Original article

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A combined parameter of changes in procalcitonin and C-reactive protein (CRP) in predicting the clinical outcome of severe pneumonia

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Abstract

***Background*: Pneumonia is an infectious disease with high mortality rates despite early diagnosis and adequate treatment. Therefore, the use of biological infection parameters is expected to improve patients' clinical outcome prognostic accuracy. In this study, we proposed a combination of decreased procalcitonin (PCT) and C-reactive protein (CRP) to predict the clinical outcome of severe pneumonia.**

***Methods*: This was a prospective cohort study of severe pneumonia patients treated in the single-center Intensive Care Unit (ICU) of Dr. Soetomo General Hospital from December 2023 to February 2024. Subjects who met the inclusion and exclusion criteria were examined for PCT and CRP within the first 24 hours of admission and repeated 96 hours later (day five). Clinical outcomes, including acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), septic shock, and 30-day mortality, were observed.**

***Results*: Thirty-five patients were enrolled for this study. Five subjects did not survive until the fifth day, and 30 subjects were eligible for analysis. A decrease of PCT >50% within five days was associated with a reduction of 30-day mortality (p=0.013) and septic shock incidence (p=0.005), whereas the decrease in CRP alone did not show any significant relationship towards any clinical outcome. The combination of a decreased PCT >50% and decreased CRP within five days could increase the prognostic specificity up to 88.9% in predicting 30-day mortality.**

***Conclusion*: Decreased PCT by more than 50% within 96 hours may predict the 30-day mortality rate and septic shock incidence in patients with severe pneumonia, while combining it with a decreased CRP expression would elevate prognostic specificity for severe pneumonia.**

Key words: Decreased procalcitonin, decreased CRP, Intensive Care Unit, severe pneumonia.

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Background

Pneumonia is a disease caused by infection in the lung parenchyma, which can be caused by bacteria, viruses, or fungi. To date, pneumonia is an infectious disease with the highest mortality and morbidity rates in the world. (1) The high incidence of pneumonia with various clinical manifestations from mild to life-threatening has prompted clinicians to create a scoring system to determine the severity of pneumonia, which needs outpatient care, hospital treatment, or even intensive care treatment. Until now, the validated pneumonia predictor modality is the pneumonia severity index (PSI). However, due to the complex criteria and age limitations, these criteria are difficult to implement in everyday

clinical settings. (2,3) Therefore, a reliable predictor marker is very important in determining the aggressiveness of therapy and changing antibiotics as an adequate form of infection management. Infection biomarkers that are commonly studied as predictors are procalcitonin (PCT) and C-reactive protein (CRP). (4,5)

PCT is a peptide hormone composed of 116 amino acids, with a molecular weight of 14.5 kDa that is produced mainly by parafollicular cells (C cells) of the thyroid gland and neuroendocrine cells in the lungs and intestine as a response to microbial toxins and increased proinflammatory cytokines such as interleukin (IL) 6, tumor necrosis factor (TNF) α, and IL-1β. (6) Various clinical studies have proven that PCT can be used as a biomarker in determining the presence of infections, especially bacterial infections, when to start administering antibiotics, the duration, and when to stop them. (7) PCT begins to increase within 3 hours after infection, reaches its peak concentration within 24 hours, and will slowly decrease to near normal when the infection is resolved. Due to its short half-life and specificity for bacterial infections, PCT is often used as a guide in administering antibiotics. (8) Several studies regarding the ability of initial PCT to predict mortality within 30 days in septic patients have shown unsatisfactory results. (9) Another study measuring serial changes in PCT on mortality showed a significant relationship but had low specificity. (10)

CRP is a homopentameric acute phase inflammatory protein, which was first discovered in 1930 by Tillet and Francis while researching infections caused by Pneumococcus. (11) The increase in CRP expression is triggered by pro-inflammatory cytokines such as IL6, TNF-α , and IL-1. The role of CRP in infection is also evident in the increase in CRP expression up to 1000 times normal in bacterial infections. As with PCT, CRP reaches peak concentrations within 24 hours when inflammation is present and decreases within 18 to 24 hours when inflammation subsides. (12) A study by Wu et al. showed that CRP can increase up to 76.2% in bacterial infections. Apart from that, an increase in CRP is also associated with the severity of pneumonia, where CRP of more than 10 mg/l is associated with the incidence of severe pneumonia. (13)

