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Correlation Between Serum Procalcitonin Levels and 28-Day Mortality in Patients with Surgical Sepsis and Septic Shock

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Rezumat

Corelația dintre nivelurile serice de procalcitonină și mortalitatea la 28 de zile la pacienții cu sepsis chirurgical și șoc septic

Context: Sepsisul este o urgență medicală majoră ce înregistrează la nivel mondial aproximativ 48,9 milioane cazuri şi 11 milioane de decese, reprezentând 19,7% din toate decesele globale. Acest studiu s-a efectuat pentru a evalua corelația dintre valorile procalcitoninei şi mortalitatea la 28 de zile.
Metode: S-a efectuat un studiu retrospectiv ce a inclus pacienți cu sepsis şi şoc septic, tratați în secțiile chirurgicale ale Spitalului Clinic Județean de Urgență Sf. Apostol Andrei Galați în perioada Ianuarie 2020 – Decembrie 2021.
Rezultate: Au fost incluşi 125 de pacienți (vârsta medie de 65 de ani), majoritatea bărbați (56%, n=70). Valoarea medie a procalcitoninei la internare în grupul cu sepsis (28%, n=35) a fost de 5.98 ng/mL, iar în grupul de şoc septic (72%, n=90) a fost de 40.09 ng/mL. Cea mai semnificativă corelație a fost între valoarea procalcitoninei la externare, mortalitatea la 28 zile ($r = 0.437$; $p < 0.0001$) şi scorul SOFA ($r = 0.356$; $p < 0.0001$).
Concluzii: Procalcitonina la externare s-a corelat pozitiv cu mortalitatea la 28 zile şi scorul SOFA. Valoarea procalcitoninei la externare poate fi utilizată în prognosticul pacientului cu sepsis chirurgical, dar pentru rezultate mai bune se recomandă asocierea dintre procalcitonină, scorul SOFA şi starea clinică a pacientului.

Cuvinte cheie: sepsis chirurgical, şoc septic, procalcitonină, scorul SOFA

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Abstract

Background: Sepsis is a major medical emergency accounting for approximately 48.9 million cases and 11 million deaths worldwide, representing 19.7% of all global deaths. This study was conducted to evaluate the correlation between procalcitonin values and 28-day mortality.

Methods: A retrospective study was conducted that included patients with sepsis and septic shock, treated in the surgical departments of the Sf. Apostol Andrei Galați County Emergency Clinical Hospital between January 2020 and December 2021.

Results: 125 patients (mean age 65 years), mostly men (56%, n=70) were included. The mean procalcitonin value at admission in the sepsis group (28%, n=35) was 5.98 ng/mL, and in the septic shock group (72%, n=90) was 40.09 ng/mL. The most significant correlation was between procalcitonin at discharge, 28-day mortality ($r = 0.437$; $p < 0.0001$) and SOFA score ($r = 0.356$; $p < 0.0001$).

Conclusions: Procalcitonin at discharge was positively correlated with 28-day mortality and SOFA score. The procalcitonin value at discharge can be used in the prognosis of the patient with surgical sepsis, but for better results the association between procalcitonin, SOFA score and the clinical status of the patient is recommended.

Key words: surgical, sepsis, septic shock, procalcitonin, SOFA score

Introduction

Sepsis is a major medical emergency that registers worldwide approximately 48.9 million cases and 11 million deaths, representing 19.7% of all global deaths (1). Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (2,3,4).

In sepsis, following contact with the invading pathogen agent, a systemic inflammatory response is initiated that involves both inflammatory and anti-inflammatory processes, humoral and cellular reactions and endothelial, hematopoietic, metabolic, and hepatic abnormalities (5,6), which can converge to more serious complications, such as disseminated intravascular coagulation (DIC), multiple organ dysfunction syndrome (MODS) (7) and septic shock, the most serious complication of sepsis, which is associated with high mortality (8).

To prevent the complications of sepsis, an early diagnosis is necessary, which can be done with the help of biomarkers. The most important characteristic of a biomarker is its potential to influence clinical decision making (9).

