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Serum procalcitonin is a sensitive marker for septic shock and mortality in secondary peritonitis

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Abstract

Background: Serum procalcitonin (PCT) is considered to be a sensitive marker for the early recognition of severe infection. The aim of this study was to review the diagnostic accuracy of serum procalcitonin levels to predict the risk of septic shock and mortality in patients with secondary peritonitis.

Methods: We carried out a retrospective review of patients (November 2010 to November 2012) admitted to the surgical intensive care unit (ICU) with secondary peritonitis classified into localised peritonitis (LP) or diffuse peritonitis (DP) groups. Organ dysfunction was assessed with the SOFA score. Demographic data was collected as well as results for neutrophil count, C- reactive protein, blood lactate, and PCT levels. The primary end-point was ICU mortality.

Results: From a total of 222 patients, 123 were allocated to the LP group and 99 to the DP group. Severe sepsis was observed in 41.9% of all patients in the DP group. The PCT levels increased significantly in the DP group, with the development of septic shock in 29 patients. Higher PCT levels were associated with an increased risk for septic shock with a cut-off value of 15.3 ng mL^{-1} and an increased risk for mortality with a cut-off value 19.6 ng mL^{-1}. A total of 59.1% of those who developed septic shock died.

Conclusion: An increase in PCT levels is an indirect sign of diffuse secondary peritonitis and this is associated with an increased risk of septic shock. Increased PCT level on admission is associated with an increased risk of mortality in this category of patients.

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Key words: secondary peritonitis, procalcitonin, septic shock, mortality

The incidence of sepsis is increasing worldwide [1, 2] and this has stimulated clinicians and scientists to combine efforts to understand better the mechanisms of inflammation and sepsis. Early recognition of life-threatening conditions could result in improved outcomes. Lewis Thomas postulated in the early 1970s: "Our arsenals for fighting off bacteria are so powerful…that we are more in danger from them than the invaders" [3]. However, various attempts to interfere in the different steps of the pathophysiological inflammatory pathways have not yet fulfilled our expectations.

Although there are several promising biomarkers for sepsis, relatively few are actually used for diagnostic purposes [4]. This can be explained in part by the lack of specificity and sensitivity, making a broader clinical application of the available 'sepsis' biomarkers less likely. Of these biomarkers, C-reactive protein (CRP) and procalcitonin (PCT) have been used most often in clinical practice [4]. Albeit nonspecific, CRP and PCT may give an overall idea of the magnitude of the inflammatory cascade, without necessarily separating or accessing all the different underlying mechanisms. Moreover, different bacteria may cause various types of inflammatory response. Secondary peritonitis is known to be associated with the most severe forms of sepsis [5, 6]. Early prognostic markers of sepsis in these patients could have the potential to significantly improve outcomes by adapting treatment

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strategy: high concentrations of PCT could indicate an ongoing infection and poor source control leading to diffuse peritonitis, especially in those at high risk of severe sepsis and septic shock. We use PCT levels routinely in the differential diagnosis of sepsis, but we did not evaluate whether the evolution of PCT over time has a diagnostic value to identify severe sepsis patients who are at risk for developing septic shock.

The aim of this study was to assess the diagnostic accuracy of PCT to predict the risk of septic shock and mortality in patients with localised or diffuse secondary peritonitis.

METHODS

DATA COLLECTION

A retrospective chart review was performed in patients with secondary peritonitis admitted to our hospital between November 2010 and November 2012. The authorisation for the study was obtained from the Ethical Committee of Riga Stradin`s University. Patients were stratified according to the magnitude of secondary peritonitis into either a localised peritonitis (LP) group or a diffuse peritonitis (DP) group. Risk assessment was performed by calculation of the ASA (American Society of Anesthesiologists) score and Mannheim Peritonitis Index (MPI). Patient demographics were collected. Primary outcomes were the occurrence of septic shock and mortality. The results of patients in the LP group were compared to the DP group. Dynamics of inflammatory response were recorded day-by-day by means of the following variables: absolute number of neutrophil leukocytes, CRP, PCT level, blood lactate concentration, and organ dysfunction according to Sequential Organ Failure Assessment (SOFA) score, defining organ failure with a SOFA subscore of 3 or more.

STATISTICAL ANALYSIS

Assessment of normal distribution of data was provided by Kolmogorov-Smirnov test. Abnormally distributed data was compared using median with interquartile ranges by Mann-Whitney U-test. Categorical and nominal data were analysed by Pearson's chi-squared test and Fisher's exact test. Univariate — binary logistic regression analysis performed to find parameters associated with mortality and septic shock. All significant parameters were divided into subgroups — organ dysfunction, complications, treatment, laboratory analysis, severity scores. Multivariate logistic regression analysis was performed to reveal factors most closely associated with mortality and septic shock. Finally, all significant factors were included in a multivariate regression model to reveal independent mortality and septic shock risk factors. The cut-off values of PCT were calculated for the first three days separately by receiver operating characteristics (ROC) curve to identify patients who were at increased risk of septic shock and mortality. Figures were prepared using SPSS 20 and MS EXCEL 2007 software. *P* value below 0.05 was adopted as significant.

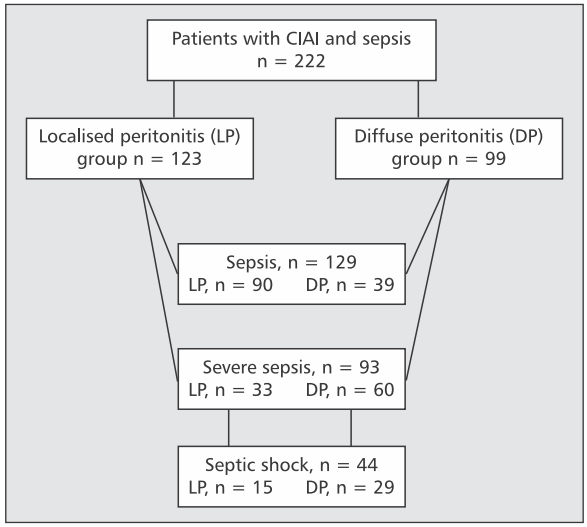


Figure 1. Distribution of the patients; CIAI — complicated intra abdominal infection

RESULTS

TYPE OF PERITONEAL INVOLVEMENT

A total of 222 patients with secondary peritonitis and sepsis were retrospectively included in the two study groups. The LP group consisted of 123 patients with localised forms of peritonitis, and the DP group consisted of 99 patients with diffuse involvement of peritoneal cavity (Fig. 1). Demographic characteristics of patients, etiology, clinical course and the type of surgical treatment are displayed in Table 1. Acute appendicitis was the most frequent cause (35%) of non-biliary localised peritonitis. Diffuse peritonitis was most often caused by lower gastrointestinal pathology (46.6%). A perforated peptic ulcer was the most frequent cause of diffuse peritonitis (27.3%) caused by upper gastrointestinal pathology. Individual risk assessment according to the ASA physical status classification system revealed significant prevalence of individual class 3 risks among DP patients. *Bacteroides spp.*, *E. coli* and *Enterococcus spp.* dominated in the bacteriological cultures taken from the infection source in both groups (Table 2).

