Diagnostic value of serum procalcitonin for diagnosis of bacterial infection in patients with chronic kidney disease under hemodialysis

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Abstract

Introduction: Bacterial infections are common causes of mortality and morbidity among chronic kidney disease (CKD) patients under hemodialysis.

Objectives: In this study the diagnostic value of serum procalcitonin for diagnosis of bacterial infections in patients with CKD under hemodialysis was assessed.

Patients and Methods: In this cross-sectional comparative investigation, 47 patients with CKD under hemodialysis were enrolled to the study. We studied the relationship of serum procalcitonin (PTC) and C-reactive protein (CRP) levels (before and after dialysis) with “positive bacterial culture” and “systemic inflammatory response syndrome (SIRS)” results. Sensitivity and specificity were determined by ROC test.

Results: Serum PTC before and after dialysis as well as the CRP before dialysis had no significant association with positive bacterial culture (P=0.492, P=0.1 and P=0.268 respectively), however after-dialysis CRP had a significant association with positive bacterial culture (P=0.032).

Conclusion: According to the obtained results, it may be concluded that the diagnostic value of serum PTC for diagnosis of positive culture bacterial infections in hemodialysis patients is not satisfactory since the serum CRP level especially after dialysis is more useful.

Key point

In a study on 47 patients with CKD under hemodialysis, we found that serum C-reactive protein had better applicability versus procalcitonin and the increase in C-reactive protein had a better predictive value.

Introduction

Chronic kidney disease (CKD) is seen in ten percent of Americans adults (1,2). Hemodialysis is the main dialysis method with 23% mortality rate, since among them infection is the main cause of death (3). The relative risk of mortality in hospitalized hemodialysis patients with bacteremia and septicemia, in first six months of starting the dialysis is seven times more versus non-hospitalized subjects (4), with even higher hospital admission for septicemia in hemodialysis versus peritoneal dialysis cases (5). End-stage renal disease cases are susceptible to systemic bacteremia with worse prognosis and more complications (6-8). Patients under hemodialysis are susceptible to catheter and blood infections (9). The symptoms of infection in these patients are usually mild and non-specific since, the usual laboratory markers are affected by uremic status such as leukocyte count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and interleukins including interleukin 6 (IL-6), IL-1b, and also TNF-alpha (10,11). CRP is a sensitive non-specific index for infection (12), since ESR and leukocyte (WBC) count, are not useful to differentiate infectious and non-infectious etiologies (13). Additionally, microbiological cultures may be slow and non-sensitive (14,15). Procalcitonin (PCT) is currently introduced with half-life of 25-30 hours showing infection in serum levels over 0.5 ng/mL (16). It increased in patients with bacterial and fungal infections that have normal renal function (17). Despite other markers, it is not increased in viral and local infections and also non-infectious inflammations (18,19). PCT may be removed by renal pathway due...
to small molecular size (20). However, it is not the main metabolic route (21); it may be increased in CKD cases (22,23). Regarding the interaction between PCT level with vitamin D, aluminum toxicity, beta 2 microglobulin and secondary hyperparathyroidism, these parameters should be considered in metabolic assessment (24). High rate of bacterial infections in CKD cases may make difficult differentiation between non-infectious inflammations (25), antibiotic resistance, and dysregulation of cytokine expression in cases under empirical antibiotic therapy (26-29). This condition led to a need for further accurate methods in hemodialysis patients (30,31).

**Objectives**

In this study the diagnostic value of serum PTC for diagnosis of bacterial infections in patients with CKD under hemodialysis was assessed.