Several biomarkers have been proposed in numerous clinical trials for their ability to diagnose sepsis (10,11). Among them, procalcitonin (PCT) has been considered as the "absolute champion" (12), which can differentiate bacterial sepsis from severe non-infectious diseases, (6,13) from localized infection, and from viral infection (14,15), having a role in early diagnosis, prognosis, monitoring, disease severity assessment, and antibiotic management guidance (9,16-20). Thus, PCT through its multiple roles could have a significant impact on patient survival.

PCT is a peptide precursor of calcitonin, synthesized by thyroid C cells and neuroendocrine cells of the lung and intestine, which under normal physiological conditions, shows low serum levels (< 0.05 ng/mL) (6,21). PCT becomes detectable in serum within 4 hours of the onset of sepsis with a half-life of 22–26 hours, and peak levels occur between 12 and 48 hours after onset (9).

PCT is a useful biomarker in the early diagnosis of sepsis in both medical and

surgical patients. This was confirmed by a meta-analysis with surgery patients, where PCT diagnosed the sepsis better than C-reactive protein (CRP) (22). In addition to diagnosis, PCT also plays an important role in patient prognosis. Serum PCT levels increase significantly with increasing sepsis severity and organ dysfunction (20), having a negative impact on postoperative complications and outcomes (23) being closely related to mortality rates (24).

PCT decreases once the bacterial infection is controlled and thus provides information about the solution to the disease, being useful in the decision to discontinue the antibiotic, which can decrease mortality by decreasing the side effects associated with antibiotic therapy (16). A study of 472 patients with daily PCT measurements concluded that a high peak PCT level and a 1 day increase in PCT are independent predictors of mortality and the relative risk of mortality increases for each day of increasing the PCT value (17).

Materials and Methods

Study Design, Variables, and Population

We conducted a retrospective study in the Sf. Apostol Andrei Emergency County Clinical Hospital of Galați, Romania using the data of patients with infectious pathology of surgical cause, treated in the surgical departments including the ICU between January 2020 and December 2021. Sociodemographic variables included age and sex. The clinical and laboratory variables included the time from the onset of symptoms to presentation in the emergency room, the condition of the patients at presentation, the time elapsed from admission to surgery, the Charlson Comorbidity Index (CCI), the SOFA (Sepsis-related Organ Failure Assessment) score, anatomical site of infection, germs isolated from cultures, and PCT values. Exclusion criteria were age below 18 years, death within 72 hours of surgery, conservative treatment, antibiotic therapy ≥ 24 hours before admission, dialysis, chemotherapy 90 days previously, immunosuppressive therapy. The primary objective was patient outcome. We evaluated the 28-day mortality of all patients included in the study from the time of hospital presentation and correlated it with PCT values. A total of 125 patients (70 men and 55 women) were included in the study.

Determination of PCT in Serum

Venous blood samples for determination of serum PCT levels were obtained on admission, 24 hours postoperatively, and at discharge. The samples were collected in vials without anticoagulant with a volume of 6 ml. The vials were stored at room temperature for 30 minutes and then centrifuged for 10 minutes at 4000 rpm to obtain the serum. Measurement of serum PCT levels was performed with the automated Atellica IM 1600 Analyzer (working method: chemiluminescence using advanced acridinium ester technology). The measurement range was 0.04–50 ng/mL, with coefficients of variation below 15%. The detection limit was 0.03 ng/mL, and for values higher than 50 ng/mL, the 1/20 dilution was applied.

Statistical Analyses

Concerning statistics, we used XLSTAT software for correlations between the variables analyzed. As function, we used Principal Component Analysis and Pearson coefficient calculation. Values of $p < 0.05$ were considered as statistically significant.

Ethics Approval

The study was approved by the Ethics Committee of the Sf. Apostol Andrei County Emergency Clinical Hospital of Galați (no. 25060) retrospectively registered on October 5, 2022, which waived the need for the patients' informed consent due to the retrospective observational nature of the study. All methods and regulations of this study were performed in accordance with the Declaration of Helsinki and the STROBE guidelines (25).

