Original research

# Procalcitonin as a biomarker for acute kidney injury in patients with sepsis and septic shock

*Procalcitonina como biomarcador de daño renal agudo en pacientes con sepsis y choque séptico*

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**Abstract**

**Introduction:** Up to 60% of patients with sepsis develop acute kidney injury. Procalcitonin indicates the presence of sepsis and could predict acute kidney injury.

**Objectives:** To determine the values of procalcitonin as a predictive biomarker of acute renal injury and its complications in the sepsis spectrum.

**Methods:** Cross-sectional study. Procalcitonin was measured during the 24 hours of hospitalization. We determined the area under the curve, standard error, sensitivity and specificity of procalcitonin values related to acute renal injury. **Results:** A total of 72 patients aged 51 years (range 18-79); 35 (48.6%) were male, 44 (61.1%) presented sepsis, 14 (19.4%) had septic shock, 11 (15.3%) severe sepsis and 3 (4.2%) sepsis-induced hypotension. We found an elevation of procalcitonin (>0.5 ng / mL) in 54 (75%) patients; presented acute renal injury 42 (58.3%) cases; KDIGO 1 in 19 (45.2%), KDIGO 2 in 12 (28.6%) and KDIGO 3 in 11 (26.2%) patients; of them 37 (88.1%) had procalcitonin >0.5 ng/mL (OR 5.65, 95% CI 1.73-18.42, $p$ <0.01). the area under the curve 0.75 (95% CI 0.63 - 0.86 $p$ <0.0001); the value of procalcitonin of 2,565 ng/mL had the highest validity predicting acute renal injury, with sensitivity of 61.9%, specificity of 80%, a positive predictive value of 44.52%, negative predictive value of 56.18%, LR + of 0.80 and an LR - 0.77

**Conclusion:** In the sepsis spectrum, the level of procalcitonin >2,565 ng / mL at hospital admission predicts acute kidney injury.

**Key words:** acute renal injury, acute renal failure, biomarker; procalcitonin; sepsis, prediction.

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**Resumen**

**Introducción:** hasta el 60 % de los pacientes con sepsis desarrollan daño renal agudo. La procalcitonina indica la presencia de sepsis y puede predecir un daño renal agudo.

**Objetivos:** determinar los valores de procalcitonina como biomarcador predictor de daño renal agudo y sus complicaciones en el espectro de sepsis.

**Métodos:** estudio transversal. Se midió procalcitonina durante las 24 horas de hospitalización. Se determinó el área bajo la curva, el error estándar, la sensibilidad y especificidad de los valores de procalcitonina relacionado con daño renal agudo.

**Resultados:** un total de 72 pacientes con edad de 51 años (rango 18 –79); 35 (48,6 %) casos eran hombres, 44 (61,1 %) presentaron sepsis, 14 (19,4 %) choque séptico, 11 (15,3 %) sepsis severa y 3 (4,2 %) hipotensión inducida por sepsis. Encontramos una elevación de procalcitonina (>0,5 ng/mL) en 54 (75 %) pacientes; presentaron daño renal agudo 42 (58,3 %) casos; estadio KDIGO 1 en 19 (45,2 %), KDIGO 2 en 12 (28,6 %) y KDIGO 3 en 11 (26,2 %) pacientes; de ellos 37 (88,1 %) presentaron procalcitonina >0,5 ng/mL (OR 5,65, IC 95 % 1,73 – 18,42; p<0,01). El área debajo de la curva 0,75 (IC 95 % 0,63 – 0,86 $p$ <0,0001); el valor de procalcitonina de 2,565 ng/mL tuvo la mayor validez prediciendo daño renal agudo, con sensibilidad de 61,9 %, especificidad de 80%, un valor predictivo positivo de 44,52 %, valor predictivo negativo de 56,18 %, LR+ de 0.80 y un LR- de 0.77

**Conclusión:** en el espectro de sepsis, el nivel de procalcitonina >2,565 ng/mL al ingreso hospitalario predice daño renal agudo.

**Palabras clave**: lesión renal aguda; marcador, insuficiencia renal aguda, injuria renal aguda, procalcitonina; sepsis, predicción.