The primary objective of this study was to determine the prognostic ability of the combination parameter changes in PCT and CRP while predicting 30-day mortality in patients with severe pneumonia. The secondary aim was to establish the correlation between changes in PCT and CRP and severe pneumonia patients' clinical outcomes, including organ dysfunction (worsening ARDS, AKI, and septic shock incidents).

Method

This study was an observational prospective cohort study to assess the correlation between changes in PCT and CRP towards severe pneumonia patients' clinical outcomes. This study protocol was approved by the Ethical Committee of the Faculty of Medicine, Airlangga University/Dr. Soetomo General Academic Hospital (0852/KEPK/XII/2023). All adult patients over 18 years who were admitted to the ICU due to severe pneumonia were enrolled in this study. This research was a single-center study conducted from December 2023 to February 2024 in the Intensive Care Unit of Dr. Soetomo General Academic Hospital. Severe pneumonia was defined according to American Thorax Society criteria. Written consent was collected from their next of kin prior to the study. We excluded all patients on immunosuppressant medication, corticosteroids equal to hydrocortisone 1 mg/kg/day for more than 1 month, and chemotherapy. Pregnant patients and patients with organ transplant history, cancer, and human immunodeficiency virus (HIV) were also excluded from this study. Patients were followed during the hospital stay and contacted by phone on day 30 to record patient mortality and clinical outcomes. Clinical outcomes that were measured in this study were worsening acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), and septic shock. ARDS was diagnosed using the Berlin criteria, and worsening ARDS was determined by the worsening of partial pressure of oxygen (PaO2) divided by the fraction of inspired oxygen (FiO2) (P/F ratio). Deteriorating acute kidney injury was diagnosed using the Kidney Disease: Improving Global Outcomes (KDIGO) criteria. Septic shock was determined by the Sequential Organ Failure Assessment (SOFA) score of more than 2 and the need for vasopressor for more than 4 hours. SOFA score was calculated every 3 days.

Arterial blood samples for PCT and CRP analyses were drawn within 24 hours (first day) of Intensive Care Unit (ICU) admission and 96 hours thereafter (fifth day). Failure to obtain blood samples within this period was the dropout criterion. Serum PCT levels were measured with ALINITY i B·R·A·H·M·S PCT for the quantitative determination of PCT in human serum on the automated ALINITY i analyzer from Abbott with a sensitivity of 30 pg/ml. Serum CRP levels were measured with ALINITY C CRP VARIO WR CAL KIT for the quantitative determination of CRP in human serum on the automated ALINITY i analyzer from Abbott. Data are presented as median, absolute value, per-

centage, or mean±standard deviation. Analysis of results was divided into PCT group 1 and PCT group 2. PCT group 1 was defined as a decrease of PCT within five days of treatment greater than 50%, whereas PCT group 2 was defined as a decrease of PCT within five days of treatment less than 50% or an increase. CRP measurements were also divided into CRP group 1 and CRP group 2, which differed using the same calculation method as the PCT group. A p-value of less than 0.05 was considered to be statistically significant in all tests. The analyses were performed using SPSS 23.0 software (SPSS Inc., Chicago, IL, USA).

Result

Patient population

The study involved 35 patients. Thirty subjects completed the study, while five others died before the fifth day. **Table 1** presents all subject characteristics. During the 30-day observation, 23 out of 30 patients were classified as PSI class IV and V; 18 of them did not survive.