DYNAMICS OF PCT CONCENTRATIONS

PCT levels were significantly higher on all three consecutive days from admission in the DP group, peaking on day 2, followed by a decrease in both groups (Fig. 2A). Concentration of PCT was closely related to clinical course of disease and outcome. PCT level on admission was significantly higher and neutrophil level lower, although not significantly, in patients who developed septic shock (Table 3). Significant elevation of PCT concentration was observed in non-survivors starting from day 1 until day 7 (Fig. 3A). Higher similar values of PCT levels were observed in both groups on day 2 among deceased patients compared to those who survived (Fig. 4A). PCT test was a reliable predic-

Table 1. Demographic data, aetiology, surgical treatment, laboratory analysis, complications, organ dysfunctions and outcomes in all patients and comparing DP vs. LP group

Parameter	Total n = 222	Diffuse n = 99	Local n = 123	*P*
Male/Female	117/105 (52.7/47.3%)	53/46 (53.5/46.5%)	64/59 (52.0/48.0%)	0.824
Age (yrs)	65 (77–49)	69 (79–53)	63 (75–47)	0.099
Female age (yrs)	68 (78–54)	65 (79–55)	68 (77–53)	0.854
Male age (yrs)	63 (74–57)	71 (79–48)	61 (72–44)	0.031
Biliary pathology	55 (24.8%)	8 (8.1%)	47 (38.2%)	< 0.001
Lower GI pathology	43 (19.4%)	35 (35.4%)	8 (6.5%)	< 0.001
Intra-abdominal abscess	16 (7.2%)	1 (1.0%)	15 (12.2%)	0.001
Upper GI pathology	33 (14.9%)	27 (27.3%)	6 (4.9%)	< 0.001
Diverticulitis	15 (6.8%)	11 (11.1%)	4 (3.3%)	0.029
Appendicitis	55 (24.8%)	12 (12.1%)	43 (35.0%)	< 0.001
Other pathology	5 (2.3%)	5 (5.1%)	0 (0.0%)	0.017
Diffuse peritonitis	62 (28.1%)	62 (62.6%)	–	0.005
Total peritonitis	37 (16.7%)	37 (37.4%)	–	
Abscess	77 (34.8%)	–	77 (63.1%)	0.015
Local peritonitis	45 (20.4%)	–	45 (36.9%)	
ICU admission	115 (51.8%)	76 (76.8%)	39 (31.7%)	< 0.001
US drainage	54 (24.3%)	4 (4.0%)	50 (40.7%)	< 0.001
Operations	144 (64.9%)	99 (100%)	45 (36.6%)	< 0.001
Operations at admission	138 (62.2%)	59 (59.6%)	79 (64.2%)	0.479
Re-operation	16 (7.2%)	12 (12.1%)	4 (3.3%)	0.011
VAAC	8 (3.6%)	8 (8.1%)	0 (0%)	0.001
CRP (mg L^{-1}) day 1	165 (259–60)	164.3 (278 – 26)	167.3 (250–84)	0.208
PCT (ng mL^{-1}) day 1	4.9 (17–1.5)	7.5 (22 — 2.8)	1.9 (5.6 — 0.3)	0.002
Blood lactate (mmol L^{-1}) day 1	1.7 (2.5–1.2)	1.9 (2.9 –1.2)	1.4 (2.2–1.0)	0.297
Neutrophils count (G L^{-1}) day 1 (peak)	10.8 (14.3–7.5)	9.3 (13.4–5.9)	11.7 (14.7–9.2)	0.001
CRP (mg L^{-1}) peak level	223 (300–152)	216.6 (300–157)	231.4 (304–125)	0.709
PCT (ng mL^{-1}) peak level	11.9 (38–3.9)	16.9 (42–7.7)	4.6 (21–1.6)	0.003
Blood lactate (mmol L^{-1}) peak level	2 (2.7–1.6)	2.1 (2.8–1.7)	1.7 (2.4–1.1)	0.044
Sepsis	129 (58.1%)	39 (39.4%)	90 (73.2%)	0.001
Severe sepsis	93 (41.9%)	60 (60.6%)	33 (26.8%)	0.001
Septicaemia	13 (5.9%)	6 (6.1%)	7 (5.7%)	0.907
Septic shock	44 (19.8%)	29 (29.3%)	15 (12.2%)	0.001
Pneumonia	31 (14.0 %)	17 (17.2%)	14 (11.4%)	0.216
Pleural effusion	49 (22.1%)	28 (28.3%)	21 (17.1%)	0.045
ARDS	4 (1.8%)	3 (3.0%)	1 (0.8%)	0.326
Mechanical ventilation	45 (20.3%)	29 (29.3%)	16 (13.0%)	0.003
Cardiovascular dysfunction	48 (21.6%)	33 (33.3%)	15 (12.2%)	< 0.001
Liver dysfunction	13 (5.9%)	1 (1.0%)	12 (9.8%)	0.007
Renal dysfunction	25 (11.3%)	16 (16.2%)	9 (7.3%)	0.038
Haematological dysfunction	12 (5.4%)	6 (6.1%)	6 (4.9%)	0.699
Pulmonary dysfunction	59 (26.6%)	40 (40.4%)	19 (15.4%)	< 0.001
Neurological dysfunction	6 (2.7%)	4 (4.0%)	2 (1.6%)	0.411
MODS	44 (19.8%)	30 (30.3%)	14 (11.4%)	0.001
MPI points	24.5 (32–18)	31 (36–26)	19 (23–15)	< 0.001
ICU stay (days)	5 (8–3)	5 (8–3)	6 (8–3)	0.738
Hospital stay (days)	12 (18–8)	12 (16–8)	12 (19–8)	0.528
ICU mortality*	22 (9.9%)	18 (18.2%)	4 (3.3%)	< 0.001
Hospital mortality	33 (14.9%)	24 (24.2%)	9 (7.3%)	< 0.001

