemodilution with resuscitation fluids, incompletely replaced biological fluid losses which contain large quantities of trace elements, and redistribution due to selective selenium uptake in body tissues for metabolic use (e.g. GPx synthesis). Chronic deficiency cannot be ruled out as selenium intake in most parts of Europe is low.$^{13}$ Our data do not allow identification of the exact mechanism underlying the selenium deficiency in our ICU patients.

The degree of organ dysfunction/failure seems to be a major determinant of the evolution of plasma selenium concentrations as these values paralleled the SOFA score. The SIRS group had higher plasma selenium concentrations at inclusion than ICU controls; however, the latter group had lower initial SOFA scores which reflect a greater degree of organ dysfunction in this group. Conversely, Forceville and colleagues$^5$ reported lower plasma selenium concentrations in patients with SIRS; however, they defined SIRS according to restrictive criteria mandating the presence of organ failure, which is
equivalent to the definition of severe SIRS in our study. Moreover, SIRS represents manifestations of an underlying disease process and is not itself a separate clinical entity. Nevertheless, despite the poor specificity of the SIRS criteria, our observations do not exclude an association between SIRS and plasma selenium concentrations as these decreased in the SIRS group during the ICU stay but increased in ICU controls without SIRS.

In accordance with previous literature, our study showed a consistent decrease in plasma selenium concentrations during the ICU stay in all subgroups, except for ICU controls. Interestingly, we observed a tight association between plasma selenium and all components of organ dysfunction/failure, suggesting a universal role of selenium in body defence mechanisms against tissue damage. Several factors might contribute to extra- and intracellular augmentation of oxidant stress in ICU patients, promoting the accumulation of reactive oxygen species and consumption of antioxidative factors, including selenium. The more severe the trauma, SIRS, or sepsis, the larger the depletion of antioxidants appears to be. It is interesting to speculate that the distribution of selenium in the different body compartments may also change during severe illness, but this has not yet been demonstrated. In serum or plasma, selenium is bound to GPx (40%), albumin (10%), and selenoprotein-P (50%). We found a positive correlation between plasma selenium concentration and serum albumin concentrations and the selenium/albumin ratio paralleled plasma selenium concentrations throughout the study period.

The relationship between plasma selenium concentrations and the clinically used parameters of inflammation/infection has not been studied previously. In our study, the minimum plasma selenium concentration was inversely correlated to the maximum leucocyte count, the maximum serum CRP, the maximum serum PCT, and the maximum serum IL-6. These results suggest an important association between plasma selenium concentrations and infectious processes which might be independent of the relationship to the presence of SIRS or organ dysfunction/failure. Further studies are needed to confirm this theory.

Our results also demonstrate an association between plasma selenium concentrations and parameters of blood coagulation in critically ill patients. Selenium regulates the arachidonic acid cascade by controlling the concentration of lipid peroxides, as well as the biosynthesis of thromboxane A2, and proinflammatory lipoxygenase products.
thromboxane A2/prostacyclin ratio, thereby increasing vasoconstriction and blood coagulation. Therefore, selenium may protect against cardiovascular disease as GPx is able to combat the oxidative modification of lipids and reduce platelet aggregation. It should be emphasized, however, that several factors may have contributed to the disturbance in blood coagulation, including tissue injury, infection, and the use of anticoagulants.

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**Fig 2** Scatter plots representing the minimum plasma selenium (µg litre\(^{-1}\), x-axis) vs the maximum leucocyte count (×10\(^3\) µl\(^{-1}\), y-axis), the maximum serum CRP (µg ml\(^{-1}\), y-axis), the maximum IL-6 (pg ml\(^{-1}\), y-axis), and the maximum PCT (log ng ml\(^{-1}\), y-axis). Linear regression lines with 95% confidence intervals are fitted (dashed lines), \(P<0.01\) for all correlations.