**Patients and Methods**

**Study design**

In this cross-sectional comparative study, 47 patients with CKD under high flux hemodialysis three times weekly (each time 4 hours) in hemodialysis sections of two hospitals in Tabriz, Iran in 2018 were enrolled. Inclusion criteria were age older than 18 years, CKD, suspicion of bacterial infections (according to weakness, fever, chills after dialysis in last two weeks, painful or inflamed fistula, discharge, redness and warmth at catheter site, upper/lower respiratory tract infections, upper/lower urinary tract infection, skin and soft tissue infection, diabetic ulcer, peritonitis, intra-abdominal wound, other infection foci, radiological/ultrasound evidences for infectious focus, and minimally two systemic inflammatory response syndrome (SIRS) criteria (32). Exclusion criteria were rheumatologic diseases/malignancy, current surgery, burn in last 4 weeks, antibiotic therapy longer than 48 hours and rheumatologic diseases/malignancy, current surgery, burn in last 4 weeks, antibiotic therapy longer than 48 hours and rheumatologic diseases/malignancy, current surgery, burn in last 4 weeks, antibiotic therapy longer than 48 hours and rheumatologic diseases/malignancy, current surgery, burn in last 4 weeks, antibiotic therapy longer than 48 hours and rheumatologic diseases/malignancy, current surgery, burn in last 4 weeks, antibiotic therapy longer than 48 hours.

The culture was positive in 20 cases (42.6% including 9 cases of blood culture, 10 patients with urine culture, 1 catheter culture, 1 wound culture, 1 ascites culture, and 1 case of wound culture). Gram staining was positive in 77.8%. Urine culture was positive in 21.3% that was gram-positive in 10%. The microbial germs were pseudomonas, *E. coli*, Klebsiella, enterococci, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and streptococci in 1, 10, 4, 3, 3, 4, and 1 case. The results of cell count and biochemical tests are shown in Table 1.

As shown in Table 2, the serum levels of PCT and CRP had no significant difference before and after dialysis (*P* > 0.05). The laboratory measurements in variables are shown in Table 3 while among them only hemoglobin and ionized calcium were significantly different.

**Data analysis according to culture results**

The PTC level before and after dialysis was not related to infection (*P* = 0.492 and 0.1). Additionally no significant association was found for CRP and infection before dialysis. However, post-dialysis CRP was significantly related to infection (*P* = 0.032) with AUC of 0.684 and sensitivity and specificity of 80% and 70.4% with cut-off 66. AUC for WBC and PMN was 0.699% (Figure 1).

As shown in Table 4, PCT before and after dialysis and CRP before dialysis were not related to culture results (*P* > 0.05); serum CRP after dialysis had a significant difference between culture positive and culture negative...
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Patients ($P = 0.032$). Serum PCT and CRP were not differed according to mortality in patients ($P > 0.05$). Serum PCT before and after dialysis and CRP before dialysis were not related to ICU admission ($P > 0.05$); however, after dialysis, CRP levels were significantly higher in ICU admitted cases ($P = 0.044$).

**Data analysis according to SIRS results**

As shown in Figure 2, the WBC, PMN, lymphocyte and platelet were significantly differed between positive and negative SIRS groups ($P < 0.05$) with AUC of 100%, 97.5%, 100%, and 95%, respectively. Moreover, as demonstrated in Figure 3 and Table 5, the initial PCT ($P = 0.011$) and final PCT ($P = 0.003$) and the final CRP ($P = 0.004$) had significant difference according to SIRS with AUC of 72.5%, 76.4%, and 75.9%, respectively.

**Discussion**

In this study, the diagnostic value of serum PTC for diagnosis of bacterial infections in patients with CKD under hemodialysis was assessed. In this study, the base for comparison was conducted once by culture and once by SIRS. For culture comparison, the PCT before dialysis had AUC of 56% and after dialysis, it was 65%. It was 60% and 68% for CRP before and after dialysis, respectively.

El-Sayed et al (30) reported that PT had sensitivity and specificity of 80% and 35% with cut-off point of 0.5. Similarly, they reported that PCT had no good sensitivity and specificity like our study when comparing by culture. Lee et al (28) reported, a significantly higher serum PCT in infection cases. They considered cut-off point of 0.75

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**Table 1.** Cell count and biochemical tests in patients

| Factor               | Mean     | Median   | Standard Deviation | Minimum | Maximum |
|----------------------|----------|----------|--------------------|---------|---------|
| WBC (count/mL)       | 13544.04 | 10900.00 | 6697.19            | 4500.00 | 36200.00 |
| Neutrophil (%)       | 80.12    | 83.65    | 13.77              | 13.20   | 96.30   |
| Lymphocyte (%)       | 14.20    | 10.90    | 11.03              | 2.70    | 85.80   |
| Hemoglobin (g/dL)    | 9.82     | 9.50     | 1.62               | 6.00    | 13.40   |
| MCV (fl)             | 88.03    | 87.70    | 7.52               | 62.00   | 106.00  |
| Platelet (count/mL)  | 225000   | 2040     | 91732              | 65000   | 436000  |
| Albumin (g/dl)       | 3.12     | 3.30     | 0.72               | 1.30    | 4.10    |
| Total calcium (mg/dL)| 8.19     | 8.20     | 1.12               | 4.80    | 11.60   |
| Ionized calcium (mg/dL)| 1.02 | 1.01     | 0.15               | 0.72    | 1.58    |
| Phosphorous (mg/dL)  | 5.27     | 4.60     | 2.36               | 1.40    | 12.30   |