Legend: ICU — intesive cave unit, US — ultrasound, MODS — multiple organ dysfunction syndrome, GI — gastrointestinal, VAAC — vacuum assisted abdominal closure, ARDS — acute respiratory distress syndrome, MPI — Manheim peritonitis index, CRP — C-reactive protein, PCT — procalcitonin, *ICU mortality for the subgroup of patients admitted to ICU was 22/115 n 19.1%

Table 2. Source of infection in comparison of LP and DP group (expressed as %)

Bacteria	LP group n = 123	DP group n = 99
Bacteroides	18	19.9
E. coli	16.7	18.4
Enterococcus	10.5	16.1
Enterococcus sp	8.6	11
Enterococcus gallinarum	0.9	0.7
Enterococcus faecalis	0.5	2.2
Enterococcus faecium	0.5	1.5
Enterococcus specificus	0.5	0.7
Streptococcus	14.4	11.8
Klebsiella	6.4	8.8
Kl. oxytoca	1.4	2.9
Kl. pneumoniae	5	5.9
Candida	1.9	6.6
Candida albicans	0	1.5
Candida species	1.4	4.4
Candida glabrata	0.5	0.7
Prevotella	2.3	5.1
Ps. aeruginosa	3.6	2.2
Other	25.7	11.1

tor of increased risk of mortality for all three consecutive days from admission in patients with severe sepsis, with the highest median PCT level on day 1, cut-off value PCT 19.6 ng mL^{-1} with 88.9% sensitivity and 87.9% specificity (Fig. 5B). The predictive value of PCT was analysed in 93 patients with severe sepsis. On the third day from admission, PCT was a reliable predictor for septic shock in patients with severe sepsis: ROC analysis showed an area under curve (AUC) of 0.707, with confidence interval (CI) 0.529–0.885; $P = 0.045$. The cut-off value for the development of septic shock was 15.3 ng mL^{-1} with 63.2% sensitivity and 71.4% specificity (Fig. 5A).

We found a positive correlation between blood lactate levels and PCT levels on admission, R = 0.56, $P < 0.001$. Linear regression model revealed that PCT may be an indirect predictor of an increase of blood lactate level during the first two days from admission, 1st day $r^2 = 0.119$, $P = 0.025$; 2nd day $r^2 = 0.181$, $P = 0.004$.

CONCENTRATION OF CRP, ABSOLUTE NEUTROPHIL COUNT

Analysing routine laboratory inflammatory markers, we did not find a significant variation in median CRP concentration between groups from day 1 onwards reaching the

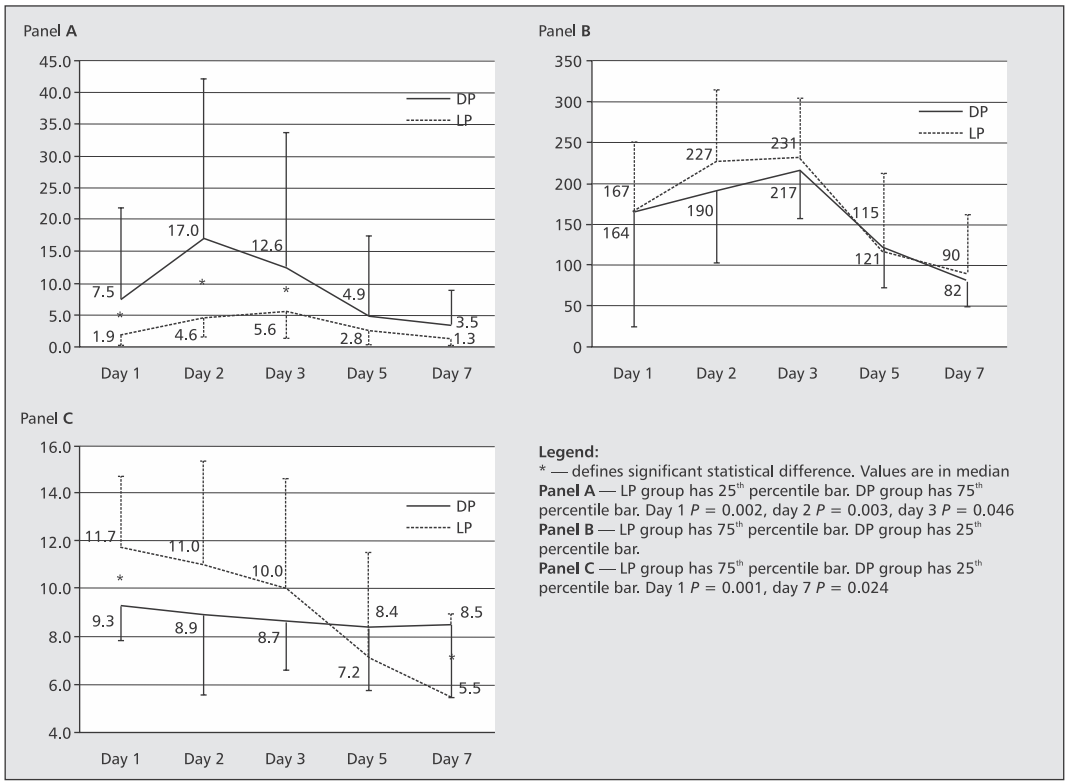


Figure 2. Dynamics of inflammatory biomarkers in LP and DP groups. Panel A — PCT (ng mL^{-1}), panel B — CRP (mg L^{-1}), panel C — neutrophil count (G L^{-1})

Table 3. Demographic data, aetiology, surgical treatment, laboratory analysis, complications, organ dysfunctions and outcomes in severe sepsis patients and comparing patients with and without septic shock

