



Procalcitonin is a reliable marker of severe systemic infection in neutropenic haematological patients with mucositis

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For Peer Review

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Running head: procalcitonin and mucositis

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22 Patients with neutropenia are exposed to a high risk for infections in which fever is often
23 the unique symptom (1). Systemic infections remain the main cause of mortality in these
24 patients therefore, the policy for infection management is to promptly administer empirical
25 antibiotic therapy in order to avoid the increased risk of mortality related to the treatment delay
26 (2). However, microbiological diagnostic tests are not sufficiently rapid, sensitive or specific to
27 indentify the microbial causes of fever, and a considerable number of patients suffer febrile
28 episodes over a prolonged period without a definite microbiological aetiology.

29 Procalcitonin (PCT) (3) has become increasingly popular as a novel marker of infection.
30 Several studies have underscored its value in clinical conditions by identifying infectious
31 processes (4, 5, 6). The use of this marker in haematological patients has provided controversial
32 results and no agreement exists about the capacity of PTC to differentiate fever by other
33 inflammatory processes such as mucositis and Graft versus Host diseases (GVHD) (7-11).

34 In order to evaluate the usefulness of PCT in diagnostic and therapeutic approaches to
35 fever in haematological patients, we evaluated the values of PCT, C-reactive protein (CRP) and
36 erythrocyte sedimentation rate (ESR) in the course of febrile neutropenia by assessing the
37 influence of mucositis and GVDH on these three parameters.

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The demographics and the clinical characteristics of the study population are shown in Table 1. One hundred and sixteen infectious events were observed, 50% of them occurring in patients with mucositis. Nine (30%) subjects out of 30 transplanted patients developed GVHD. FUO, pneumonia, sepsis and infection of CVC were the most common clinical features associated with fever.

In order to assess the power of the investigated inflammatory parameters in discriminating the clinical severity of infection episodes, the median values of PCT, CRP and ESR as measured during the major events were compared with those recorded during the minor events. During major infectious events, the PCT levels were significantly higher at any considered time-point (PCT1: 0.55 vs 0.13 ng/ml, $p<0.001$; PCT2: 1.04 vs 0.21 ng/ml, $p<0.001$; PCT3: 0.54 vs 0.16 ng/ml, $p<0.001$), CRP was significantly higher only at times one and two (CRP1: 112 vs 56 mg/dl, $p=0.001$; CRP2: 150 vs 104 mg/dl, $p=0.02$) and the ESR values were not significantly different at any time.

Figure 1 shows the results of the PCT and CRP determinations during febrile major and minor events in patients with and without mucositis. The analysis showed that the PCT values were significantly higher at all three time-points during major events compared to minor events, regardless of the presence of mucositis. On the contrary, the values of CRP were significantly higher at the time-point one in patients with major events and mucositis, and at time-point one and two in those with major events without mucositis, compared to patients with minor events.

The sensitivity and specificity of PCT and CRP to identify major infectious events in patients with mucositis was evaluated through ROC curves (Fig. 2). The area under the curve accounts for the statistical significance for PCT1 (68%; 95% CI: 54 to 82; $p=0.016$), PCT2 (68%; 95% CI: 53.9 to 81.7; $p = 0.02$) and PCT3 (65%; 95% CI: 51 to 80; $p = 0.035$). Otherwise, the area under the ROC