In this study, 53.3% of the subjects were male, and 46.7% were female, with a median age of 58 years, ranging from 19 to 89 years old. Comorbidities found in the research subjects included cerebrovascular disease (36.7%), hypertension (60%), diabetes mellitus (33.3%), chronic heart failure (23.3%), renal dysfunction (30%), chronic obstructive pulmonary disease (3.3%), and liver dysfunction (6.7%), which may contribute to patient outcome. Community-acquired pneumonia (CAP) accounted for 43.3%, while the remaining 56.7% were hospital-acquired pneumonia (HAP). Among subjects with severe pneumonia, microbial culture results showed dominance of multidrug-resistant (MDR) gram-negative bacteria at 53.3%, followed by Gram-positive bacteria at 30%, and non-MDR gram-negative bacteria at 16.7%. The median duration of ICU stay and ventilator use in this study was 9.5 and 9 days, respectively, with a 60% mortality rate for severe pneumonia in the ICU.

Procalcitonin, CRP, and clinical outcome

The analysis results of the decrease in CRP and PCT on the worsening of ARDS showed no significant relationship with respective p-values of 0.521 and 0.691 ($p>0.05$). The relationship between decreased CRP and PCT with the worsening of AKI also showed non-significant results with p-values of 0.384 and 0.554, respectively. The occurrence of septic shock and decrease in CRP (CRP group 1 and group 2) showed a non-significant relationship. However, PCT group 2 was proven to correlate with an increase in the incidence of septic shock by 8.4 times, compared to PCT group 1, with a sensitivity of 66.7% and a specificity of 91.7% (p-value 0.005). This result is shown in **Tables 2 and 3**.

PCT, CRP, and 30-day mortality

Data in **Tables 2 and 3** indicated that PCT group 2 was associated with an increase in mortality rate up to 2.7 times compared to PCT group 1. This prognostic ability had a sensitivity of 75% and a specificity of 77.8%. However, decreased CRP did not show any significant results in predicting mortality, as shown in **Tables 4 and 5**.

The combination of a decrease in PCT group 1 with a decrease in CRP expression was associated with an increased survival rate of up to 2.75 times, with a sensitivity of 50% and a specificity of 88.9% (p-value 0.034), as shown in **Tables 6 and 7**.

Discussion

Changes in PCT, CRP, and clinical outcome

High PCT expression is always presumed to be related to the incidence of sepsis. Sepsis and septic shock are conditions that occur due to dysfunction of the immune response to invading infections, leading to life-threatening organ impairment. The release of lipopolysaccharide (LPS) by gram-negative bacterial cell membranes or other similar substances acting like LPS by yeast and gram-positive bacteria is a pathogenic component that triggers severe inflammation. Proinflammatory cytokines such as TNF-α, IL-1, and IL-6 play a significant role in this exaggerated inflammatory response, which can cause endothelial damage, microvascular dysfunction, mitochondrial dysfunction, and increased apoptosis, ultimately leading to organ dysfunction and hemodynamic instability. (14)

A previous study by Schuetz et al. in 2017 reported the ability of PCT to provide a rapid depiction of infection severity, coupled with its short half-life post-infection resolution, makes PCT a precise predictor of septic shock events. (9) Karlsson et al. stated the same thing about high PCT expression on the first day of infection and the incident of septic shock. (15) In this recent study, we found that an increase or decrease of PCT less than 50% within 5 days was correlated with an increased occurrence of septic shock up to 8.4 times compared to the other group. These findings reaffirm the strong association between PCT and the occurrence of infection. Thus, if an infection is not effectively managed, the incidence of septic shock will likely increase. On the contrary, the change in CRP expression did not correlate with the clinical outcomes of patients, including ARDS, AKI, or septic shock. This might be due to the fact that changes in CRP expression were

influenced by various factors other than infection. (5) The presence of severe comorbidities, which we did not analyze further in this study, may influence the inflammatory response and change in CRP expression.

Changes in PCT, CRP, and mortality

PCT is an infection biomarker associated with an infection's severity, especially bacterial infections. (16) It begins to increase within 3 hours post-infection and reaches its peak concentration within 24 hours. PCT also has a short half-life; therefore, it decreases to normal levels within 24 hours after the infection is resolved. (4) Therefore, a significant decrease in PCT expression indicates that triggers such as bacterial endotoxins or proinflammatory cytokines like TNF-α, IL-1β, and IL-6 have begun to subside, and the infection has been controlled, which ultimately correlates with the survival rate of severe pneumonia patients. (16) This profile showed us that a decrease in PCT was an advantage as a predictor of mortality in severe pneumonia, as seen in this recent study. As seen in **Figure 1**, the box plot diagram illustrates the difference in PCT expression within the first 24 hours and 96 hours later between the survivor and non-survivor groups. It shows that the survivor group exhibits a significant decrease in PCT expression of more than 50% (PCT group 1), whereas the non-survivor group tends to experience a decrease in PCT less than 50% or an increase in PCT expression (PCT group 2).