Parameter	Severe sepsis n = 93	With septic shock n = 44	Without septic shock n = 49	*P*
Female/Male	45/48 (48.4/51.6%)	30/14 (68.2/31.8%)	15/34 (30.6/69.4%)	< 0.001
Age (yrs)	73 (81–62)	74 (81–62)	72 (80–62)	0.920
Female age (yrs)	74 (81–62)	76 (82–64)	74 (77–58)	0.433
Male age (yrs)	72 (82–63)	72 (74–49)	74 (82–62)	0.180
Biliary pathology	20 (21.5%)	10 (22.7%)	10 (20.4%)	0.786
Lower GI pathology	31 (33.3%)	13 (29.5%)	18 (36.7%)	0.463
Intra-abdominal abscess	6 (6.5%)	3 (6.8%)	3 (6.1%)	0.892
Upper GI pathology	16 (17.2%)	9 (20.5%)	7 (14.3%)	0.431
Diverticulitis	10 (10.8%)	7 (15.9%)	3 (6.1%)	0.183
Appendicitis	6 (6.5%)	0 (0.0%)	6 (12.2%)	0.028
Other pathology	4 (4.3%)	2 (4.5%)	2 (4.1%)	0.899
Diffuse peritonitis	25 (28.1%)	9 (21.4%)	16 (34.0%)	0.185
Total peritonitis	33 (37.1%)	20 (47.6%)	13 (27.7%)	0.057
Abscess	20 (22.5%)	11 (26.2%)	9 (19.1%)	0.437
Local peritonitis	11 (12.4%)	2 (4.8%)	9 (19.1%)	0.054
LP group	33 (35.5%)	15 (34.1%)	18 (36.7%)	0.790
DP group	60 (64.5%)	29 (65.9%)	31 (63.3%)	
ICU admission	85 (91.4%)	43 (97.7%)	42 (85.7%)	0.062
Ultrasound guided drainage	20 (21.5%)	11 (25.0%)	9 (18.4%)	0.437
Operations	68 (73.1%)	34 (77.3%)	34 (69.4%)	0.392
Operations at admission	51 (54.8%)	21 (47.7%)	30 (61.2%)	0.192
Re-operation	13 (14.0%)	6 (13.6%)	7 (14.3%)	0.928
VAAC	7 (7.5%)	4 (9.1%)	3 (6.1%)	0.704
CRP (mg L^{-1}) day 1	195 (292–61)	221 (295–133)	168 (290–37)	0.108
PCT (ng mL^{-1}) day 1	6 (22.5–2.8)	11.8 (40.7–3.6)	4.8 (15.2–1.8)	0.049
Blood lactate (mmol $L^{-1)}$ day 1	1.9 (2.6–1.3)	2.0 (3.2–1.6)	1.6 (2.5–1.2)	0.353
Neutrophils count (G L^{-1}) day 1 (peak)	10.6 (14.7–5.9)	10.5 (15.5–5.3)	11.1 (14.4–8.2)	0.261
CRP (mg L^{-1}) peak level	239 (304–152)	216 (329–154)	243 (291–148)	0.524
PCT (ng mL^{-1}) peak level	16.9 (45.6–4.5)	29.4 (73.9–9.2)	10.9 (33.4–4.2)	0.016
Blood lactate (mmol L^{-1}) peak level	2.0 (2.7–1.7)	2.1 (2.8–1.6)	1.9 (2.6–1.7)	0.573
Septicaemia	11 (11.8%)	9 (20.5%)	2 (4.1%)	0.015
Pneumonia	23 (24.7%)	18 (40.9%)	5 (10.2%)	0.001
Pleural effusion	33 (35.5%)	20 (45.5%)	13 (26.5%)	0.057
ARDS	4 (4.3%)	3 (6.8%)	1 (2.0%)	0.257
Mechanical ventilation	39 (41.9%)	26 (59.1%)	13 (26.5%)	0.001
Cardiovascular dysfunction	48 (51.6%)	44 (100%)	4 (8.2%)	< 0.001
Liver dysfunction	12 (12.9%)	6 (13.6%)	6 (12.2%)	0.842
Renal dysfunction	25 (26.9%)	18 (40.9%)	7 (14.3%)	0.004
Haematological dysfunction	12 (12.9%)	9 (20.5%)	3 (6.1%)	0.061
Pulmonary dysfunction	59 (63.4%)	32 (72.7%)	27 (55.1%)	0.078
Neurological dysfunction	6 (6.5%)	3 (6.8%)	3 (6.1%)	0.892
MODS	43 (46.2%)	39 (88.6%)	4 (8.2%)	< 0.001
MPI points	32 (26–37)	34 (37–30)	28 (33–26)	0.001
ICU stay (days)	6 (9–4)	6 (8–4)	6 (14–4)	0.236
Hospital stay (days)	15 (21–11)	16 (24–8)	15 (19–12)	0.592
ICU mortality	22 (23.7%)	21 (47.7%)	1 (2.0%)	< 0.001
Hospital mortality	30 (32.3%)	26 (59.1%)	4 (8.2%)	< 0.001

Legend: GI — gastrointestinal, VAAC — vacuum assisted abdominal closure, ARDS — acute respiratory distress syndrome, MPI — Manheim peritonitis index, MODS — multiple organ dysfunction syndrome, CRP — C-reactive protein, PCT — procalcitonin, US — ultrasound