Results

Patients were divided into two groups as sepsis and septic shock. Of the 125 patients, 70 (56%) were discharged cured and 55 (44%) died in hospital. The group with sepsis included 35 (28%) patients of whom 20 (57.14%) were discharged cured and 15 (42.86%) died. The group with septic shock included 90 (72%) patients of whom 50 (55.55%) were discharged cured and 40 (44.44%) died. Of the total 125 patients, 48 were aged < 65 years and 77 were aged ≥ 65 years. The mean age in all patients was 65 years (range 22 - 89), in the group with sepsis it was 64.77 years (range 26 - 88) and in the group with septic shock it was 65.2 years (range 22 - 89).

The time elapsed from the onset of symptoms to presentation to the emergency room was < 12 hours for 26 (20.8%) patients, between 12 and 24 hours for 62 (49.6%) patients, between 24 and 72 hours for 29 (23.2%) patients, > 72 hours in the case of 8 (6.4%) patients. On presentation to the emergency room 64 (51.2%) patients were conscious, 34 (27.2%) obnubilated, 22 (17.6%) with stupor, and 5 (4.0%) in coma. The time elapsed from admission to surgery was < 6 hours for 112 (89.6%) patients and between 6 and 12 hours for 13 (10.4%) patients. The mean of days of stay in ICU was 6.27 (range 1 - 24). The sepsis group had a mean of 6.4 days and the septic shock group had a mean of 6.22 days. The mean of hospitalization days was 19.84 days (range 5 - 75). The sepsis group had a mean of 23.4 days (range 7 - 75) longer than the septic shock group which had a mean of 6.22 (range 1 - 24) (*Table 1*).

Depending on the anatomical site, the infection was most frequently located in the abdomen in 67 (53.6%) cases, the urinary tract in 20 (16%) cases, soft tissue in 13 (10.4%) cases, lung in 11 (8.8 %) cases, anorectal in 6 (4.8%) cases, pelvic / genital in 5 (4%) cases, and ENT in 3 (2.4%) cases.

Blood culture was performed in 32 (25.6%) patients, it was negative in 12 (37.5%) cases and positive in 20 (62.5%) cases. Gram-positive bacteria predominated in 13 (65%) cases (MR-CoNS = 11, Staphylococcus aureus MSSA = 2) and gram-negative bacteria were identified in 7 (35%) cases (Klebsiella pneumoniae = 3, Escherichia coli = 2, Acinetobacter baumannii = 1, Propionibacterium acnes = 1).

Wound cultures were performed in 74 (59.2%) patients, 14 (18.92%) cultures were negative and 60 (81.08%) positive. Gram negative bacteria predominated with 58 positive cultures (Escherichia coli = 19, Klebsiella pneumoniae = 15, Proteus mirabilis = 8, Pseudomonas aeruginosa = 6, Acinetobacter baumannii = 6, Enterobacter cloacae = 2, Providencia stuartii = 1, Leuconostoc pseudomesenteroides = 1) followed by gram-positive bacteria identified in 16 cases (Staphylococcus aureus MSSA = 9, MR-CoNS = 2, Enterococcus faecium = 3, Enterococcus faecalis = 2). In 16 cultures from the wound, multiple germs were isolated (2 germs in the case of 12 cultures and 3 germs in the case of 4 cultures) (*Table 2*).

CCI had a mean of 3.89 (range 0 - 10). The sepsis group had a mean CCI of 3.51 lower than the septic shock group with a mean CCI of 4.04.

The mean of SOFA score in all patients was 6.24 (range 2 - 15). The sepsis group had a slightly lower trend with a mean SOFA score of 6.22 (range 2 - 14) compared to the septic shock group with a mean of SOFA score of 6.25

Table 1. Demographic data, days of stay in the ATI and in the hospital

Characteristics	All (n=125)	Sepsis (n=35)	Septic shock (n=90)
Gender M/F, n (%)	70 (56%) / 55 (44%)	19 (54%) / 16 (46%)	51 (57%) / 39 (43%)
Age, mean ± SD (min-max)	65.14 ± 14.75 (22 - 89)	64.77 ± 15.68 (26 - 88)	65.20 ± 14.46 (22 - 89)
Days of stay in ICU, mean ± SD (min-max)	6.27 ± 5.47 (1 - 24)	6.4 ± 5.54 (1 - 24)	6.22 ± 5.48 (1 - 24)
Days of hospital stay, mean ± SD (min-max)	19.84 ± 13.40 (5 - 75)	23.4 ± 15.33 (7 - 75)	18.45 ± 12.40 (5 - 63)