**Table 2.** Renal and inflammatory markers before and after dialysis

| Factor               | Mean     | Median   | Standard Deviation | Minimum | Maximum |
|----------------------|----------|----------|--------------------|---------|---------|
| Urea-before (mg/dL)  | 138.95   | 120.00   | 64.55              | 48.00   | 325.00  |
| Urea-after (mg/dL)   | 90.00    | 87.70    | 48.30              | 62.00   | 267.00  |
| Cr-before (mg/dL)    | 6.77     | 5.87     | 3.19               | 3.00    | 16.13   |
| Cr-after (mg/dL)     | 9.46     | 4.58     | 2.21               | 1.83    | 11.80   |
| PCT-before (ng/mL)   | 2.72     | 1.18     | 4.52               | .05     | 24.75   |
| PCT-after (ng/mL)    | 3.48     | 1.25     | 6.91               | .04     | 33.00   |
| CRP-before (mg/L)    | 73.37    | 67.00    | 35.27              | 2.20    | 136.30  |
| CRP-after (mg/L)     | 74.95    | 67.00    | 36.49              | 2.80    | 148.00  |

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**Figure 1.** ROC curve for after-dialysis CRP.
for PCT leading to sensitivity and specificity of 76% and 80%. However, these findings were lower in our study according to culture that was improved according to SIRS. Accordingly, Herget-Rosenthal et al (30) reported sensitivity and specificity of 89 and 81 percent for cut-off point of 0.5 for PCT that was higher than CRP amounts of sensitivity and specificity in their study; however in our study CRP had better sensitivity and specificity in comparison to PCT, according to culture results.

Similar to our study, Steinbach et al (33) reported an increase in PCT and CRP levels with lower diagnostic value for PCT against CRP. Duamea et al (34) reported bacterial infection in 58 out of 82 patients showing with higher PCT in infection cases leading to sensitivity and specificity of 93 and 79 percent with cut off 0.5. In our study, the PCT had not good results in comparison to culture results, but better results were seen when compared by SIRS. In the study by Fadel et al (35) among 102 patients of CKD with 34 culture positive cases showed sensitivity and specificity of 94% and 88% for PCT with a cut of point of 0.5, respectively. These results were low in our study compared to the culture results, but improved by SIRS.

### Conclusion
In our investigation, PCT has not acceptable diagnostic value in detection of bacterial infection in CKD patients on hemodialysis. Among the possible causes for these