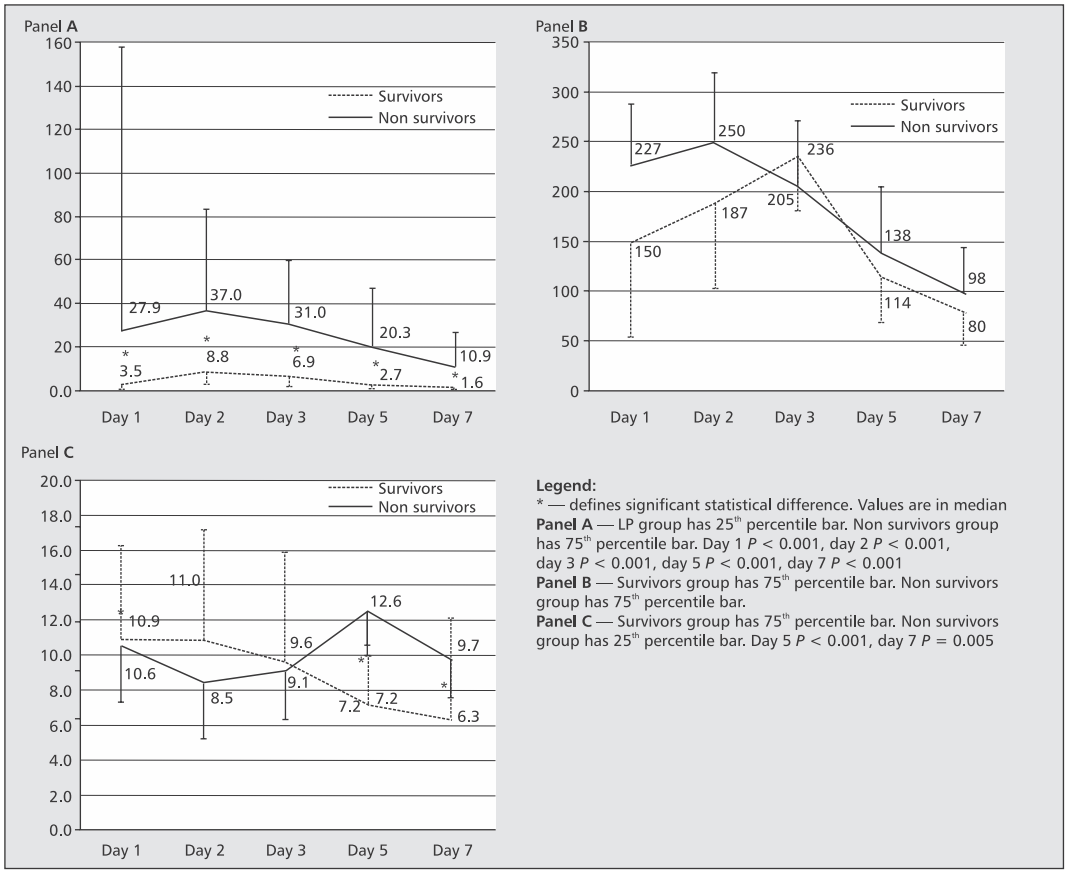


Figure 3. Dynamics of inflammatory biomarkers in survivors and non survivors. Panel A — PCT (ng mL^{-1}), panel B — CRP (mg L^{-1}), panel C — neutrophil count (G L^{-1})

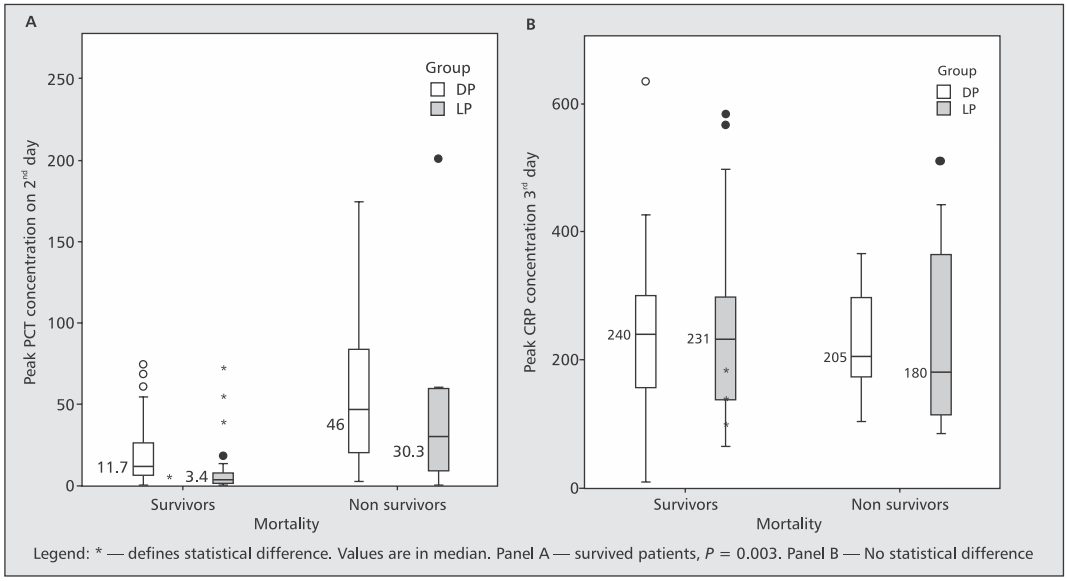
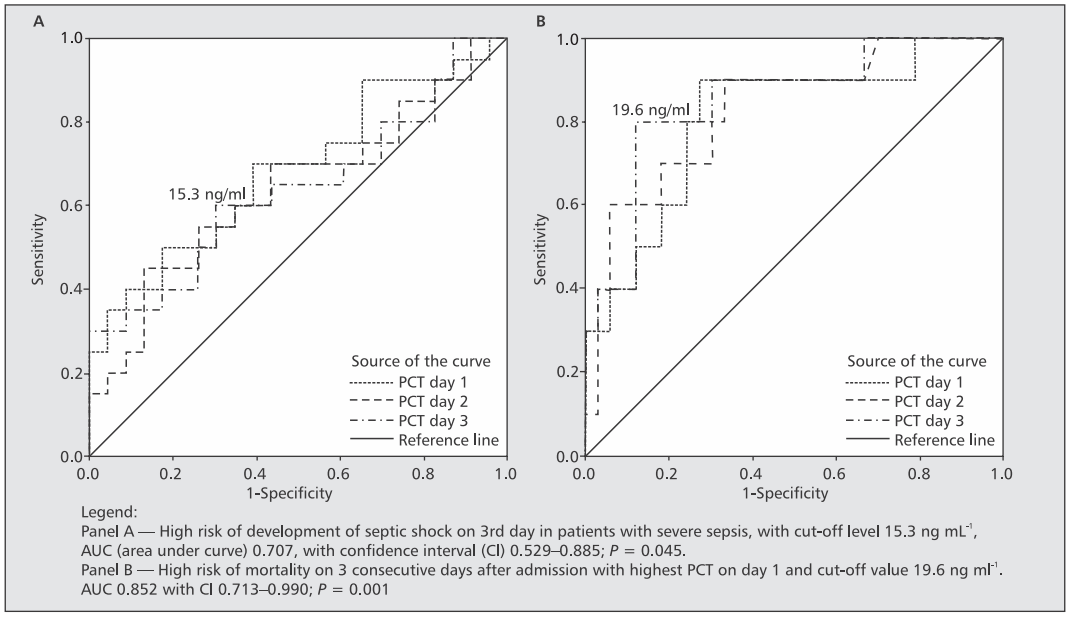


