Northwestern Med J. 2023;3(3):180-188 doi: 10.54307/NWMJ.2023.80299

Serum procalcitonin levels in open heart surgery patients and its relationship with mortality and morbidity

Açık kalp cerrahisi yapılan hastalarda serum prokalsitonin düzeyleri ve bunun mortalite ve morbidite ile ilişkisi

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Attf/Cite as: Deniz M, Şahin N, Aydoğdu Titiz T, Bayezid Ö. Serum procalcitonin levels in open heart surgery patients and its relationship with mortality and morbidity. Northwestern Med J. 2023;3(3):180-188.

ABSTRACT

Aim: The release of procalcitonin (PCT) has been suggested to be related to the type of surgery and cardiopulmonary bypass (CPB). We aimed to investigate the associations of PCT with hemodynamic stability, type of cardiac surgery, and complications.

Methods: Our study was conducted in 2015 on 76 adult patients divided into three groups according to types of surgery: group I consisted of coronary artery bypass grafting with CPB, group II consisted of cardiac valve replacement, and group III included left ventricle assist device implantation. The patients' serum PCT values were measured preoperatively before induction, 24 and 48 hours postoperatively, and when a complication occurred.

Results: Preoperative PCT levels of the groups were similar. The PCT level in group I was lowest preoperatively, highest in postoperative 24 hours, and showed a decline postoperatively from 24 hours to 48 hours. In group II, the PCT level was increased in postoperative 24 and 48 hours compared to the preoperative level, and there was no difference between postoperative 24- and 48-hour values. In group III, the PCT level was lowest preoperatively and highest in postoperative 24 hours, while the postoperative 48-hour value was lower than the 24-hour value. Intensive care unit (ICU) stay with a higher P1PCTlevel correlated with longer ICU stay. There were no differences between patients with PCT levels \geq 0.5 and <0.5 regarding the duration of postoperative mechanical ventilation (MV), inotropic agents, and hospitalization. Patients with higher P2PCThad a longer duration of ICU stay, postoperative MV, and hospitalization. There was a correlation between the P2PCT level and the risk of complications.

Conclusion: Increased postoperative PCT levels were associated with complications, longer durations of of hospitalization, ICU stay, and postoperative MV. We suggest that PCT might be a marker for early diagnosis of complications and follow-up of the clinical course.

Keywords: Open-heart surgery, procalcitonin, mortality, left ventricular assist device

ÖZ

Amaç: Prokalsitonin salınımının cerrahinin tipi ve karmaşıklığı ve kardiyopulmoner bypass ile ilişkili olduğu öne sürülmüştür. Bu çalışmada prokalsitoninin (PCT) hemodinamik stabilite, kalp cerrahisi tipi ve komplikasyonlar ile ilişkisini araştırmayı amaçladık.

Yöntem: Çalışmamız 2015 yılında cerrahi tiplerine göre grup I koroner arter bypass greftleme, grup II KPB ile kalp kapak replasmanı ve grup III sol ventrikül destek cihazı implantasyonu olmak üzere üç gruba ayrılan 76 erişkin hasta üzerinde yapılmıştır. Hastaların serum C-reaktif protein (CRP) ve PCT değerleri ameliyat öncesi, indüksiyon öncesi, ameliyat sonrası 24 saat (P1PCT) ve 48 saat (P2PCT) ve komplikasyon oluştuğunda ölçüldü.

Bulgular: Grupların preoperatif PCT düzeyleri benzerdi. Grup I'de PCT düzeyi ameliyat öncesi en düşük, ameliyat sonrası 24 saat en yüksek ve ameliyat sonrası 24'den 48 saate kadar düşüş gösterdi. Grup II'de PCT düzeyi postoperatif 24 (P1PCT), 48 saatte preoperatif düzeye göre artmıştı ve postoperatif 24 ile 48 saat (P2PCT) arasında fark yoktu. Grup III'te