The numbers are described as mean ± standard deviation and min-max values; M - male; F - female

Table 2. Detection of bacteria in blood culture and from foci area

Bacteria	Blood culture (n=20)	Cultures from foci area (n=74)
Gram-negative bacteria	*7*	*58*
Escherichia coli	2	19
Klebsiella pneumoniae	3	15
Proteus mirabilis	-	8
Pseudomonas aeruginosa	-	6
Acinetobacter baumannii	1	6
Others	1	4
Gram-positive bacteria	*13*	*16*
MR-CoNS	11	2
Staphylococcus aureus MSSA	2	9
Enterococcus faecium	-	3
Enterococcus fecalis	-	2

MR-CoNS, Methicillin-resistant coagulase negative staphylococci

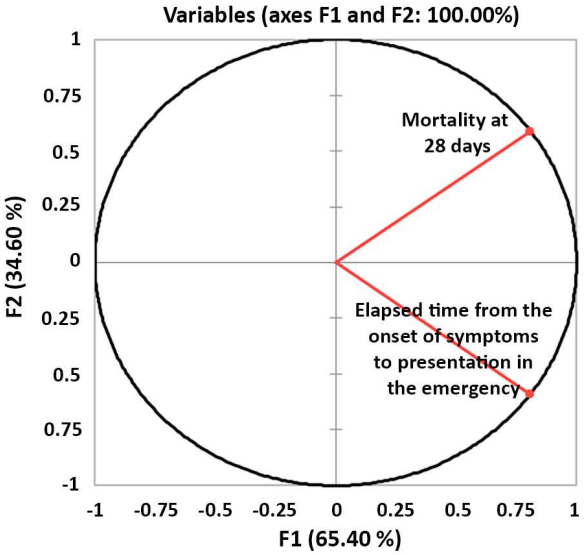

Figure 1. Correlation between the time elapsed from the onset of symptoms to presentation to the emergency room and 28-day mortality

(range 2 - 15), but they recorded approximately equal values.

The mean of PCT on admission was 30.54 ng/mL (range 2.09 - 418.6), at 24 hours post-operatively it decreased to 19.08 ng/mL (range 0.21 - 321.02), at discharge it decreased to 10.63 ng/mL (range 0.07 - 348.21). The sepsis group had a mean of PCT on admission of 5.98 ng/mL (range 2.09 - 9.49), 24 hours after surgery of 4.19 ng/mL (range 0.21 - 11.83) and at discharge of 4.29 ng/mL (range 0.07 - 32.7). The septic shock group had a mean of PCT on admission of 40.09 ng/mL (range 10.2 - 418.6), at 24 hours postoperatively of 24.87 ng/mL (range 2.11 - 321.02) and at discharge of 13.09 ng/mL (range 0.12 - 348.21) (*Table 3*).

The statistical analysis between the time elapsed from the onset of symptoms to the presentation in the UPU and 28-day mortality revealed a correlation with statistical significance (*Fig. 1*), p = 0.0004; the Pearson coefficient (r) has the value of 0.304. 28-day mortality after diagnosis recorded a percentage of 29.03% in patients with a time interval of 12-24 hours between the onset of symptoms and presentation to the emergency room; 48.27% in patients with a time interval of 24-72 hours between the onset of symptoms and presentation to the emergency room; 50% of patients with a time interval of more than 72 hours between the onset of symptoms and presentation to the emergency room.

