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# Correlation of serum C-reactive protein and procalcitonin levels in infections of kidney transplant recipients

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## ABSTRACT

***Objectives.*** Procalcitonin is a propeptide of calcitonin and has been increasingly used as a biomarker of infection. The aim of this study was to evaluate correlation of serum C-reactive protein (CRP) and procalcitonin (PCT) levels of kidney transplant patients hospitalized due to infection. ***Methods.*** There were 121 patients who had kidney transplant in our center between September 2012 and February 2017 and patients with a diagnosis of infection or rejection were included in the study. Simultaneous 106 serum CRP and PCT levels at the beginning or during any time of treatment for post-transplant infection, cytomegalovirus (CMV) positivity, BK viremia and rejection were evaluated. ***Results.*** Median and interquartile ranges of CRP and PCT serum levels were 40 mg/l [24.7-64.9] and 0.19 ng/ml [0.1-0.61], respectively. A significant positive correlation between serum CRP and PCT levels of the patients were observed (r=0.490, $p<0.001$). When serum CRP levels were grouped as <50 mg/l, 50-100 mg/l and >100 mg/l, correlations with serum PCT levels were as r=0.461 ($p<0.001$), r=-0.52 ($p=0.860$) and r=0.488 ($p=0.153$), respectively. Serum levels of PCT did not increase in CMV and BK virus infections and rejection. ***Conclusions.*** Serum CRP and PCT levels were correlated as a whole in the study, whereas serum CRP levels of 50-100 mg/l and >100 mg/l did not show a statistically significant correlation. Stability of PCT levels in viral infections and rejections might be an advantage for the follow-up of solid organ transplants. We need prospective trials of PCT measurements for the evaluation of post-transplant infections.

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***Keywords:*** C-reactive protein, procalcitonin, correlation, kidney transplantation

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## Introduction

Systemic infection is a very common complication after solid organ transplantation and is associated with increased morbidity and mortality [1, 2]. Infections that develop after kidney transplantations might be associated with acute cellular rejection, graft failure, graft loss and even death [3-5]. Mediators like serum C-reactive protein (CRP), cytokines and interleukins increase with systemic infections. Among those CRP is the most widely used clinically and serum levels of <5 mg/l are accepted as normal. But serum CRP levels increase in vascular occlusive diseases, malignancies, trauma and bacterial, viral, fungal and protozoal infections [6]. Procalcitonin (PCT), a species-specific propeptide of calcitonin, is a glycoprotein of 116 amino acids with a molecular weight of 13 kD. Its origin and function are unknown. Gene structure and gene-locus are described by Le Moullec *et al.* [7]. PCT is believed to be secreted by peripheral monocytes, liver and other tissues in response to cytokines such as tumor necrosis factor, interleukin 6, granulocyte colony stimulating factor and endotoxins from bacterial wall [8, 9]. PCT usually does not increase with viral infections. Because interferon γ that is secreted due to viral particles prevents PCT production. Serum PCT levels below 0.5 g/l is usually accepted as normal. PCT has come to use in solid organ transplants recently [10, 11]. The purpose of this study is to evaluate correlation between synchronous serum PCT and CRP levels at the beginning and during treatment of kidney transplant patients hospitalized for infections.

## Methods

There were 121 patients (108 living kidney donor, 13 cadaveric) who had kidney transplant in our center, University of Health Sciences, Gazi Yasargil Training and Research Hospital, Diyarbakir, Turkey between September 2012 and February 2017. Patients with a diagnosis of infection or rejection were included in the study. The study is retrospective and compatible with the Helsinki declaration in 2008. All patients gave informed consent. Synchronous serum CRP and PCT levels were measured before and/or during treatment of hospitalized patients for infection. A total of simultaneous 106 serum samples were taken. Correlation between 97 serum CRP and PCT levels were evaluated. These cases were hospitalized for post-transplant infections. Nine cases were rejection, cytomegalovirus (CMV) and BK virus (BKV). Three subgroups of serum CRP levels, <50 mg/l, 50-100mg/l and>100mg/l, were correlated with serum PCT levels. Demographic data, immunosuppressive protocols, presence of rejection, loss of graft and patient, postoperative infections, BK nephropathy (BKN), CMV infection were all evaluated retrospectively (Table 1-3).

**Table 1.** Descriptive data of the kidney transplant cases.

| **Number of patients** | **n=121** |
|---|---|
| **Gender M/F** | |
| Recipient | 68/53 |
| Donor | 47/71 |
| **Age (years)** | |
| Recipient | 34.9 (12-68) |
| Donor | 42.3 (23-72) |
| Follow up period (months) | 26 [6-46] |
| **Donor type** | |
| Live | 108 (89.2%) |
| Cadaveric | 13 (10.7) |
| Preemptive | 43 (35.5%) |
| **Operation of donor** | |
| Open nephrectomy | 79 |
| Laparascopic nephrectomy | 32 |
| **Induction** | |
| None | 15 (13%) |
| ATG | 65 (53.7%) |
| Basiliximab | 41 (33.8%) |