Received: 27.01.2023 **Accepted:** 04.07.2023 **Publication date:** 01.10.2023

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ORCID: 0000-0001-5604-6372 Akdeniz University, Faculty of Medicine, Department of Cardiovascular Surgery, Antalya, Türkiye PCT düzeyi ameliyat öncesi en düşük ve ameliyat sonrası 24 saat en yüksek iken, ameliyat sonrası 48 değeri 24 değerinden daha düşüktü. P1PCT düzeyleri ≥0.5 ve <0.5 olan hastalar arasındaki tek anlamlı fark, daha uzun yoğun bakım ünitesinde (YBÜ) kalış süresi ile ilişkili olarak daha yüksek PCT düzeyi ile YBÜ'de kalış içindi. PCT düzeyleri ≥ 0,5 ve <0,5 olan hastalar arasında postoperatif mekanik ventilasyon, inotropik ajanlar ve hastanede yatış süreleri açısından fark yoktu. P2PCT>0.5 olan hastaların yoğun bakımda kalış süreleri, postoperatif mekanik ventilasyon ve hastanede yatış süreleri daha uzundu. Grup II'nin P1PCT seviyeleri ile VFT, CPBT ve AT ölçümleri arasında ve Grup II'nin P2PCT ve AT ölçümleri arasında pozitif korelasyonlar vardı. Spesifik komplikasyonlar ile PCT seviyeleri arasında herhangi bir korelasyon mevcut değildi. Tek korelasyon, P2PCT seviyesi ile genel olarak komplikasyon riski arasındaydı.

Sonuç: Artmış postoperatif PCT seviyeleri genel olarak komplikasyon gelişimi, hastanede ve YBÜ'de daha uzun kalış süreleri ve postoperatif MV ile ilişkili olduğundan, prokalsitoninin komplikasyonların erken teşhisinde ve klinik seyrin takibinde bir belirteç olabileceğini düşünüyoruz.

Anahtar kelimeler: Acık kalp cerrahisi, prokalsitonin, mortalite, sol ventriküler destek cihazı

INTRODUCTION

Preoperative evaluation, perioperative followup, postoperative complications, and their management are of utmost importance in preventing perioperative mortality and morbidity in open-heart surgery. Patient age, comorbidities, functional capacity, and type and duration of surgery are also essential. Perioperative monitoring and postoperative management play a significant role in preventing early complications. Electrocardiography, hemodynamic monitoring, CK-MB, troponins, and brain natriuretic peptide (BNP) are commonly used to diagnose perioperative myocardial infarction and cardiac failure in open-heart surgery. These indicators provide an advantage in determining the prolongation of early postoperative cardiovascular support, intensive care, and hospital stay, and in predicting mortality and morbidity.

Procalcitonin (PCT) is released from the parafollicular thyroid cells as a precursor of calcitonin and is a 16-amino acid peptide (1). The normal serum PCT level is below 0.05 ng/mL.PCT levels above 0.5 ng/mL have diagnostic value in various inflammatory processes, primarily those caused by bacterial endotoxins. The type and complexity of the surgery and the duration of CPB have been claimed to be proportional to serum PCT levels.

Procalcitonin is a valuable indicator for predicting outcomes in patients with acute mesenteric ischemia of venous or arterial origin (2). Moreover, it helps diagnose mesenteric ischemia in patients admitted due to intestinal obstruction (3). Various studies have reported higher complication rates

in patients with elevated PCT levels after cardiac surgery (4,5).

Although numerous indicators and classification systems have been used to predict postsurgical complications, determining specific indicators of postoperative complications is of utmost importance for early diagnosis and treatment. Procalcitonin is a marker known to increase in both infectious and septic conditions. The origin of PCT in the inflammatory response is not yet fully understood; however, Procalcitonin has been suggested to be modulated by cytokines and lipopolysaccharides (6).

Increases in cytokine levels are more significant after cardiac surgery and CPB than after other surgical procedures (7). This cytokine "burst" has a progression similar to the systemic inflammatory response syndrome and creates difficulties in diagnosing infections, which are postoperative complications. Therefore, markers that would provide information on the development of postoperative complications are of great importance.

In our literature review, while there were numerous studies on coronary artery bypass grafting (CABG), heart valve surgery (HVS), and pediatric cardiac surgery, we encountered only one study investigating the relationship between left ventricular assist device (LVAD)implantation and serum PCT levels. In our study, we aimed to investigate the PCT trends in cardiac surgeries, including LVAD implantation, on serum PCT levels. In addition, we aimed to investigate whether

hemodynamic stability was associated with PCT levels by using close intraoperative hemodynamic monitoring and to determine the association of C-reactive protein (CRP), another commonly used indicator of PCT levels.

