# Procalcitonin kinetics after burn injury and burn surgery in septic and non-septic patients – a retrospective observational study

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## Introduction

Early sepsis diagnosis is of the utmost importance for the correct management of burn patients, because of its marked impact on outcomes and survival [1]. However, the systemic inflammatory response (SIR) triggered by burns mimics sepsis presentation and complicates its early diagnosis [2]. Biomarkers and their kinetics may aid this differentiation [3]. Serum procalcitonin (PCT) is one of the most studied biomarkers and exhibits fair accuracy and good correlation with sepsis severity [4]. Nevertheless, few studies have evaluated the perioperative changes in PCT levels in burn patients, and its utility in burn patients has been questioned due to an alleged high-rate of false-positives [5]. The present study evaluated the PCT kinetics utility in distinguishing sepsis from SIR during the first days after burn injury and after subsequent surgical interventions.

## Methods

### Study plan

This was a retrospective observational study of all burn patients admitted to the Coimbra's Burns Unit (Portugal) between January 2011 and December 2014 who presented with a total burn surface area (TBSA) ≥ 15% and who underwent subsequent surgery. A total of 145 patients were included in the analysis. Sepsis was diagnosed according to American Burn Association criteria. PCT kinetics were investigated **a)** during the first five days after burn injury and **b)** preoperatively and during the five days after surgery in three subsets of patients, including those with no preoperative and no postoperative sepsis (NN), no preoperative but postoperative sepsis (NS), and preoperative and postoperative sepsis (SS).

### Statistical analysis

Qualitative variables (gender and mortality) were described as counts and quantitative variables (age, TBSA and ABSI - Abbreviated Burn Severity Index) as the means and standard deviations. The number of surgical interventions and PCT values were described as medians and interquartile ranges (IQR). Comparisons between sepsis and non-sepsis groups were performed using Fisher's exact test for qualitative variables and Mann-Whitney U test for quantitative variables. Friedman's test was used for time

comparisons of PCT levels. To evaluate the discriminatory power of PCT levels on consecutive days, receiver operating characteristic (ROC) curves and comparative analysis of the area under the curve (AUC) were performed. Kruskal Wallis test was used for the comparison of PCT kinetics between the three subgroups of perioperative patients and Mann-Whitney U test with Bonferroni correction for multiple comparison of the specific pairs. A *p*-value ≤0.05 was considered significant.

## Results

The ABSI score, TBSA and mortality were higher in the patients who developed at least one sepsis episode [*n*=60] compared to the non-sepsis group [*n*=85] ($p<0.05$) (Table 1). PCT levels during the **first five days after burn injury** were significantly higher in the septic patients compared with the non-sepsis group ($p\leq0.001$), and values >1.00 ng/mL were clearly associated with sepsis ($p<0.001$) (Fig. 1, Table 2). Study participants underwent a total of 283 **surgical interventions**, with a median of three interventions per patient (IQR of [2.00-5.25]). Their distribution by preoperative/postoperative sepsis status was 142 (50.2%) in NN; 62 (21.9%) in NS; and 79 (27.9%) in SS. The time evolution of PCT levels between the perioperative days in each of the three subgroups was statistically different ($p<0.001$). They exhibited a parallel course that peaked on the second postoperative day and returned to preoperative levels on the third day or later. Moreover, PCT levels were significantly different among the sepsis groups (NS and SS) compared with the non-sepsis (NN) group ($p<0.001$). The lowest PCT values were found in NN, and the highest values were observed in SS; the NS values were intermediate (Fig. 2, Table 3). The discriminatory power of PCT levels increased over time, through the consecutive days after burn surgery (Fig. 3, Table 4).

## Discussion and conclusions

The results confirmed that PCT values evolved in parallel with sepsis. PCT consistently showed good potential to discriminate between septic and non-septic patients, including after a burn surgery, particularly when PCT kinetics were dynamically assessed. Fisher's exact test and Mann-Whitney U test allowed a statistical analysis between the sepsis and non-sepsis groups of the counts and the means or medians, respectively. Friedman's test permitted a PCT time evolution assessment, showing a difference in perioperative patients. Kruskal Wallis test was initially used to compare the three subgroups and Mann-Whitney U test with Bonferroni correction permitted specific comparisons between the pairs. The ROC curves and the increasing AUC over the consecutive days after surgery supported the importance of dynamically assessing PCT kinetics [6]. Therefore, PCT kinetics may aid the diagnosis of sepsis, differentiating true sepsis from the SIR, after burn injury and after surgical interventions in burn patients.