ATG=anti-thymocyte globulin, M=male, F=female

**Table 2.** Clinical results of the kidney transplant patients.

| **Patient number** | **n=115** |
|---|---|
| **Rejection** | |
| Humoral | 2 (1.6%) |
| Cellular | 4 (3.2%) |
| Humoral+Cellular | 1 (0.8%) |
| **Graft loss** | |
| CAN | 1 (0.8%) |
| BKN | 1 (0.8%) |
| RAP | 1 (0.8%) |
| Rejection | 1 (0.8%) |
| **CMV** | |
| Infection | 2 (1.6%) |
| Disease | 0 |
| **BKV** | 4 (3.2%) |
| **BKN** | 1 (0.8%) |

CAN= chronic allograft nephropathy, BKN= BK nephropathy, RAP=renal artery pseudoaneurysm, CMV= serum C-reactive protein; BKV=BK viremia

*Immunosuppression and Prophylaxis*

**Table 3.** Post-transplant hospitalization rates due to infection.

| Cause of hospitalization | Number of hospitalization (n) | Number of CRP and PCT samples (n) |
|---|---|---|
| Urinary tract infection | 91 | 35 |
| Pneumonia | 11 | 4 |
| Gastroenteritis | 32 | 11 |
| Herpes Zoster | 2 | 0 |
| Abscess of breast | 1 | 0 |
| Tuberculosis | 2 | 2 |
| Brucellosis | 1 | 1 |
| Invasive aspergillosis | 1 | 1 |

CRP= serum C-reactive protein; PCT= procalcitonin

Basiliximab (20 mg at days 0 and 4 of operation) or anti-thymocyte globulin (ATG; for high risk patients, 3 mg/kg during operation and 1.5 mg/kg at postoperative days 1 and 2) were used as induction treatment. Methylprednisolone 1000 mg was given intraoperatively. Methylprednisolone dose was decreased by half everyday and 20 mg oral prednisolone was started on the 6th postoperative day for daily use. Oral prednisolone dosage was reduced gradually to reach 5 mg a day at the first year after transplantation. Calcineurin inhibitors (tacrolimus or cyclosporin) and mycophenolate mofetil (MMF; 2 g a day in two divided doses) or mycophenolate sodium (MMF; 1440 mg a day, in two divided doses) were used as maintenance immunosuppression. MMF was used as 600 mg/m$^2$ in two divided doses in children. We considered both mycophenolate mofetil and mycophenolate sodium in doses described above as the same drugs in our study. Everolimus was used in only one case (plasma level of the drug was targeted as 8-10 mg/dl). Trimethoprim/sulfamethoxazole and valganciclovir (450 mg a day) was prescribed for pneumocytis jirovecii and CMV prophylaxis for 6 months after the transplantation. Acute rejection was diagnosed by kidney biopsy. Acute cellular rejection was treated with intravenous pulse methylprednisolone or ATG depending on the severity of the rejection.

*Determination of PCT and C-Reactive Protein*

A total of 106 serum samples were measured for CRP and PCT levels simultaneously. CRP and PCT measurements were performed by immuno turbidimetric method on Cobas c702 (Roche Diagnostics, Germany) instrument and immunoassay method on Cobas c702 (Roche Diagnostics, Germany) instrument, respectively. Interassay coefficients of variation values were below 3% for both tests.

*Diagnostic Criteria and Follow-Up*

All patients were followed-up closely for renal functions, clinical infection, BKV and CMV after kidney transplantation. Clinical infection was diagnosed on the basis of positive culture or serology combined with the use of appropriate antibiotic treatment or in the absence of microbiological confirmation, on the basis of fever (above 38°C) combined with the use of appropriate treatment. Urinary tract infection was established by clinical symptoms: fever and chills, flank pain, and irritative voiding symptoms (e.g., urgency, frequency, and dysuria), nausea or vomiting, inflammatory status, and positive urine culture [12, 13]. Enterocolitis was established through diarrheal syndrome (symptoms: fever, abdominal swelling, nausea, vomiting, diarrhea, rectal bleeding, sluggishness) with inflammatory status and/or positive culture [14]. Rejection was diagnosed by biopsy. First BKV tests were done on 1st postoperative month. All transplanted patients were tested for BKV from their serum by polymerase chain reaction (PCR) monthly in the first year after transplantation. Cases with >500 copies/ml by two or more consecutive measurements were accepted as having viremia. Tests for CMV were performed every 3 months after 6th postoperative month. Viremia detection was accepted as CMV infection, presence of symptoms were considered as CMV disease.

*Statistical Analysis*

Statistical analyses were performed using the SPSS software version 15. The variables were investigated using visual (histogram, probability plots) and analytical methods (Kolmogorov-Simirnov/ Shapiro-Wilk'stest) to determine whether or not they are normally distributed. While investigating the associations between non-normally distributed and/or ordinal variables, the correlation coefficients and their significance were calculated using the Spearman test. A 5% type-I error level was used to infer statistical significance.