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3 61 curve was statistical significant for CRP1 (68%, 95% CI: 54 to 81; p=0,019), but not for CRP2 (54%,
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6 62 95% CI: 38.8 to 68.9; p = 0.6) and CRP3 (48%, 95% CI: 33 to 63; p = 0.8). Moreover, in patients with
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8 63 mucositis, PCT2 values of ≤ 0.5 ng/ml and ≤ 0.2 ng/ml discriminates major infectious events with
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11 64 sensitivities of 48% and 79% and specificities of 70% and 52%, respectively.
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13 65 A bacterial isolate was obtained in 50/59 (85%) major infectious events and in 22/57 (38%)
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16 66 minor events. Gram-negative isolates were significantly more frequent during major events
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18 67 compared to minor events (44/59 vs. 4/ 57, p <0.001).
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21 68 The PCT values, but not the CRP values, were significantly higher at all three time-points in
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23 69 patients with a Gram-negative isolate relative to patients with an isolate other than a Gram-
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26 70 negative (PCT1: 1.9 vs 0.2 ng/ml, p=0.001; PCT2: 3.5 vs 0.4 ng/ml, p<0.001; PCT3: 0.7 vs 0.4 ng/ml,
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28 71 p=0.005). Moreover, a PCT2 value of ≥ 0.98 ng/ml was found to discriminate between the
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31 72 presence or absence of a gram-negative bacterial isolation during fever with a sensitivity of 80%
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33 73 and a specificity of 78%.
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36 74 The study of PCT and CRP was conducted separately on the group of transplant patients
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38 75 with the occurrence of GVHD. To this end, only patients at risk of GVHD (allogeneic, haploidentical
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41 76 and umbilical cord blood transplants) have been considered. GVHD occurred in 12 out of 30
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43 77 patients, and it was skin-localised in 11/12 cases and bowel-localised in 1 case. Major infectious
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46 78 events occurred in 9/12 cases and in all of these patients high levels of PCT (>1.3 ng/ml) were
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48 79 detected at all three time points. During minor infectious events, the values of PCT1, 2 and 3 were
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51 80 ≤ 0.2 ng/ml regardless of GVHD.
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3 81 The present study shows that PCT is a reliable marker of infection in patients with
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6 82 haematological neoplasms and febrile neutropenia. A fair number of publications (7-11, 12-16)
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9 83 have evaluated the utility of PCT as a marker of infection in neutropenic patients with solid-organ
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11 84 cancer or haematological malignancy. Overall, these studies showed a correlation between an
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13 85 elevation of PCT and the presence of infection. However, in a recent review (9) that explored
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16 86 studies published between January 1990 and October 2006, the authors were unable to reach
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18 87 definitive conclusions about the usefulness of PCT in febrile neutropenia because of the
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21 88 heterogeneity of the populations evaluated and the variability of the results obtained in the
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23 89 different articles.

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26 90 In our study, the significant increase of PCT during infectious events was not affected by
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28 91 inflammatory conditions such as mucositis and GVHD. To date, only two articles have addressed
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31 92 the role of PCT in haematological patients with neutropenic fever and mucositis and / or GVHD,
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33 93 and they came to conflicting conclusions. Both these studies used the LUMI Test B.R.A.H.M.S. to
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36 94 assess the levels of PCT. Blijlevens et al. (7) demonstrated the inability of PCT to discriminate
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38 95 between infection and other inflammatory conditions in 12 haematological transplanted patients.
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41 96 In particular, the authors found out that GVHD rather than infection accounted for the increase of
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44 97 PCT. Fleischhack et al. (11), in a study including paediatric patients with haematological or solid
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46 98 tumours without infections, concluded that chemotherapy-induced tissue damage (such as severe
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49 99 mucositis) did not cause considerable increases of the PCT plasma levels. Some considerations can
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51 100 be made to justify these different results. In the first study, the limited number of patients
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54 101 impacted the statistical evaluation of the results; in the second study, none of the patients was
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56 102 transplanted and half of the febrile events occurred in children with solid tumours.
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103 In our study, the levels of PCT at all three time-points detected during the course of major
104 infectious events in patients with and without mucositis were significantly higher than in patients
105 with minor infections. Regarding the influence of GVHD on the PCT increase in our study
106 population, although the sample size does not allow statistical evaluation, it is clear that the PCT
107 was not affected by GVHD and values greater than 1 ng / ml are present only in patients with
108 severe infections regardless of the simultaneous occurrence of GVHD.