A previous study by Schuetz in 2011 showed a decrease in PCT expression within the first and the fifth day, which was associated with a reduction in mortality rates of severe pneumonia patients in the ICU. (9) This finding differs slightly from our study results, where the mortality rate only decreased when there was a reduction in PCT of more than 50%. Another finding was also reported by Karlsson et al. in 2010, where a decrease in PCT of less than 50% was significantly associated with an increase in mortality rates in patients with severe sepsis in the ICU, while high PCT (above 10 ng/ml) didn't have any predictive value. (15) The latest study by Schuetz et al. in 2018 also found that a decrease in PCT of more than 80% was correlated with a reduction of mortality rates in septic patients with a sensitivity of 77% and specificity of 39%. (10) These similar findings further strengthen the strong correlation between the decrease in PCT and patient mortality. The difference between this study and ours lies in the cut-off value of PCT 50% and the sensitivity and specificity rates. Several factors that may influence these differences were the disparity in sample source, infection source, type of bacterial infection, initial SOFA score, and variance in the timing of PCT evaluation (day 4 vs. day 5). Therefore, an additional sample size may be needed for a more comparable result.

CRP is an acute-phase protein that is highly sensitive to inflammation. CRP expression increases in several conditions, such as rheumatoid arthritis, chronic autoimmune, cardiovascular disease, severe trauma, and infections. (12) As an acute-phase protein, CRP expression in the body could increase up to 1000 times the initial level. A different result from the PCT is that a decrease in CRP alone does not show any capacity to predict mortality in patients with severe pneumonia. However, when we analyzed further the combination of a decrease in CRP and a decrease in PCT of more than 50% (PCT group 1), we found that it can enhance the specificity of PCT in predicting severe pneumonia mortality up to 88.9%.

Conclusion

The 5-day decrease in PCT can predict 30-day mortality rates and the incidence of septic shock in patients with severe pneumonia. Combining the decrease in PCT with the decrease in CRP can enhance the specificity of this prognostic capability.

Table 1. Patient demographic characteristic

Characteristic	Values
Gender, n (%)	
- Male	16 (53.3)
- Female	14 (46.7)
Age, median (range)	58 (19-89)
Comorbidity, n (%)	
- Cerebrovascular disease	11 (36.7)
- Hypertension	18 (60)
- Diabetes mellitus	10 (33.3)
- Chronic heart disease	7 (23.3)
- Chronic kidney disease	9 (30)
- Chronic obstructive pulmonary disease	1 (3.3)
- Liver dysfunction	2 (6.7)
Types of pneumonia, n (%)	
- Community-acquired pneumonia	13 (43.3)
- Hospital-associated pneumonia	17 (56.7)
Sputum culture, n (%)	
- Gram negative bacteria	21 (70)
* Non-multiple drug resistant	5 (16.7)
* Multiple drug resistant	16 (53.3)
- Gram positive bacteria	9 (30)
* Multiple drug resistant	1 (3.3)
Mortality, n (%)	
- Survivors	12 (40)
- Non-survivors	18 (60)
Pneumonia severity index score, n (%)	
- Class II	4 (13.3)
- Class III	3 (10)
- Class IV	5 (16.7)
- Class V	18 (60)
Length of Intensive Care Unit stay, median (range)	9.5 (5-34)
Length of ventilator day, median (range)	9 (3-33)
Initial measurement, median (range)	
- Procalcitonin	1.85 (0.07-100)
- C-reactive protein	8.4 (1.91-41.16)
Outcome complication, n (%)	
- Worsening acute respiratory distress syndrome	9 (30)
- Worsening acute kidney injury	10 (33.3)
- Septic shock incidents	12 (40)