## Bibliography

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## Figures

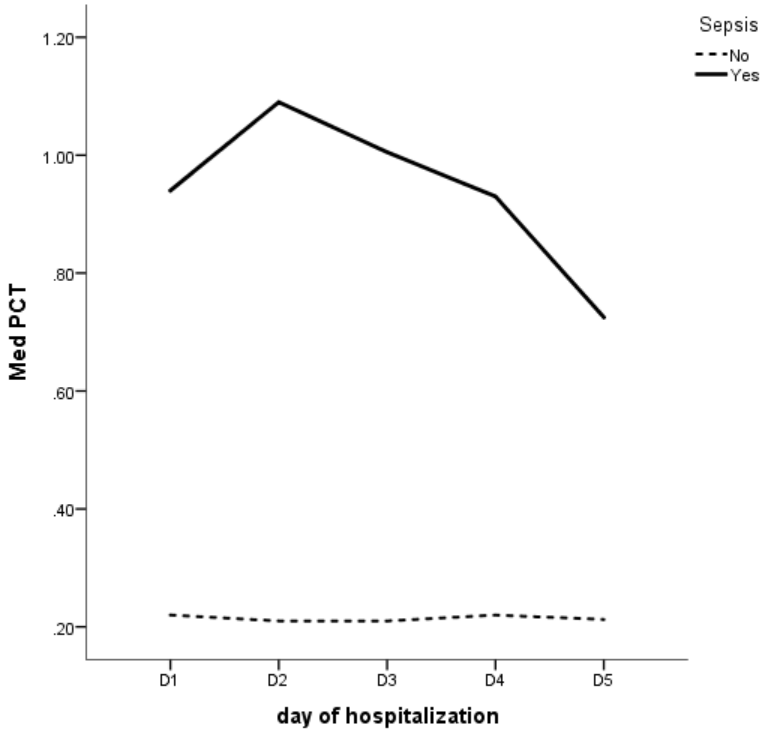


**Figure 1.** Median PCT levels observed in the first five days after burn injury in septic (Yes) and non-septic (No) patients

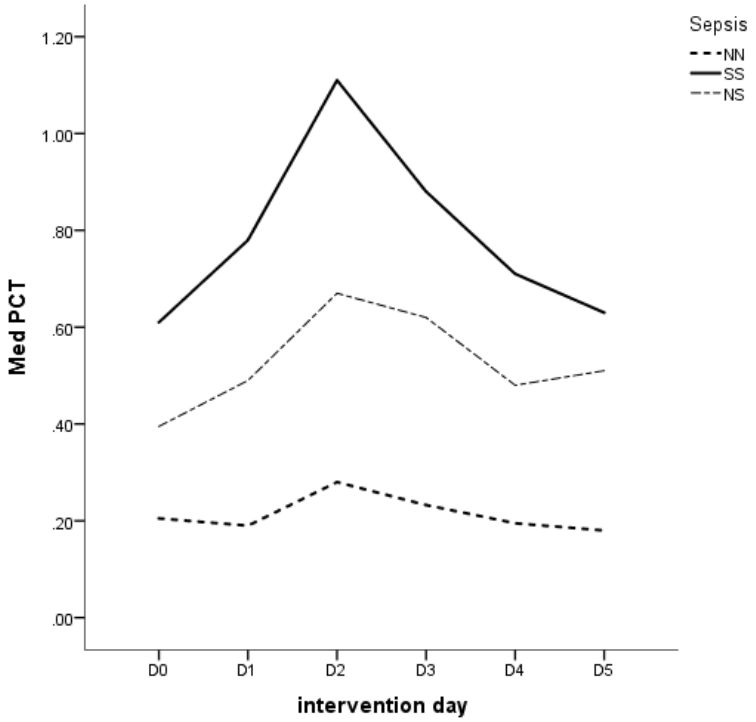


**Figure 2.** Median PCT levels observed form preoperative day (D0) till the fifth postoperative day (D5) for NN, NS, SS groups

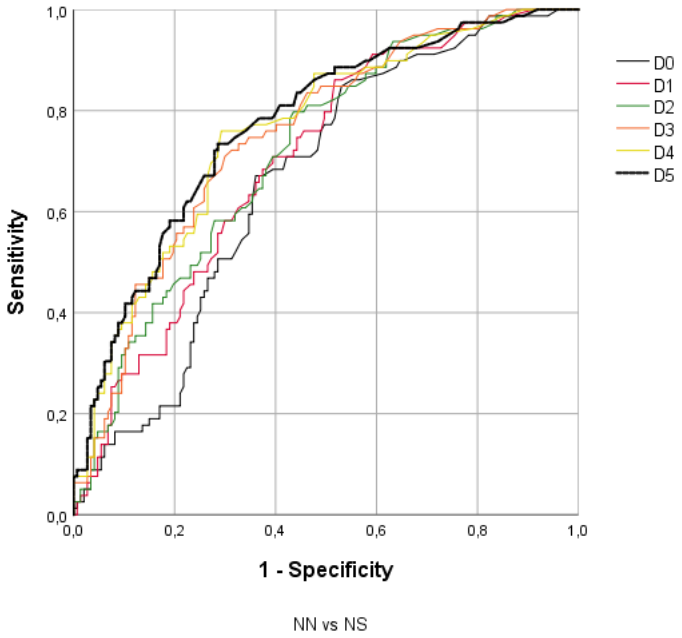


**Figure 3.** ROC curves for the discriminatory power of PCT levels between septic and non-septic patients preoperatively and in the first five days after burn surgery