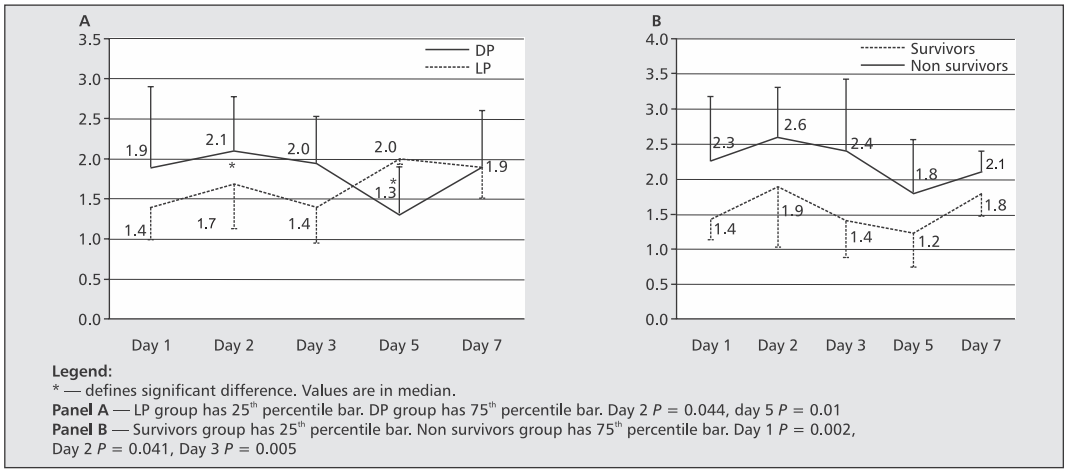
Figure 4. Comparison of peak levels of inflammatory biomarkers in LP and DP group divided in survivors vs non survivors. Panel A — PCT (ng mL^{-1}), panel B — CRP (mg L^{-1})

maximum value 72 hours after admission (Fig. 2B). Also there were no significant differences of median CRP concentration in survived and deceased patients, but maximum CRP concentration in non-surviving patients was on the second



Legend:
Panel A — High risk of development of septic shock on 3rd day in patients with severe sepsis, with cut-off level 15.3 ng mL^{-1}, AUC (area under curve) 0.707, with confidence interval (CI) 0.529–0.885; $P = 0.045$.
Panel B — High risk of mortality on 3 consecutive days after admission with highest PCT on day 1 and cut-off value 19.6 ng ml^{-1}. AUC 0.852 with CI 0.713–0.990; $P = 0.001$

Figure 5. ROC curve analysis. The accuracy and cut-off values of PCT concentration at 3 consecutive days after admission in prediction of septic shock and mortality. Panel A — septic shock; Panel B — mortality



Legend:
* — defines significant difference. Values are in median.
Panel A — LP group has 25th percentile bar. DP group has 75th percentile bar. Day 2 $P = 0.044$, day 5 $P = 0.01$
Panel B — Survivors group has 25th percentile bar. Non survivors group has 75th percentile bar. Day 1 $P = 0.002$, Day 2 $P = 0.041$, Day 3 $P = 0.005$

Figure 6. Dynamics of blood lactate concentration (mmol L^{-1}) in DP and LP groups and in survivors vs non survivors. Panel A — DP and LP group, panel B — survivors vs non survivors

day after admission (Fig. 3B). Survivors as well as deceased patients had no difference in CRP peak level between the DP and the LP group (Fig. 4B).

Another inflammatory marker, the absolute number of neutrophils, was significantly lower in the DP group compared to the LP group on day 1, $P = 0.002$. In the LP group, it decreased towards day 7 reaching significantly lower values compared to DP, $P = 0.024$ as shown in Figure 2C. There was no difference in absolute neutrophil count in the first three consecutive days after admission comparing survived to deceased patients. On days 5 and 7 in deceased patients, absolute neutrophil count reached its maximum and was statistically higher compared to surviving patients (Fig. 3C).

MPI, SOFA SCORE AND BLOOD LACTATE

Postoperative calculation of MPI revealed that 83 individuals in the DP group had MPI > 21 points, compared to 24 patients in the LP group, $P < 0.001$. MPI was significantly higher in patients with diffuse peritonitis, median of 31 (IQR 36–26) vs. 19 (IQR 23–15) in the LP group, $P < 0.001$.

Table 4. Multinomial logistic regression analysis for factors predicting septic shock

Parameter	Likelihood ratio χ^2	*P* value	Odds ratio (confidence interval 95%)
Gender (Female)	6.37	0.028	11.49 (1.30–101.45)
Age (yrs)	0.14	0.708	0.99 (0.92–1.06)
SOFA	23.41	0.001	2.21 (1.39–3.53)
Operation at admission	0.58	0.452	2.20 (0.28–17.24)
Pneumonia	0.004	0.097	1.09 (0.64–18.49)
Hematologic dysfunction	0.13	0.719	3.18 (0.23–437.26)
Kidney dysfunction	0.51	0.479	3.07 (0.14–68.23)
Respiratory dysfunction	0.03	0.875	1.18 (0.15– 9.20)
PCT 2nd day (ng mL^{-1})	0.001	0.999	1.00 (0.956–1.06)
PCT 3rd day (ng mL^{-1})	0.24	0.663	1.01 (0.965–1.06)

Significant increases in the incidence of organ dysfunction and multiple organ dysfunction syndrome (MODS) with higher SOFA scores were seen in the DP group, $P = 0.001$. Overall median SOFA score in patients who developed MODS was 12 (IQR 9–15).

Blood lactate levels were higher on the first three days after admission in the DP group, reaching significant statistical difference on day 2, $P = 0.044$ (Fig. 6A).

Blood lactate levels were fairly similar between patients with sepsis and severe sepsis; a statistical difference appeared at 72 hours after admission in patients who developed severe sepsis with MODS, 1.96 mmol L^{-1} (2.6––1.4) vs. 0.9 (1.0–0.8) in patients without severe sepsis, $P = 0.032$. Significantly elevated blood lactate concentrations were observed during three consecutive days after admission in the patients who died (Fig. 6B).

OUTCOMES

Severe sepsis developed in 60 patients from the DP group, compared to 33 from the LP group ($P = 0.001$). Incidence of septicaemia was similar, while septic shock developed significantly more often in the DP group ($P = 0.001$) (Table 3). Septic shock developed in 44 (19.8%) patients and they had significantly higher SOFA scores: 12 (IQR 10–14) vs. 5 (IQR 3–7) in patients without septic shock, $P < 0.001$. The median hospital stay and the length of stay in ICU did not differ between the LP and DP groups, or between patients with septic shock and without it. Mortality rate in patients with septic shock reached 59.1% vs. 8.2% in patients with severe sepsis but without septic shock, $P < 0.001$ (Table 3). Multinomial logistic regression analysis revealed SOFA score and female gender as significant independent predictors of septic shock (Table 4).