Table 2. PCT, CRP, and clinical outcome

Parameter		Worsening ARDS		p-value	Worsening AKI		p-value	Septic shock		p-value
		Yes (n=9), n (%)	No (n=21) , n (%)		Yes (n=10), n (%)	No (n=20), n (%)		Yes (n=12), n (%)	No (n=18), n (%)	
Δ PCT	PCT group 1	3 (23.1%)	10 (76.9%)	0.69	4 (30.8%)	9 (69.2%)	0.55	1 (7.7%)	12 (92.3%)	0.005
	PCT group 2	6 (35.3%)	11 (64.7%)		6 (35.3%)	11 (64.7%)		11 (64.7%)	6 (35.3%)	
Δ CRP	CRP group 1	2 (22.2%)	6 (25.6%)	0.54	4 (40%)	4 (20%)	0.38	2 (16.7%)	6 (33.3%)	0.419
	CRP group 2	7 (31.8%)	15 (68.2%)		6 (27.3%)	16 (72.7%)		10 (45.5%)	12 (54.5%)	

Legend: PCT=procalcitonin; CRP=C-reactive protein; ARDS=acute respiratory distress syndrome; AKI=acute kidney injury.
Δ PCT is the decrease in serum PCT on the first and fifth day. If it was more than 50%, it fell into Group 1, whereas if it was less than 50% or increased, it fell into Group 2.
Δ CRP is the decrease in serum CRP on the first and fifth day. If it was more than 50%, it fell into Group 1, whereas if it was less than 50% or increased, it fell into Group 2.

Table 3. PCT odds ratio towards septic shock

Risk estimation of septic shock	Value	Confidence interval	
		Upper limit	Lower limit
PCT group 2	8.403	55.55	1.239

Legend: PCT=procalcitonin.
Odds ratio between PCT group 2 compared to PCT group 1 towards septic shock occurrence.

Table 4. PCT, CRP, and 30-day mortality

Parameter		Survivor (n=12)	Non-survivors (n=18)	p-value
Δ PCT	PCT group 1	9	4	0.013
	PCT group 2	3	14	
Δ CRP	CRP group 1	3	5	0.6
	CRP group 2	9	13	

Legend: PCT=procalcitonin; CRP=C-reactive protein.
Δ PCT is the decrease in serum PCT on the first and fifth days. If it was more than 50%, it fell into group 1, whereas if it was less than 50% or increased, it fell into group 2.
Δ CRP is the decrease in serum CRP on the first and fifth days. If it was more than 50%, it fell into group 1, whereas if it was less than 50% or increased, it fell into group 2.

Table 5. PCT odds ratio towards mortality

Risk estimation	Value	Confidence interval	
		Upper limit	Lower limit
Odds ratio PCT group 2	2.674	6.211	1.151

Legend: PCT=procalcitonin.
Odds ratio between PCT group 2 compared to PCT group 1 towards mortality.

Table 6. The correlation between the combination of PCT and CRP with mortality

Parameter	Survivor (n=12)	Non-survivors (n=18)	p-value
PCT group 1 + decreased CRP	6	2	0.034
PCT group 2 + increased CRP	6	16	

Legend: PCT=procalcitonin; CRP=C-reactive protein.

Table 7. The odds ratio of the combination of PCT and CRP with mortality

Risk estimation of mortality	Value	Confidence interval	
		Upper limit	Lower limit
Odds ratio PCT group 1+ decreased CRP	2.750	1.247	6.065