MATERIALS AND METHODS

This was a prospective, observational clinical trial. After approval from the Ethical Committee for Medical Research, Faculty of Medicine, Akdeniz (code:2012-KAEK-20/No:287, date: 10.06.2015), 76 patients older than 18 years were included in the study and were divided into three groups, according to the type of surgery as follows: group I, n=37 (49%) CABG; group II, n=18 (24%) heart valve surgery (HVS); and group III, n=21 (27%) LVAD implantation. Descriptive statistics were presented frequency, percentage, mean, standard deviation, median, minimum, and maximum. The Shapiro-Wilk test was used to test the normality assumption. The Mann-Whitney U test was used to analyze the differences between the measurements of the two groups when the data were not normally distributed, and the independent samples t-test was used when the data were normally distributed. The Kruskal-Wallis test was used for nonparametric comparison of the three groups and the Bonferroni-Dunn procedure was used as a post hoc test for significant results. For analysis of temporal changes in PCT levels in all groups, the Friedman test was used when the

data did not comply with a normal distribution, and the Bonferroni–Dunn procedure was used as a posthoc test for significant results. The associations between continuous variables that were not normally distributed were analyzed using the Spearman's correlation test. The statistical significance was set at p < 0.05. The Statistical Package for the Social Sciences software package (version 22.0) was used for statistical analysis.

RESULTS

We studied 76 patients; 4 patients died, 6 patients had renal replacement therapy, and 9 patients had stayed in the hospital for more than 28 days. There was no significant difference between mortality and morbidity in terms of PCT level.

The ejection fraction (EF) measurements of the groups are presented in Table 1 as means and medians. The mean EF measurements in groups I and II were significantly higher than those in group III (p=0.001).

The differences among the preoperative, postoperative 24-h (P1PCT), and postoperative 48-h (P2PCT) PCT values are presented in Table 2. In group I, the PCT level was the lowest in the preoperative levels and highest in the P1PCT measurement, whereas the PCT value decreased in the P2PCT levels compared to the P1PCT measurement. In group II, the P1PCT and P2PCTlevels were increased compared to the

Table 1. Patient characteristics of study, Body Mass Index (BMI), Diabete Mellitus (DM), Hypertension (HT). Ejection Fraction (EF), CPB time (CPBT), CCT (cross-clamp time), and AT (anesthesia time).

		Group I	Group II	Group III	р
Gender n(%)	female	13 (35.1)	12 (66.7)	4 (19)	0.008
	male	24 (64,9)	6 (33,3)	17 (81)	0.008
Age(years)		61,9±8,9	61,6±7,6	51,5±8,4	<0,05
BMI (kg/m²)		$26,1\pm7,1$	25,7±6,2	25,3±5,9	>0,05
Smoking n(%)		17(62,9)	11(64,7)	1(4,7)	<0,001
DM		8(29,6)	5 (27,7)	1 (4,7)	<0,001
HT		16 (59,2)	10 (55,5)	4 (19)	<0,001
EF(%)		55,14±9,7	59,88±3,76	18,45±3,62	<0,001
CPBT(min)		135,1±28,9	152,8±83,1	90,2±35,1	<0,05
CCT(min)		$85,4\pm18,9$	97,1±24,6	-	>0,05
AT(min)		301,8±27,8	303,1±99,3	270±57,5	>0,05

Table 2. The differences among the prPCT, P1PCT, and P2PCT procalcitonin values in each group.

	Group I		G	roup II	G	р	
	n	Mean±SD	n	Mean±SD	n	Mean±SD	
prPCT	36	0,18 ±0,38	17	0,16±0,38	21	0,48±1,59	<0,001
P1PCT	33	1,72±2,18	17	8,25±23,99	21	8±13,11	<0,001
P2PCT	33	0.74 ± 1.15	17	13,09±32,76	21	6,97±15,89	<0,001

Table 3. The relationships of the PCT value with with intraoperative mechanical ventilation-free time (IOMVF), CPB time (CPBT), CCT (cross clamp time), and AT (anesthesia time). Positive correlation between P1PCT levels in group II and, IOMVF, CPBT, and AT.