**Fig 3** Box plots representing initial (\(\lambda\)) and minimum (\(\eta\)) plasma selenium concentrations according to ICU outcome. *\(P<0.05\) compared with baseline.
Plasma selenium was lower on admission and decreased more markedly during the ICU stay in non-survivors than in survivors. A cut-off minimum plasma selenium concentration of 36 μg litre⁻¹ predicted ICU mortality with high sensitivity and specificity. The association between low plasma selenium concentrations and a possible deleterious effect on morbidity and mortality is probably related to its antioxidant, regulatory, and immune functions. Selenium integrated in GPx reduces, and thereby detoxifies, inorganic and organic peroxides to their respective alcohols at the expense of (typically) glutathione. This function helps to maintain membrane integrity,₂³ ₂⁴ protects prostacyclin production,₂³ ₂⁴ and reduces the likelihood of propagation of further oxidative damage to biomolecules such as lipids, lipoproteins, and DNA.₂³ ₂⁴ GPx is also involved in redox signalling and regulatory processes, such as inhibition of lipoxygenase and apoptosis.₂⁵ On the other hand, selenium deficiency may activate some proinflammatory genes because selenium inhibits transcription factors, such as activator protein-1 or nuclear factor-κ B, involved in the transcription of inflammatory mediators (e.g. tumour necrosis factor-α).₂⁶ Previous studies have shown not only an association between low selenium concentrations and early mortality but also unfavourable long-term outcomes.₃ ₂⁷

These described observations are unlikely to be an epiphenomenon, as low endogenous stores of antioxidants are associated with an increase in free radical generation, an augmentation of the systemic inflammatory response, subsequent cell injury, increased morbidity, and even higher mortality in the critically ill.₂² ₂₈ Supplementation with selenium has been shown to improve antioxidant capacity, as demonstrated by increased GPx activity,₂⁹ and in a recent multicentre randomized controlled study, including 238 critically ill patients with severe SIRS, sepsis, and septic shock, i.v. administration of 1000 μg of sodium selenite for 15 days was associated with improved survival compared with the placebo-treated group.₃₀

Our study has several limitations. First, like all assays, the assay utilized in this study can be prone to interference in vivo and in vitro; however, the samples from all groups were handled in an identical fashion. Secondly, we measured selenium concentrations in plasma and not whole blood; however, the concentration of selenium in plasma is about 80% of that in whole blood.₃¹ Also, serum or plasma selenium is well correlated to erythrocyte GPx activity at low, or fairly low, selenium intakes.₃₂ At higher intakes, GPx activity reaches a plateau.₃₂ In their randomized controlled trial, Angstwurm and colleagues showed that GPx activity and whole blood selenium concentrations were within the upper normal range during selenium treatment, but remained significantly low in placebo-treated patients. This has also been shown in patients with trauma.₃₃ Moreover, Zima and colleagues showed a parallel decrease in selenium concentrations in plasma, erythrocytes, and whole blood. Thirdly, although patients in each group were included consecutively, the whole population cannot be considered as a representative cohort of surgical patients. In addition, the ICU controls were patients admitted after cardiac surgery mostly after coronary artery bypass grafting with shorter ICU LOS than the patients with severe SIRS or septic shock. The decrease in plasma selenium concentrations in this group could be related to the known proinflammatory reactions associated with the heart–lung machine, so that the results may not be applicable to every surgical ICU patient. Finally, selenium supplementation in our study was provided mostly enterally, with unpredictable bioavailability in critically ill patients; therefore, the adequacy of selenium intake and its relationship to the decreased selenium concentrations in our study may be difficult to judge.

Fig 4 ROC curve for ICU mortality prediction. The solid line represents the SAPS II score (AUC=0.903; 95% CI: 0.819–0.987, P<0.01) and the dashed line represents the minimum plasma selenium concentration (AUC=0.867; 95% CI: 0.753–0.981, P<0.01).
activity of GPx in plasma and erythrocytes. Nevertheless, it must be acknowledged that even without prescribed supplements, patients receive trace elements hidden in blood products, in albumin and crystalloid solutions. Nonetheless, our data confirm the data from the recent randomized controlled trial suggesting that high doses of selenium should be provided to ICU patients suffering from SIRS, organ dysfunction/failure, or infections.

In conclusion, we found plasma selenium concentrations to be generally low in critically ill patients, with a more pronounced decrease during the ICU stay in the presence of organ failure, especially during infection. Lower plasma selenium concentrations were associated with higher levels of organ failure, especially during infection. Lower plasma selenium concentrations were associated with higher degrees of tissue damage, with the presence of infection or organ dysfunction/failure, and with increased ICU mortality. Our data support the need for studies investigating selenium homeostasis.

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