The condition of patients at presentation correlated with 28-day mortality (*Fig. 2*), r = 0.4; p < 0.0001. 28-day mortality from presentation day was recorded in 80% of

Table 3. CCI, SOFA score, and PCT values

Characteristics	All (n=125)	Sepsis (n=35)	Septic shock (n=90)
CCI, mean ± SD (min-max)	3.89 ± 2.58 (0 - 10)	3.51 ± 2.26 (0 - 10)	4.04 ± 2.69 (0 - 10)
SOFA score, mean ± SD (min-max)	6.24 ± 3.62 (2 - 15)	6.22 ± 3.68 (2 - 14)	6.25 ± 3.62 (2 - 15)
PCT (ng/mL) on admission, mean ± SD (min-max)	30.54 ± 41.78 (2.09 - 418.6)	5.98 ± 2.20 (2.09 - 9.49)	40.09 ± 45.84 (10.2 - 418.6)
PCT (ng/mL) at 24 h postoperative, mean ± SD (min-max)	19.08 ± 31.04 (0.21 - 321.02)	4.19 ± 2.40 (0.21 - 11.83)	24.87 ± 34.91 (2.11 - 321.02)
PCT (ng/mL) at discharge, mean ± SD (min-max)	10.63 ± 33.47 (0.07 - 348.21)	4.29 ± 6.70 (0.07 - 32.7)	13.09 ± 39.00 (0.12 - 348.21)

The numbers are described as mean ± standard deviation and range

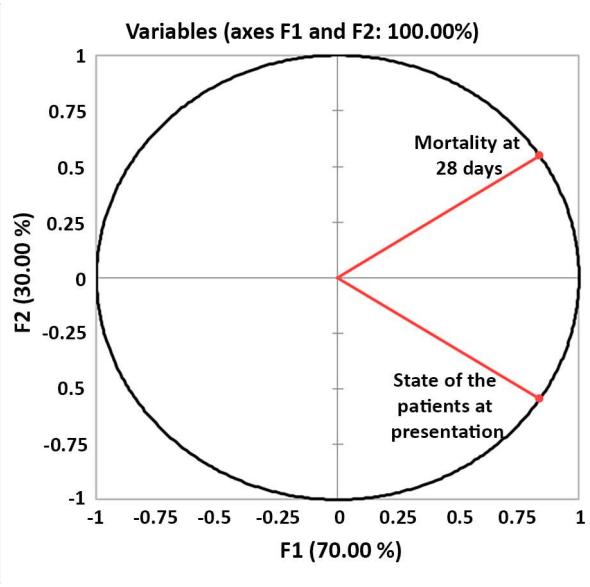

Figure 2. Correlation between patient condition on presentation and 28-day mortality

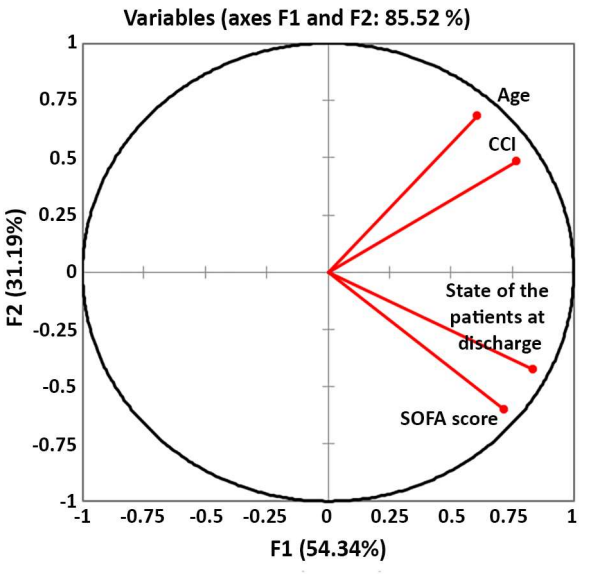

Figure 3. Correlation of CCI with age, state at discharge, and SOFA score

comatose patients, 63.63% of stupor patients, 55.9% of stupefied patients and 9.37% of conscious patients.

The number of days of treatment in ATI and 28-day mortality show a very weak correlation without statistical significance, r = 0.146; p = 0.103. The analysis of the principal components between the CCI, age, the condition of the patients at discharge and the SOFA score (*Fig. 3*) indicates correlations with statistical significance, the strongest being the one between the SOFA score and the condition of the patients at discharge, r = 0.743; p < 0.0001. The values of the Pearson coefficient for the correlations between CCI and age, respectively CCI and the condition of the patients at discharge, are 0.634; p < 0.0001, respectively 0.424; p < 0.0001.