Group	PCT		IOMVF (minutes)	CPBT (minutes)	CKT (minutes)	AT (minutes)
		r	0,06	0,191	0,11	0,025
	prPCT (ng/ml)	р	0,728	0,264	0,523	0,884
		n	36	36	36	36
		r	-0,281	-0,156	-0,149	-0,104
Group I	P1PCT (ng/ml)	р	0,113	0,385	0,409	0,563
		n	33	33	33	33
		r	-0,281	-0,084	-0,173	-0,021
	P2PCT (ng/ml)	р	0,114	0,644	0,336	0,908
		n	33	33	33	33
		r	-0,07	-0,07	0,025	0,14
	prPCT (ng/ml)	р	0,784	0,784	0,922	0,579
		n	18	18	18	18
		r	0,485*	0,486*	0,414	0,727**
Group II	P1PCT (ng/ml)	р	0,048	0,048	0,098	0,001
		n	17	17	17	17
		r	0,447	0,472	0,18	,511*
	P2PCT (ng/ml)	р	0,072	0,056	0,488	0,04
		n	17	17	17	17
Group III		r	0,005	0,031		0,039
	prPCT (ng/ml)	р	0,983	0,893		0,866
		n	21	21		21
		r	0,229	0,216		0,075
	P1PCT (ng/ml)	р	0,317	0,347		0,747
		n	21	21		21
		r	0,213	0,212		0,098
	P2PCT (ng/ml)	р	0,354	0,356		0,673
		n	21	21		21

Table 4. The relationships between PCT and the development of postoperative complications in general.

			Prpct			p1pct			p2pct	
		<0,5 %	≥0,5 %	р	<0,5 %	≥0,5 %	р	<0,5 %	≥0,5 %	р
Complication	Absent	83,1%	75,0%	0.541	93,8%	78,2%	0,272	93,5%	72,5%	0,023
	Present	16,9%	25,0%	0,541	6,3%	21,8%		6,5%	27,5%	

preoperative PCT value, whereas no difference was found between the P1PCT and P2PCT levels. Similar to the group I, the PCT level was the lowest in the preoperative levels and highest in the P1PCT levels, whereas the PCT value decreased in the P2PCT measurement compared to the P1PCT measurement in group III.

The differences between the patients with P1PCT measurements <0.5 and \geq 0.5 ng/mL in terms of the postoperative mechanical ventilation duration (PMVD), inotrope requirements (PIRD), and durations of intensive care (ICSD) and hospital stays(HSD) are presented in Figure 1. The only difference between the two groups was the

duration of ICU stay; patients with a P1PCT value of ≥0.5 ng/mL had a longer duration of ICU stay than those with a P1PCT value of <0.5ng/mL. No significant differences were observed in the duration of postoperative mechanical ventilation, postoperative inotrope requirement, or hospital stay between the two groups.

The differences between the patients with P2PCT measurements <0.5 ng/mL and ≥0.5 ng/mL regarding the PMVD, PIRD, ICSD, and HSD are presented in Figure 2. Patients with a P2PCT value ≥0.5 ng/mL had more prolonged mechanical ventilation, intensive care, and HSD than those with a P2PCT value <0.5 ng/mL. No significant difference was observed in the duration of postoperative PIRD between the groups.

The relationships between PCT measurements (intraoperative mechanical ventilation-free time [IOMVFT]), CPB duration, CCT, and AT measurements were investigated. According to the correlation tests, positive correlations between group II's P1PCT measurement and the duration of mechanical ventilation (r=0,485; p=0,048), CPBT (r=0.486; p=0.048), and AT (r=0.727; p=0.001)were determined. In addition, the P2PCT value in group II was positively correlated with AT (r=0,511; p=0,036). The results are presented in Table 3. There was no relationship between CRP level and IOMVFT, and CPB duration, CCT, and AT measurements were investigated.

The relationships between PCT levels and postoperative complications are presented in Table 4. According to the correlation tests, there was no significant relationship between PCT level and any complication. The only positive correlation was between the P2PCT value and the development of complications in general (p=0.023), which signifies that if PCT levels do not normalize, complications will occur.

DISCUSSION

Studies have shown that bacterial endotoxins are the most important factor affecting PCT levels (8). Although not as much as infection, surgical trauma may also affect PCT levels. A significant elevation of PCT levels was observed, particularly following esophagectomy. Such an elevation was suggested to be because of the bacterial translocation that developed due to transient bacterial contamination during surgery. Following surgical trauma, another possible cause of PCT elevation is the release of cytokines during wound healing (9).