109 In some studies (12, 17, 18) it was reported that PCT elevation could be significantly higher
110 in patients with Gram-negative bacteraemia than in those with Gram-positive bacteraemia.
111 Kocazeybek and coworkers (18) in a study on patients with infectious endocarditis found that the
112 median serum PCT level of Gram-positive-related endocarditis was 2.92 ng/ml, whereas this level
113 was 8.62 ng/ml in cases of endocarditis due to gram-negative bacteria. Charles and colleagues
114 (17), in a review on bacteraemia in critically ill patients, observed that a high PCT value was found
115 to be independently associated with Gram-negative bacteraemia and that a PCT level of 16.0
116 ng/ml yielded an 83% positive predictive value and a 74% negative predictive value. In our study,
117 values of PCT of ≥ 0.98 ng/ml were able to discriminate between the presence and absence of
118 Gram-negative bacteraemia with a sensitivity of 80% and a specificity of 78%. This is of great
119 importance in relation to the clinical severity of Gram-negative bacteraemia in patients with
120 neutropenia and suggest the use of PCT in guiding the choice of empirical antibiotic therapy during
121 febrile neutropenia.

122 In conclusion, our experience indicates that the determination of PCT at the given time-
123 points might represent a valuable tool to predict the occurrence of major infectious episodes in
124 patients with febrile neutropenia, even in presence of confounding associated conditions such as
125 mucositis and/or GVHD. This would allow an early and appropriate antibiotic therapy to be

administered in a very high-risk population such as the one including patients with haematological malignancies and chemotherapy-related febrile neutropenia.

Methods

Patients

From January 2008 to December 2008, 116 febrile episodes occurring in 88 neutropenic patients were investigated. All the patients were affected with haematological neoplasms and 30 of them underwent stem cell transplantation (SCT).

Fever was defined as a single measurement of a temperature of 38.5°C or two or more measurements of 38°C. Neutropenia was defined as an absolute neutrophils count $<1000/\text{mm}^3$. Infection events included all episodes of fever associated with evidence of microbiological isolations. Sepsis, septic shock, bacteraemia (BSI) and pneumonia were defined as major infectious events; a fever of unknown origin (FUO), infections of the site of insertion of the central venous catheter (CVC), sinusitis, Herpes simplex virus manifestations and folliculitis were defined as minor infectious events.

BSI was defined as a microbial growth in one blood culture bottle; however, at least two positive blood cultures bottles collected from different sites were required for microorganisms usually considered as potential contaminants (i.e., coagulase-negative *Staphylococcus* species). Haemoculture samples were collected upon the first appearance of fever and then on every occasion in which fever was $\geq 38^\circ\text{C}$. Sepsis was defined by the presence of fever or hypothermia, tachypnea and tachycardia. Instances of sepsis associated with hypotension not corrected by proper fluid therapy were scored as septic shock.

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3 148 Pneumonia was assumed in cases in which typical clinical and radiological findings were
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6 149 seen on the chest radiograph obtained upon fever onset. CVC infection was suspected in presence
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9 150 of skin inflammation or vein thrombosis at the CVC insertion site. Episodes of fever not associated
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11 151 with microbiological or clinical evidence of infection were regarded as FUO.

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13 152 Oral and gastrointestinal mucositis was defined and graded according to the Common
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16 153 Terminology Criteria for Adverse Events (CTCAE) version three (19). Acute GVHD was evaluated
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18 154 according to the standard criteria (20)

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21 155 **PCT, ESR and CPR evaluations**

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23 156 PCT was determined by a commercially available immunoluminetric assay, LUMI Test PCT
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26 157 kit (B.R.A.H.M.S. Diagnostica, Berlin Germany). Values greater than or equal to 0.5 ng/ml were
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29 158 considered to be pathological in accordance with the manufacturer's instructions (Al-Nawas &
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31 159 Shah, 1996). The precision of the test was estimated in accordance with CLSI guidelines EP5-A
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33 160 (evaluation of precision performance of clinical chemistry devices). The inter-assay coefficient
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36 161 variation at PCT value of 0.1 ng/ml was 15%, 0.2 ng/ml was 10% and >0.3ng/ml was <6%.