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## Tables

**Table 1.** Study population

| Characteristics | No Sepsis | Sepsis[#] | p-value |
|---|---|---|---|
| Number of patients | 85 | 60 | |
| Gender (male/female) | 45/40 | 39/21 | 0.115 |
| Age (years)[$] | 56.49 (±18.15) | 58.43(±21.89) | 0.517 |
| ABSI[a] score[$] | 7.69 (±2.82) | 9.17 (±2.20) | 0.000* |
| TBSA[b] (%)[$] | 29.97 (±19.94) | 34.6 (±17.26) | 0.000* |
| Mortality (No/Yes) | 84/1 | 24/36 | 0.004* |

[*]p-values < 0.05

[$]Values are the means and corresponding standard deviations

[#]At least one day with sepsis in the first five days after burn episode

[a]Abbreviated Burn Severity Index

[b]Total Burn Surface Area

**Table 2.** Statistical analysis of PCT kinetics in the first five days post-burn injury in septic and non-septic patients

| Sepsis | Statistic | D1 | D2 | D3 | D4 | D5 | p-value* |
|---|---|---|---|---|---|---|---|
| **No** | n | 64 | 70 | 72 | 69 | 62 | |
| | Median [IQR][a] | 0.215 [0.090-0.578] | 0.205 [0.09-0.723] | 0.210 [0.08-0.668] | 0.215 [0.102-0.695] | 0.213 [0.118-0.618] | 0.557 |
| **Yes** | n | 50 | 53 | 52 | 53 | 52 | |
| | Median [IQR][a] | 1.085 [0.188-5.440] | 1.650 [0.235-4.010] | 1.130 [0.335-2.920] | 1.060 [0.355-2.927] | 0.725 [0.340-2.105] | 0.288 |
| | **p-value**** | 0.001 | 0.000 | 0.000 | 0.000 | 0.000 | |

* Friedman test
** Mann-Whiney U test
[a]Interquartile ranges

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**Table 3.** Statistical analysis of PCT kinetics from preoperative day (D0) till the fifth postoperative day (D5) for NN, NS and SS groups

| Sepsis | Statistic | D0 | D1 | D2 | D3 | D4 | D5 | p-value* |
|---|---|---|---|---|---|---|---|---|
| NN[b] | n | 212 | 208 | 198 | 186 | 163 | 149 | |
| | Median [IQR][a] | 0.190 [0.110-0.560] | 0.200 [0.101-0.615] | 0.280 [0.120-0.758] | 0.223 [0.118-0.553] | 0.195 [0.110-0.430] | 0.180 [0.100-0.360] | 0.000 |
| NS[c] | n | 104 | 103 | 102 | 100 | 87 | 80 | |
| | Median [IQR] [a] | 0.405 [0.219-0.935] | 0.510 [0.240-1.360] | 0.640 [0.313-1.590] | 0.625 [0.283-1.438] | 0.540 [0.260-1.970] | 0.515 [0.273-2.045] | 0.000 |
| SS[d] | n | 74 | 74 | 74 | 69 | 65 | 62 | |
| | Median [IQR] [a] | 0.653 [0.233-2.193] | 0.790 [0.288-2.518] | 1.115 [0.413-2.990] | 0.880 [0.380-3.115] | 0.710 [0.300-1.950] | 0.580 [0.248-1.520] | 0.000 |
| | p-value** | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | |
| | Multiple comparison (p-value***) | | | | | | | |
| (NN[b],NS[c]) | | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | |
| (NN[b],SS[d]) | | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | |
| (NS[c],SS[d]) | | 0.339 | 0.225 | 0.135 | 0.294 | 1 | 1 | |

* Friedman test

** Kruskal Wallis test

*** Mann-Whiney U test with Bonferroni correction

[a]Interquartile ranges

[b]No preoperative sepsis and no postoperative sepsis (NN)

[c]No preoperative but postoperative sepsis (NS)

[d]Preoperative and postoperative sepsis (SS)

**Table 4.** ROC curves for the discriminatory power of PCT levels between septic and non-septic patients preoperatively and in the first five days after burn surgery

| Area Under the Curve (AUROC) | | | |
|---|---|---|---|
| **Day** | **Area** | **Asymptotic 95% Confidence Interval** | |
| | | **Lower Bound** | **Upper Bound** |
| D0 | 0.662 | 0.591 | 0.733 |
| D1 | 0.701 | 0.633 | 0.770 |
| D2 | 0.717 | 0.649 | 0.784 |
| D3 | 0.752 | 0.686 | 0.815 |
| D4 | 0.760 | 0.696 | 0.824 |
| D5 | 0.771 | 0.708 | 0.834 |

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