Few studies have been conducted on PCT kinetics following surgery. One of the most significant studies on this subject was the study conducted by Meisner et al., which investigated PCT kinetics following various types of surgery. In that study, PCT kinetics were investigated in 130 patients who had undergone various surgical procedures. It was reported that minor and aseptic surgeries did not affect PCT, whereas high PCT levels were determined after abdominothoracic and major procedures (9). Procalcitonin levels can spontaneously reach 1 ng/mL after minor and aseptic procedures and 2 ng/mL after cardiac surgery.

In contrast, a patient in whom PCT concentration reaches 10 ng/mL after uncomplicated surgery should be carefully investigated for infection. In their study on the effect of cardiopulmonary bypass surgery on PCT levels, Aouifi et al. divided their patients into three groups as follows: group I, patients who underwent CABG and cardiopulmonary bypass; group II,patients who underwent CABG only; and group III, patients who underwent HVS. The authors investigated the PCT levels in the preoperative period and for 5days in the postoperative period and reported that the PCT level increased in all three groups, not exceeding 5 ng/mL, reached its peak value on the 1st postoperative day, and returned to its normal level on the 5th postoperative day. Very high PCT levels were determined in 10patients who developed complications (7 patients, circulatory failure; 2patients, active endocarditis; and1patient, septic shock). In these patients, the serum PCT levels ranged between 6.2–230 ng/mL.

In conclusion, the development of postoperative complications should be suspected when PCT concentrations > 5 ng/mL are measured. Additionally, PCT is a marker superior to CRP for monitoring postoperative complications (10). In the study conducted by Kallel et al., PCT levels were measured preoperatively and at 4-h, 24-h, 48-h, 72-h, and 96-h serum samples of 40 patients who underwent CABG and HVS under CPB. The PCT level peaked on the 1st postoperative day (0.96±1.00 ng/mL) and progressively decreased on the following postoperative days. When the two groups were compared, it was found that the PCT level did not correlate with the type of surgery (11).

Serum PCT levels were correlated with organ dysfunction in sepsis and APACHE II scores (12,13). Moreover, PCT levels were well correlated with the severity of organ dysfunction, as evaluated by the SOFA score. Meisner et al. reported that PCT levels were well correlated with the maximal SOFA scores in the first two postoperative days in 208 patients who underwent CPB.

Meisner et al. determined the correlation between postoperative PCT levels and the development of SIRS, respiratory failure, and requirement for inotropic support (13). Similarly, Dörge et al. reported that patients who developed postoperative organ failure had higher PCT levels than those with a complication-free postoperative period (4). Adamik et al. ¹⁴ showed that PCT levels did not change in patients responding to treatment following CPB and with complications, mainly when renal and hepatic dysfunction developed in addition to respiratory and circulatory failure.

Hennig et al.¹⁵ investigated markers that could predict the development of post-LVAD right ventricular failure and determined statistically significantly high PCT levels in the failure group (PCT levels 0.322 vs. 0.106 mg/dL; p=0.048). They also found statistically significant increases in endothelin-1 and neopterin levels, in addition to increased PCT levels.

Kettner et al. ¹⁶ investigated the dynamics of post-LVAD PCT and reported that even though it was an inflammatory marker, its level did not explicitly increase due to infection after the LVAD procedure. On the contrary, they reported that in patients with increased PCT levels, the overall risk of postoperative complication development increased.

In our study, the PCT levels were investigated preoperatively and, on the 1st, and 2nd postoperative days in the three groups of patients undergoing CABG, HVS, and LVAD. In all groups, PCT levels increased and peaked on the 1st postoperative day. In group I patients in whom CABG was performed under CBP, the mean PCT value was 1.72 ng/mL(p<0.001) on the 1st postoperative day, and the maximal value was 9.3 ng/dL. In group II patients who underwent HVS, the mean value was 8.25 ng/mL (p<0.001) and the maximal value was 100 ng/mL. In group III patients who underwent LVAD implantation, the mean PCT level was 8 ng/mL (p<0.001), and the maximal value was 55.9 ng/mL. The PCT levels tended to decrease on the 2nd postoperative day in all three groups. Fifteen patients developed postoperative complications. We determined elevated PCT levels in these patients during the complications. When the present complications caused new complications, PCT levels were also high. The serum PCT levels varied within the range of 1.07-100 ng/mL in these patients. In their extensive study, Loebe et al. investigated the preoperative PCT levels of 691 patients in whom CABG, heart valve replacement, aortic surgery, and CABG+ heart valve replacement were performed with CBP. The serum PCT levels of survivors were measured daily until they were transferred from the intensive care unit to the surgical ward, and the serum PCT levels of the deceased patients were measured daily until their death. They found a significant correlation between CBP duration and serum PCT levels (p<0.01). They determined significant relationships with the type of surgery, requirement for vasopressor support, and requirement for intra-aortic balloon pump support (17). We determined positive correlations