| Table 3. Laboratory markers in cases with positive and negative culture |
|-----------------------------------------------|
| Variable          | Culture | Mean       | Standard Deviation |
| Age (y)           | Positive | 68.1500    | 17.10712          |
|                   | Negative | 57.8148    | 16.82955          |
| WBC (count/mL)    | Positive | 15400.0000 | 5906.90942        |
|                   | Negative | 12169.2593 | 7017.42169        |
| PMN%              | Positive | 84.1600    | 10.12492          |
|                   | Negative | 77.0154    | 15.50478          |
| Lymphocyte%       | Positive | 10.2650    | 7.59226           |
|                   | Negative | 17.2415    | 15.49021          |
| Hb (g/dl)         | Positive | 10.1650    | 1.58056           |
|                   | Negative | 9.4077     | 1.55356           |
| MCV (fl)          | Positive | 86.9842    | 8.27864           |
|                   | Negative | 88.8000    | 6.98478           |
| PLT (count/mL)    | Positive | 23150.0000 | 100021.9512       |
|                   | Negative | 218480.0000| 86066.89259       |
| Urea before (mg/dl)| Positive | 143.2000   | 67.58823          |
|                   | Negative | 135.8148   | 63.33005          |
| Urea after (mg/dl)| Positive | 97.9500    | 47.16765          |
|                   | Negative | 91.5556    | 49.84695          |
| Cr before (mg/dl) | Positive | 6.7737     | 3.09715           |
|                   | Negative | 6.7733     | 3.13262           |
| Cr-after (mg/dl)  | Positive | 5.0184     | 2.39039           |
|                   | Negative | 4.9237     | 2.13659           |
| Alb (g/dl)        | Positive | 2.7857     | .77552            |
|                   | Negative | 3.3250     | .64544            |
| Ca total (mg/dl)  | Positive | 8.4000     | 1.06829           |
|                   | Negative | 8.0667     | 1.15392           |
| Ionized calcium (mg/dl) | Positive | 1.0873 | .19285          |
|                   | Negative | .9870      | .11138            |
| Phosphorus (mg/dl)| Positive | 5.4500     | 2.55671           |
|                   | Negative | 5.1556     | 2.26806           |
| BMI (kg/m^2)      | Positive | 26.5466    | 5.58320           |
|                   | Negative | 26.2575    | 4.71329           |
| GFR (mL/min/1.73 m^2) | Positive | 10.9168 | 4.61579          |
|                   | Negative | 13.0241    | 5.23973           |

| Table 4. Serum PCT and CRP in positive and negative cultures |
|-----------------------------------------------|
| Variable          | Culture | Mean       | Standard Deviation |
| PCT before (ng/mL)| Positive | 2.38       | 6.13              |
|                   | Negative | 2.22       | 2.81              |
| PCT after (ng/mL) | Positive | 4.41       | 8.08              |
|                   | Negative | 2.77       | 5.95              |
| CRP before (mg/L) | Positive | 81.58      | 38.03             |
|                   | Negative | 67.30      | 32.47             |
| CRP after (mg/L)  | Positive | 87.11      | 32.93             |
|                   | Negative | 65.95      | 36.95             |

| Table 5. PCT and CRP cut-off, sensitivity, and specificity according to SIRS |
|-----------------------------------------------|
| Variable          | Cut-off | Sensitivity | Specificity |
| PCT before (ng/mL)| 1.22    | 73.7%       | 72%         |
| PCT after (ng/mL) | 1.29    | 73.7%       | 72%         |
| CRP before (mg/L)| 60      | 66%         | 63.2%       |
| CRP after (mg/L)  | 61.1    | 60%         | 73.2%       |
differences of results between our and previous studies, small sample size, lack of matching for ionized calcium (regarding the effect on calcitonin), and subdivision according to culture results (as gold standard of infection diagnosis), may be mentioned.

In the second phase of this study, our findings are also improved when we used SIRS results for evaluation of our data instead of culture results. It means that when we used the SIRS criteria as a base for comparison, better sensitivity and specificity were obtained with more similarity to other studies. This comparison of findings according to culture and SIRS results is distinguishing point of our study. Since our study was cross-sectional, the matching ability was decreased between groups. However, two groups were matched in majority of cases. The important causes of differed results between culture and SIRS were slow-growth of some organisms, simultaneous fungal or parasitic infections, human errors, non-reliable drug history especially for self-prescribed use of antibiotics leading to high-effect in PCT versus CRP when used in current 48 hours. Among other possible causes, sampling techniques and processing methods beside the pathogen microorganisms may be also considered when culturing the samples. These are effective on culture but the SIRS factors are less affected. In addition, it should be considered that this study was first time in Iran among stable hemodialysis patients. In addition, as an important point, we assessed both PCT and CRP markers while both culture and SIRS results were applied for comparison. We found that CRP had better applicability versus PCT and the increase in CRP had a better predictive value. However, the presence of some confounding factors needs to be considered in further studies.

Limitation of the study
The main limitation of our study is the low number of patients.

Authors’ contribution
Design of the study and selecting the patients; RA, HN and NMN. Gathering the patients and data entering; NMN and HB. Data analysis; MA and NMN. Primary draft by RA and NMN. Final edition by RA, NMN and HB. All authors read and signed the paper manuscript.

Conflicts of interest
The authors declared that there was no conflict of interest.

Ethical considerations
Ethical issues including plagiarism, double publication, and redundancy have been completely observed by the authors.

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