## Results

One hundred and twenty-one patients (108 living kidney donor, 13 cadaveric) who had kidney transplant in our center betweenSeptember 2012 and February 2017 were evaluated, retrospectively. Average age of recipients and living donors were 34.9 (12-68) and 42.3 (23-72), respectively. Ten cases were at pediatric age. Male/female ratios of recipients and living donors were 68/53 and 47/71, respectively. Median and interquartile range follow-up time were 26 [6-46] months. Average duration of hospitalization was 8 (5-32) days. Postoperative discharge median and interquartile range creatinine was 1.04 [0.55-1.48] mg/dl. The most frequent reason for hospitalization was urinary tract infection. One case who used intermittant clean urinary catheterization was hospitalized 24 times for recurrent urinary tract infection due to neurogenic bladder. Simultaneous serum CRP and PCT levels were measured before and/or during treatment of hospitalized patients for infection. So total synchronous serum samples for CRP and PCT was 97. Median and interquartile ranges of CRP and PCT serum levels were 40 mg/l [24.7-64.9] and 0.19 ng/ml [0.1-0.61], respectively. Simultaneous CRP and PCT levels were measured in 3 patients with BKV and 2 patients with CMV infection. Simultaneous CRP and PCT levels were measured four out of seven cases with a diagnosis of rejection. Serum CRP levels of hospitalized renal transplant patients due to infection correlated with serum PCT level (r=0.490, $p$<0,001).When serum CRP levels were grouped as <50 mg/l, 50-100 mg/l and >100 mg/l, correlations with serum PCT levels were as r=0.461 ($p$<0.001), r=-0.52 ($p$=0.860) and r=0.488 ($p$=0.153), respectively (Table 4). Four cases with biopsy proven acute rejection had normal serum PCT levels. Serum levels of PCT and CRP did not increase in CMV infection and BKV viremia patients. CMV disease was not observed in any patient. One case had CMV infection, BKV nephropathy and invasive aspergillosis at the same time. The patient had graft loss and CRP and PCT level of the patient was as high as 250 mg/l and 47 g/l respectively. Four cases of graft loss were observed. Chronic allograft rejection (from cadaveric donor), renal artery pseudoaneurysm (from cadaveric donor) and humoral rejection were the causes of graft loss.

## Discussion

Synchronous serum CRP and PCT levels at the beginning or during any time of hospitalization for post-transplant infection were evaluated retrospectively in our study. Retrospective nature of the study and insufficient number of PCT measurements due to nonroutine use of PCT comparing to CRP measurements made sensitivity, specifity and cut-off value analysis impossible. But CRP and PCT levels showed a significant positive correlation (r=0.490, $p$<0.001) when all cases were considered. Cooper *et al.* [15] did not find a significant difference between serum PCT, serum amyloid protein and CRP levels in 43 heart, 34 lung and 33 liver transplanted patients. Serum PCT levels do not usually increase in viral infections [9]. In our study 2 CMV positive and 3 BKV patients were found. These 5 cases had normal serum PCT and CRP levels. But a patient with BKV, CMV infection and invasive aspergillosis had high serum PCT and CRP levels. Roques *et al.* [16] did not observe high PCT levels despite increased CRP levels in leukemia patients with invasive aspergillosis. But Cooper *et al.* [15] found that serum CRP, serum amyloid protein and PCT levels increased significantly in solid-organ transplant patients with fungal infections. Sometimes it is difficult to differentiate acute allograft rejection and infection clinically. In a retrospective study, Hammer *et al.* [17] observed that serum PCT levels did not increase in rejection cases of heart and lung transplants. In a prospective study by Eberhard *et al.* [18], procalcitonin values for patients with rejection were not significantly different from those of the healthy

**Table 4.** Correlation of serum C-reactive protein (CRP) and procalcitonin (PCT) levels.

| CRP level | Number of samples | r | *p* |
|---|---|---|---|
| <50 mg/L | 52 | 0.461 | <0.001 |
| 50-100 mg/L | 23 | -0.52 | 0.860 |
| >100 mg/L | 22 | 0.488 | 0.153 |
| All samples | 97 | 0.490 | <0.001 |

transplant recipients. During postoperative follow up, 7 cases had rejection. Four of the cases had PCT and CRP levels measured and PCT levels were found to be normal and 3 of these cases had higher serum CRP levels.

*The Limitations of the Study*

Our study was retrospective, serum PCT measurements did not routinely measured as serum CRP levels. So that only synchronous serum PCT and CRP levels were used for correlation analysis. Synchronous measurements were done any time during treatment, so there were no standardized or planned time for laboratory testing of these parameters. We only made correlation analysis, design of the study was not suitable to determine the usefulness of PCT measurements for the response of the therapy. In ability to determine reliability and specifity of PCT levels and retrospective nature of the study were the limiting factors of the study.

## Conclusions

In our study, serum CRP and PCT levels were significantly correlated; but when CRP levels were grouped, CRP >100 mg/l and 50-100 mg/l subgroups were not significantly correlated. Stability of PCT levels in viral infections and rejections might be an advantage for the follow-up of solid-organ transplants. We need prospective trials of PCT measurements for the evaluation of post-transplant infections.

*Conflict of interest*

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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