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38 162 ESR was determined with the VES Matic Cube 200 (Diesse Inc., FL 33012, USA), an
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41 163 automatic system using 1 ml of undiluted blood sample with K2-EDTA as an anticoagulant. Blood
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44 164 collected in the EDTA tube and accurately mixed was left to settle. By analogical sensors, the
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46 165 instrument automatically reads the erythrocyte sedimentation levels. The results obtained were
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49 166 compared with the Westergren method and then printed.

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51 167 The CRP measurement was determined with the use of a Tina-quant immunoturbimetric kit
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54 168 for CRP (latex) highly sensitive assay (Roche). The measuring range is from 0.01 to 2 mg/dl. The
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56 169 turbidity resulting from the immunoprecipitation of CRP in the serum with a specific antibody, in
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59 170 the presence of polyethylene glycol, is measured as an increase in absorbance at 340 nm and is
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proportional to the concentration of CRP in the sample. The samples were read with the Hitachi 704/705 instruments (Roche).

Blood samples to evaluate PCT, ESR and CRP were collected upon the first appearance of fever and then every day after until its resolution. For the statistical analysis, the values of three specific time-points were considered: time 1 (PCT1, ESR1 and CRP1) on the first day of fever, time 2 (PCT2, ESR2 and CRP2) on the day with the highest values during the febrile episode and time 3 (PCT3, ESR3 and CR 3) on the last day of fever.

Statistical analysis

The statistical analysis was carried out using the Mann-Whitney U test for the medians of non-parametric data and Fischer's Exact Test for the comparison of proportions. The sensitivity, specificity and area under the ROC (Receiving Operator Characteristic) curve were calculated for both PCT and CRP. For the statistical analysis, the data were stored by Excel 2003 and later processed using the software SPSS version 16.

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Legends

Figure 1

PCT (a and c) and CRP (b and d) determinations during febrile major and minor events in patients with and without mucositis.

Figure 2.

Comparison between the PCT and CRP ROC curves in febrile events in the presence of mucositis according to major infectious events. **A.** PTC1, 68% (95% CI: 54 to 82; $p=0.016$); CRP1, 68% (95% CI: 54 to 81; $p=0.019$). **B** PCT2, 68% (95% CI: 53.9 to 81.7; $p = 0.02$); CRP2, 54% (95% CI: 38.8 to 68.9; $p = 0.6$). **C.** PCT3, 65% (95% CI: 51 to 80; $p = 0.035$); CRP3, 48% (95% CI: 33 to 63; $p = 0.8$).

TABLE 1. Patients and febrile episode characteristics

Characteristic	N° (%)
Total no. of patients	88
No. of non-transplanted patients	58 (66)
LMA°	40 (69)
LLA°°	9 (16)
LMC°°°	1 (2)
LNH^	3 (5)
LT^^	1 (2)
LB^^^	2 (3)
No. of transplanted patients	30 (34)
Allogeneic	7 (23)
Autologous	14 (47)
Haploidentical	3 (10)
Umbilical cord Blood	6 (20)
Age (years)	
Median (range)	47 (16-70)
Gender	
Male	52 (59)
Female	36 (41)
Total no. of febrile episodes	116
Sepsis	21 (18)
Septic shock	9 (8)
Pneumonia	22 (19)
Bacteraemia	9 (8)
CVC*	20 (17)
FUO§	29 (25)
Other+	6 (5)
Febrile episodes associated with mucositis (in total)	58 (50)
Febrile episodes with GVHD (only in transplanted)	9 (30)

° LMA Acute myeloid leukaemia
°° Acute Lymphatic leukaemia
°°° Chronic myeloid leukaemia
^ Lymphoma non Hodgkin
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^^^ Burkitt Lymphoma
* Central venous catheter infection
§ Fever of unknown origin
+ Folliculitis, H. simplex, sinusitis