and significant relationships between serum PCT levels and MVF (r=0.485; p=0,048), CBP (r=0.486; p=.048), and durations of anesthesia (r=0.727; p=0.001) in group II patients who underwent HVS. In group II, we determined a positive correlation and significant relationship between the serum PCT level on the 2nd postoperative day and the duration of anesthesia (r=0,511; p=0,036). This is a warning sign for us to be careful about the potential development of complications when the expected decrease in serum PCT level does not occur.

In terms of predicting mortality, for a cut-off value of 34.2 ng/mL, PCT had a sensitivity of 100% and specificity of 90%, whereas its sensitivity was 100% and specificity was 65% for a cut-off value of 5 ng/ mL. In addition, PCT levels were associated with the development of postoperative complications. Lecharny et al. 18 reported a higher mean PCT level in the patient group who experienced postoperative myocardial infarction than in the patient group with a postoperative period. In their study on 52 pediatric patients undergoing cardiac surgery, Minami et al.19 determined that postoperative calcitonin levels were associated with the duration of postoperative mechanical ventilation and intensive care stay. Ina study of 25 pediatric patients undergoing cardiac surgery, Beghetti et al.20 determined significant relationships between postoperative serum PCT level, duration of intensive care stay, and inotrope requirement in the postoperative period.

In our study, the only difference between the patient groups with serum PCT levels ≥0.5 ng/mL and <0.5 ng/mL on the 1st postoperative day was the duration of intensive care stay; the patient group with higher PCT levels had a more prolonged intensive care stay (p=0.046). No differences were found in the duration of postoperative mechanical ventilation, inotropic support, or hospitalization between the patient groups with serum PCT levels ≥ 0.5 ng/mL and<0.5 ng/mL on the 1st postoperative day.

The patient group with serum PCT levels ≥ 0.5 ng/mL on the 2nd postoperative day was determined to have a more prolonged duration of postoperative mechanical ventilation (p=0.041), intensive care stay (p=0.001), and hospitalization (p=0.012) than the patient group with a PCT value <0.5 ng/mL; there was no difference regarding the duration of the postoperative inotropic support requirement between the two groups.

We investigated the relationship between serum PCT levels and prognosis. As the results of correlation tests, no significant relationships were determined between complications, such as sepsis, ARDS, acute renal failure, local infection, and low-output state, and the serum PCT levels on the 1st and 2nd postoperative days. When we questioned whether a complication had developed without specifying the type of complication, we determined a significant relationship between the serum PCT levels on the 2nd postoperative day and the development of complications (p=0.023), indicating that when the expected decrease in serum PCT level is not observed in patients undergoing open-heart surgery, a complication may develop. Such patients need to be closely followed up, and detailed investigations are required.

In our study, three patients completed the surgical procedure with an extracorporeal membrane oxygenator (ECMO) due to cardiac failure. In both patients in whom surgery was accomplished with ECMO implantation, serum PCT levels were 100 ng/mL starting from the 1st and 2nd days, and these values did not change with the development of complications. Both patients died on the 7th postoperative day with PCT levels of 100ng/mL.

We determined that postoperative serum PCT levels varied according to the type of surgery. Postoperative serum procalcitonin levels were higher in those who underwent heart valve replacement and LVAD implantation than in those who underwent CABG with CPB. We concluded that when the expected decrease in serum PCT

does not occur in the postoperative period, it may indicate the potential development of complications, such as infections. These results of high PCT levels give us hints about intensive care costs and new complications, such as intensive care infections. If PCT levels do not normalize, the possibility of complications increases. The limitations of our study were that this was a single-center study and had a small number of cases and complications. In light of these results, we believe that PCT maybe a good early biomarker to follow the clinical course.

Ethics Committee Approval: The study protocol was approved by the Medical Research, Faculty of Medicine, Akdeniz University Ethics Committee (10.06.2015 / 2012-KAEK-20/No:287).

Conflict of Interest: The authors have declared that they have no conflict of interest.

Funding: The authors have declared that they have not received any financial support.

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