Overall mortality rate was 14.9% for the whole group (n = 222), ICU mortality reached 19.1% for the subgroup of patients admitted to ICU (n = 115). Deceased patients were older, and their clinical course was more complicated by the development of organ dysfunction (Table 5). Multinomial logistic regression analysis revealed SOFA score and age to be significant independent predictors of mortality (Table 6).

DISCUSSION

Sepsis has been the leading cause of death in critically ill patients in the USA for the last 12 years and is projected to increase by 1.5% per year, mainly because of the ageing population [2]. A similar tendency has been observed in Australia and New Zealand [7] and European countries [8], and the situation is not improving [9]. Abdominal pathology leading to abdominal sepsis is common among critically ill patients and carries a 30–50% mortality rate [5, 6].

In the present study, data was analysed from patients with secondary peritonitis. With a growing incidence of patients having serious comorbidities, the risks of surgical treatment also increases. We found that Bacteroides, E.coli and Enterococcus species were most often isolated from bacteriological cultures taken from the source of infection regardless of the localised or diffuse character of the peritonitis. Similar bacterial flora in association with gastrointestinal tract pathology is reported in other studies [10, 11].

In this study, individual risk assessment using the ASA Physical Status Classification System revealed a higher prevalence of patients with class 3 in the diffuse peritonitis group. These patients were more prone to develop severe sepsis and septic shock, and this was even more frequently observed in female patients. Postoperative calculation of MPI, an index where female gender is scored as a risk factor of 5 points [12], revealed that the majority of patients with diffuse peritonitis had MPI > 21 points, associated with an increased mortality risk. However, MPI had no correlation with PCT in the present study. Reliable preoperative clinical diagnostic and treatment criteria are not sufficiently developed due to the complexity of septic response [1, 13]. It has

Table 5 Demographic data, aetiology, surgical treatment, laboratory analysis, complications, organ dysfunctions and outcomes in comparison of survivors and non survivors

	Survivors n = 189	Non survivors n = 33	*P*
Female/Male	84/105 (44.4/55.6%)	21/12 (63.6/36.4%)	0.042
Age (yrs)	62 (74–48)	79 (83–72)	< 0.001
Female age (yrs)	62 (75–52)	79 (83–73)	< 0.001
Male age (yrs)	62 (74–46)	75 (84–72)	0.003
Ultrasound guided drainage	45 (23.8%)	9 (27.3%)	0.669
Reoperation	10 (5.3%)	6 (18.2%)	0.008
Operations	119 (63%)	25 (75.8%)	0.032
Operations at admission	123 (65.1%)	15 (45.5%)	0.155
VAAC	5 (2.6%)	3 (9.1%)	0.099
Biliary pathology	46 (24.3%)	9 (27.3%)	0.765
Lower GI pathology	28 (14.8%)	15 (45.5%)	< 0.001
Intra abdominal abscess	15 (7.9%)	1 (3.0%)	0.315
Upper GI pathology	28 (14.8%)	5 (15.2%)	0.960
Diverticulitis	12 (6.3%)	3 (9.1%)	0.563
Appendicitis	55 (29.1%)	0	< 0.001
Other pathology	5 (2.6%)	0	0.345
Abscess	71 (37.8%)	6 (18.8%)	0.04
Local peritonitis	42 (22.3%)	3 (9.4%)	0.152
Diffuse peritonitis	53 (28.2%)	8 (25.0%)	0.609
Total peritonitis	22 (11.7%)	15 (46.9%)	< 0.001
ICU admission	86 (45.5%)	29 (87.9%)	< 0.001
CRP (mg L^{-1}) day 1	150 (253–54)	226 (288–77)	0.058
PCT (ng mL^{-1}) day 1	3.4 (9.4–0.7)	27.9 (157.4–14.0)	< 0.001
Blood lactate (mmol L^{-1}) day 1	1.4 (2.3–1.1)	2.3 (4.2–1.9)	0.002
Neutrophils count (G L^{-1}) day 1 (peak)	10.9 (14.3–7.6)	10.5 (15.9–4.8)	0.576
CRP (mg L^{-1}) peak level	235 (301–151)	205 (299–153)	0.887
PCT (ng mL^{-1}) peak level	8.8 (23.5–3.3)	37.0 (83.6–18.5)	< 0.001
Blood lactate (mmol L^{-1}) peak level	1.9 (2.6–1.5)	2.6 (5.7–1.7)	0.041
Severe sepsis	63 (33.3%)	30 (90.9%)	< 0.001
Septicaemia	8 (4.2%)	5 (15.2%)	0.029
Septic shock	18 (9.5%)	26 (78.8%)	< 0.001
Pneumonia	16 (8.5%)	15 (45.5%)	< 0.001
Pleural effusion	33 (17.5%)	16 (48.5%)	< 0.001
ARDS	2 (1.1%)	2 (6.1%)	0.106
Mechanical ventilation	25 (13.2%)	20 (60.6%)	< 0.001
Cardiovascular dysfunction	21 (11.1%)	27 (81.8%)	< 0.001
Liver dysfunction	8 (4.2%)	5 (15.2%)	0.029
Renal dysfunction	11 (5.8%)	14 (42.4%)	< 0.001
Haematological dysfunction	4 (2.1%)	8 (24.2%)	< 0.001
Pulmonary dysfunction	38 (20.1%)	21 (63.6%)	< 0.001
Neurological dysfunction	2 (1.1%)	4 (12.1%)	0.005
MODS	19 (10.1%)	25 (75.8%)	< 0.001
MPI points	21 (29–16)	34 (39–32)	< 0.001
ICU stay days (days)	5 (7–3)	6 (14–2)	0.526
Hospital stay days	12 (17–8)	13 (19–4)	0.495

MODS — multiple organ dysfunction syndrome, CRP — C-reactive protein, PCT — procalcitonin , GI — gastrointestinal, VAAC — vacuum assisted abdominal closure, ARDS — acute respiratory distress syndrome, MPI — Manheim peritonitis index