There is a statistically significant correlation between the SOFA score and the PCT values on admission, 24 h postoperatively and at discharge, respectively (*Fig. 4*), the strongest being the one between the SOFA score and the PCT value at discharge, r = 0.356; p < 0.0001. The values of the Pearson coefficient for the correlations between the SOFA score and the PCT value at 24 h postoperatively, respectively, on admission are 0.249; p = 0.005, respectively 0.182; p = 0.004.

The correlation between PCT and 28-day mortality (*Fig. 5*) indicates statistically significant correlation between PCT value at discharge and 28-day mortality, r = 0.437; p < 0.0001; PCT values at 24 h postoperatively correlated with 28-day mortality, but without statistical significance, r = 0.285; p = 0.057; PCT values at admission did not correlate with 28-day mortality.

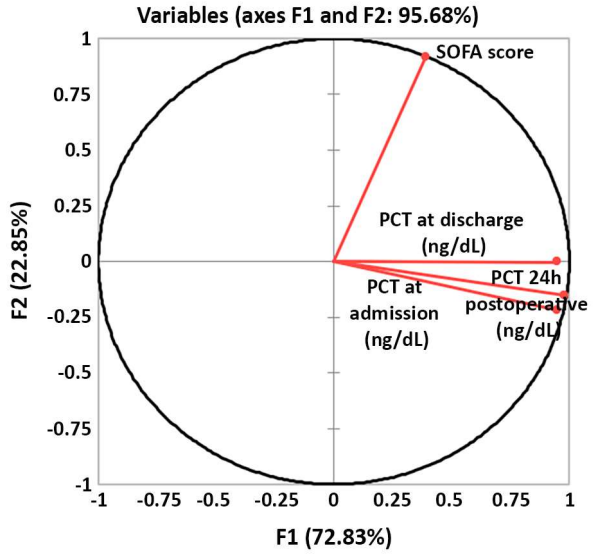

Figure 4. Correlation of PCT levels with SOFA score

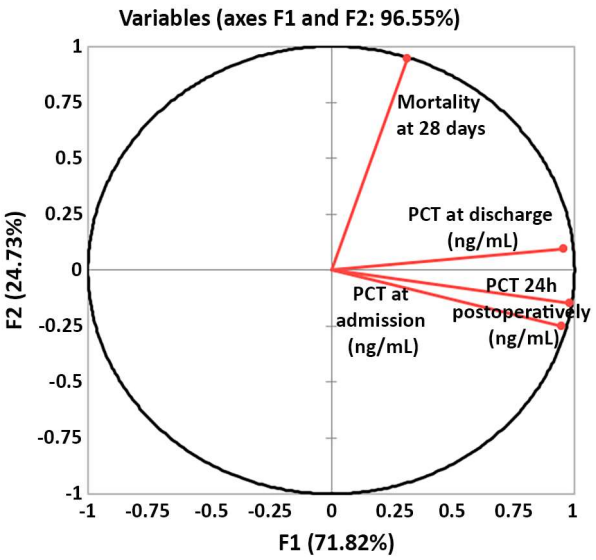

Figure 5. Correlation between PCT and 28-day mortality

Discussions

The mean age of our patients was 65 years, an age that in many studies is a dividing line between young people (< 65 years) and elderly people (> 65 years). The poor survival results in our study may also be mainly due to the advanced age (mean 65 years) where symptomatology is frequently masked. Wroblewski M et al. describes a diagnostic accuracy of only 47% of cases in geriatric patients, abdominal pain in 55% of cases, and abdominal stiffness in 34% of cases (26). Artero A. et al. concluded that patients over 65 years of age had a 13-fold higher risk of developing sepsis than younger patients (27).