Figure 1

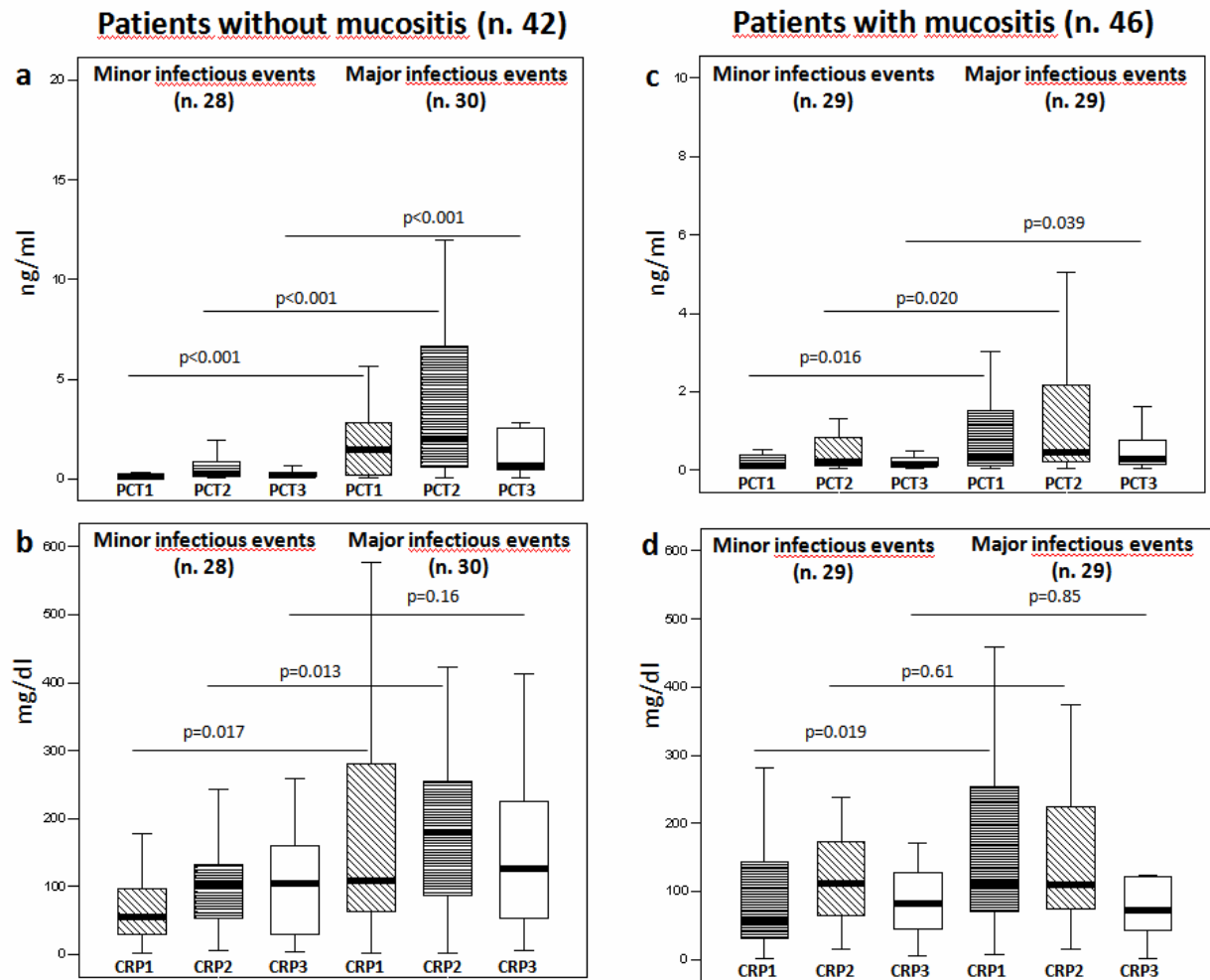


Figure 2