Table 6. Multinomial logistic regression analysis for factors predicting mortality

Parameter	Likelihood ratio χ^2	*P* value	Odds ratio (confidence interval 95%)
Heart dysfunction	0.44	0.831	1.77 (0.01–327.54)
Neurologic dysfunction	0.55	0.815	1.58 (0.03–72.73)
Age (yrs)	12.47	0.005	1.16 (1.05–1.29)
Pneumonia	3.18	0.097	8.33 (0.68–101.55)
Septic shock	0.23	0.645	3.18 (0.23–437.26)
Operation at admission	0.89	0.365	2.78 (0.30–25.49)
Re-operation	0.36	0.552	0.41 (0.02–7.64)
MPI	3.02	0.116	1.17 (0.96–1.42)
SOFA	6.04	0.023	1.44 (1.05–1.96)
ASA	4.96	0.052	10.56 (0.98–113.54)

been suggested that microorganisms may exert immunosuppressive mechanisms to weaken the immune defence of the host, consequently reducing the capacity to clear infection. Neutropenia observed in patients with severe sepsis may reflect the state of immunosuppression caused by a large inoculum of bacteria [14, 15]. In this study, the decrease of the absolute number of neutrophils observed in patients with diffuse peritonitis on admission indirectly proves the possible state of immunosuppression, or may be related to the severity of infection. Bacteria may induce immunosuppression as a primary response of the host to sepsis by apoptosis of immune cells inducing anergic response, whereas necrotic cells stimulate immune response and antimicrobial defences [16, 17].

The high PCT levels we observed may indicate the insufficient ability of the host to bind the infected locus, whereas low PCT levels may indicate that the infection is temporarily localised. This explains some discrepancies in the evaluation of PCT in severe sepsis [18]. Most studies have analysed a mixed population of ICU and focused on risk assessment and conservative treatment of sepsis without specific attention to intra-abdominal infections [18–20]. The current study was designed to evaluate how PCT levels predict the risk for septic shock in patients with severe abdominal sepsis. This may explain much higher PCT levels, especially in patients with severe sepsis and septic shock in the 72-hour period after admission. The decrease of PCT and the normalisation of neutrophils after surgical source control on day 7 indicate recovery of the host self defence system or the ability to localise the remaining infection.

Many studies have focused on haemodynamic alterations, crucial for homeostasis, during the clinical course of severe sepsis [19]. A considerable number of patients from the diffuse peritonitis group in this study had 3 ASA points, indicating a high risk of cardiovascular derangement and a need for prompt surgical strategy. Impairment of tissue perfusion was reflected by higher blood lactate concentrations at 72 hours from admission in patients with severe sepsis and MODS. A positive correlation was found between blood lactate concentrations and PCT levels on admission. The highest blood lactate concentrations were found in non-survivors, in accordance with previous results [15, 22]. The linear regression model demonstrated that an increase in PCT values is associated with increased blood lactate concentrations. Recognition of patients at increased risk of cardiovascular and multiple organ failure becomes an important priority in the early and late phases of severe sepsis [23–25].

Different scoring systems, biomarkers and metabolites of systemic inflammation and sepsis have been evaluated for clinical application starting from 12 to 72 hours from admission, including IL-1, ICAM-1, TNF-a, caspase-3, IL-8; circulating protein C and protein S and others, although they are not sufficiently sensitive or specific [4, 26–30]. The early goal-directed therapy criteria recommended by Surviving Sepsis Campaign guidelines are not suitable for all septic patients [31, 32]. The current study was aimed to evaluate whether PCT, one of the most frequently clinically used biomarkers of sepsis, could be a reliable predictor of deterioration of the clinical course of sepsis and of increased risk of septic shock in patients with secondary peritonitis.

An increase in PCT levels may also be indicative for the evolution from localized to diffuse peritonitis due to poor source control. Previously, PCT concentrations have been used to differentiate between infected and non-infected patients, demonstrating higher mortality in patients with increasing or persistently high PCT concentrations and in some studies antibacterial treatment was guided based on PCT values [33, 34]. This study supports the existing relation between the increase in PCT levels and the increased mortality in patients with secondary peritonitis and severe sepsis. A recent study demonstrated that severe forms of sepsis are associated with higher PCT concentrations, especially in patients with a positive blood culture [18, 34, 35],

although single PCT values were not predictive for patient outcomes. A rather low PCT level on admission was reported in a mixed ICU population where abdominal infection (mostly nosocomial) was recognised in one third of the patients [18]. We observed low admission PCT concentrations in patients with localised infection, and high PCT levels in patients with severe sepsis who later developed septic shock. ROC curve analysis demonstrated that PCT values were able to discriminate between survivors and non-survivors and those with or without severe sepsis and septic shock at 72 hours from admission. In non-survivors, PCT level was significantly increased during the entire 72-hour period from admission, with a higher cut-off level on day 1 and a peak level on day 2. The reported mortality from severe sepsis ranges from 26% to 40%, and 56% in patients with septic shock [5, 6, 10, 14, 18, 34], which is similar to our results where the study group represented a properly selected cohort of patients with clinically proven secondary peritonitis and severe sepsis.

While the retrospective design of this study could be considered a weakness, routine application of the PCT test in our clinical practice made it possible to evaluate PCT based on the established clinical diagnosis. A solid patient cohort and sufficiency of the available data for statistical analysis add statistical power and reliability to the clinical interpretation of the results obtained.

Sepsis is a syndrome, not a disease; as such, it can have many causes and can be related to many illnesses. Studies looking at patients with sepsis should therefore focus on specific groups in which aetiology (medical vs. surgical), organ dysfunction (SOFA score) and biomarker levels are all taken into account. That was the main reason to conduct the present study in a focused group of patients with abdominal sepsis and secondary peritonitis, looking at LP vs. DP and using PCT levels with a certain threshold to help us to identify those patients who are at risk for developing severe sepsis and septic shock at an early stage so that outcomes can be influenced by adequate treatment.

The present study however has some limitations. Firstly, the study was retrospective and merely observed the existing situation. Secondly, no interventions were performed to influence the increased PCT levels. Thirdly, the number of patients studied was relatively small.

CONCLUSIONS

An increase in PCT levels during the first 72 hours of admission is an indirect sign of diffuse secondary peritonitis, and this is associated with an increased risk of septic shock. Increased blood lactate and PCT level on admission are associated with an increased risk of mortality in this category of patients.

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