The onset from symptomatology to hospital presentation, the patient's condition at presentation and the time to operative intervention are of particular importance in the patient's survival. In our study all these data had a positive correlation with 28-day mortality and influenced the evolution of sepsis. In addition to all these variables, the existence of comorbidities significantly decreases the survival rate in sepsis, the higher CCI, the more reserved the prognosis (28). In our case, the CCI was strongly correlated with the age and condition of the patients at discharge. Associated comorbidities contributed substantially to the complications of sepsis, reflected in the increased mortality rate (44%), especially in the septic shock group which recorded a mean CCI of 4.04, being higher than in the septic shock group.

Although in 89.6% of cases the elapsed time from admission to surgery was less than 6 hours, no significant decrease in the number of deaths was observed. The mean of treatment days in ICU was around 6 days, being a rather high mean. No difference in the number of treatment days in ICU was observed between the sepsis group compared to the septic shock group. The number of treatment days in ICU and 28-day mortality did not show a statistically significant correlation.

An important variation of the SOFA score (range 2 - 15) was revealed with a mean of 6.24, where both groups had an approximately equal mean. Increasing SOFA score was strongly associated with mortality rate and can be used both prognostically and to assess the degree of organ dysfunction. Ferreira et al. noted that a SOFA score > 11 has a > 90% mortality rate, a decrease in the score in the first 48 hours was associated with less than 6% mortality, while an unchanged or increasing score was associated with a mortality rate of 37% when the initial score was between 2 - 7 and 60% when the initial score was between 8 - 11 (29).

The mean of PCT on admission was 30.54 ng/mL, at 24 hours postoperatively it was 19.08 ng/mL, and at discharge it decreased to 10.63 ng/mL. Although a decrease in PCT values is observed starting from the admission and until the discharge of the patients, the in-hospital mortality rate was quite high both in the sepsis group (42.86%) and in the septic shock group (44.44%). These rates fall within those of the study conducted by Mirea L. et al. in which mortality from sepsis varies between 20-50%, and from septic shock between 45-63% (30). If the in-hospital mortality rate in the septic shock group was acceptable, within the normal range of data from most studies in the literature, however, the in-hospital

mortality rate in the sepsis group was unacceptably high, compared to the study by Esteban A. et al. which reported an in-hospital mortality for patients with sepsis of 12.8%, and for septic shock of 45.7% (31).

A decrease in serum PCT after surgery was associated with an improvement in patients' condition at discharge, whereas an increase in serum PCT was associated with poor outcomes for both groups. The correlation between 28-day mortality and PCT value at discharge was stronger compared to PCT at 24 hours postoperatively. PCT on admission did not correlate with 28-day mortality. Thus, the PCT value at discharge could be useful in the prognosis of 28-day mortality. Jain S. et al. concluded that elevated PCT on admission is a better predictor of mortality than CRP and is useful in stratifying patients and identifying patients at higher risk of death (20). In the study by Sager R. et al. elevated PCT levels correlated with the mortality rate in patients with complicated abdominal infection after surgery (32). In contrast, Kim DW et al. argue that many recent studies have shown a negative correlation between PCT and disease severity and PCT measurement is not associated with a decrease in mortality or length of treatment in sepsis (23). Other observational studies have also questioned the reliability of PCT in postoperative patients. A meta-analysis including 2692 patients after colorectal surgery showed no advantage of PCT compared to CRP in terms of diagnostic accuracy and mortality prediction (33). According to Azevedo JR et al., a correlation between PCT level and SOFA score creates a stronger prediction in determining prognosis according to the severity of sepsis than PCT alone (34).

Conclusions

In conclusion, it was observed that despite a rapid operative intervention and a sustained intensive treatment, the mortality rate in surgical sepsis was quite high. PCT values at discharge were positively correlated with 28-day mortality and SOFA score. PCT value at discharge can be used in the prognosis of the patient with surgical sepsis. However, an overview of the advantages and limitations of PCT is necessary before applying it as a routine inflammatory biomarker with prognostic value. However, for a better prognosis it is recommended that PCT be taken into account together with the SOFA score and the patient's clinical condition.

Conflict of Interests

The authors declare that they have no conflict of interests.

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Author's Contributions

All authors contributed equally to this work, critically revised the manuscript and gave final approval to the submitted version.

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