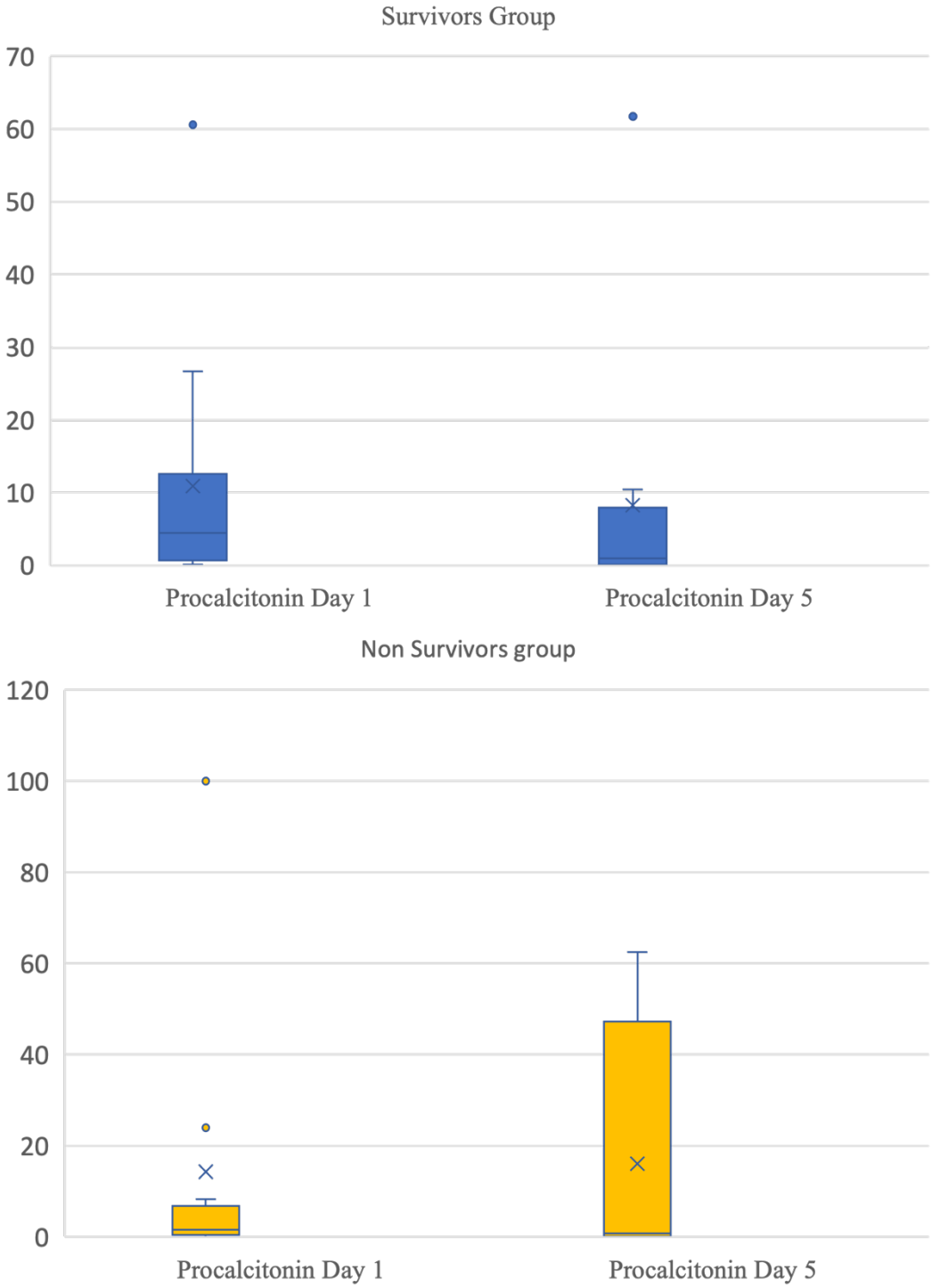
Legend: PCT=procalcitonin; CRP=C-reactive protein.
Odds ratio between PCT group 1+ decreased CRP compared to PCT group 2 + increased CRP towards mortality.

Table 8. PCT correlation with patient survivor

Parameter	Survivor (n=12)	Non-survivor (n=18)
Decrease of PCT>50%, n (%)	9 (75%)	4 (22.2%)
Decrease of PCT<50%, n (%)	0 (0%)	4 (22.2%)
Increase of PCT, n (%)	3 (25%)	10 (55.6%)

Legend: PCT=procalcitonin.

Figure 1. Box plot diagram procalcitonin between survivors and non-survivors groups



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