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## Introduction

Up to 15% of hospitalized patients develop acute kidney injury (AKI) and its incidence increases up to 40-60% in patients admitted to the intensive care unit (ICU).[1] Half of the cases are related to sepsis;[2] and the days of hospital stay, the mortality rate and the use of resources are increased.[3-6] The pathophysiology of sepsis-induced AKI includes: systemic hypotension,[7] presence of shock[8] and episodes of bacteremia by Gram-negative agents, which condition nephrotoxicity.[9] Despite recent advances in the understanding of the pathophysiology of AKI, the mortality rate remains high, mainly due to the lack of effective therapeutic options and timely detection. For this reason, it is imperative to find biomarkers that could identify the patients at risk of developing AKI, thus allowing timely intervention and improving their prognosis.[10]

Procalcitonin (PCT), is a peptide of 116 amino acids that can increase in different order of magnitude in sepsis. PCT levels > 1 ng/mL are associated with bacterial infections with sepsis or septic shock,[11,12] and they do not accumulate in the presence of renal failure,[13] since their elimination is accomplished by other routes.[14-17]

In the present study we investigated the performance of PCT as a predictor of AKI and its complications in patients with sepsis.

## Methods

Prospective, observational, cross-sectional study with definite temporality, from January to December, 2014. The objective was to determine the usefulness of PCT as a predictive biomarker of the development of AKI in patients with sepsis.

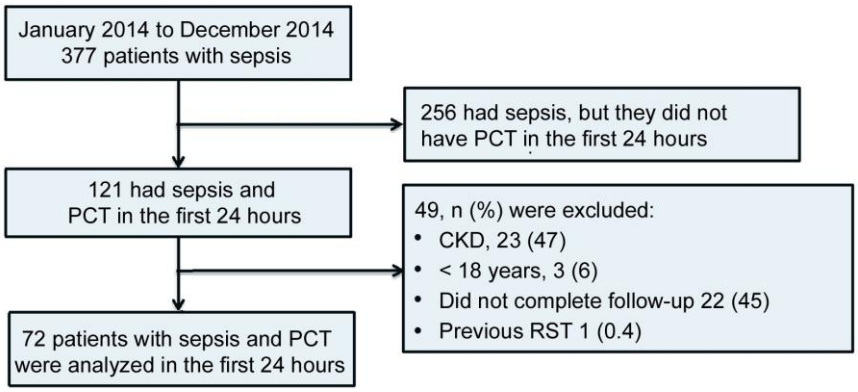
The diagnosis of sepsis was established according to the Surviving Sepsis Campaign 2012[18] and that of AKI was defined by the serum creatinine value according to the KDIGO 2012.[19] The serum PCT was determined within the first 24 hours of hospitalization, using the immunofluorescence method (B•R•A•H•M•S PCT™ sensitive KRYPTOR™, Thermo Fisher Scientific, Waltham, MA). Serum creatinine was taken every 24 hours during the hospital stay.

Informed consent letters were obtained and the study was approved by the ethics and research committee of the *Hospital Civil de Guadalajara Fray Antonio Alcalde*. Patients diagnosed with sepsis at hospital admission and who had a PCT measurement within the first 24 hours were included. Patients with previous CKD (baseline serum creatinine > 1.5 mg/dL), age <18 years, patients who had not completed the follow-up and those with previous dialysis were excluded.

A descriptive analysis was made. Comparisons between groups were made using the Chi$^2$ and Student's-T tests, as appropriate, as well as Pearson's correlation and a binary logistic regression, including the relevant variables. A receiver operating characteristic curve (ROC) was determined for the serum value of PCT at the moment of hospital admission, as well as its area under the curve (AUC), the standard error of AUC and the sensitivity and specificity of the PCT values included in the curve. The cut-off point of PCT for predicting AKI was obtained from the ROC curve, according to the principle of maximizing the Youden's Index (sensitivity + specificity - 1). The positive predictive value (PPV), negative predictive value (NPV), the positive (LR+) and negative (LR-) likelihood ratios were also calculated with the electronic statistical program SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

## Results

From January to December 2014, 377 patients with sepsis were admitted; 256 were excluded for not having PCT in the first 24 hours of admission and 49 because they met exclusion criteria, achieving a final recruitment of 72 patients (Figure 1). Thirty five (48.6 %) cases were individuals of the male gender, with an average age of 51 years (range of 18-79). The sites of infection (suspected or confirmed) were the lungs in 36 (50.0 %) cases, 15 (20.8 %) in the urinary tract, 8 (11.1 %) in the gastrointestinal tract, 4 (5.6 %) in the central nervous




ERC= enfermedad renal crónica, PCT= Procalcitonina, TSR= terapia de soporte renal.

**Figure 1.** Flowchart.

system, 2 (2.8 %) in soft tissues and 1 (1.4 %) of cardiac origin; two or more sites of infection were detected in 6 (8.3 %) cases. The distribution of the sepsis spectrum was 44 (61.1%) cases with sepsis, 11 (15.3%) with severe sepsis, 14 (19.4%) with septic shock and 3 (4.2%) with sepsis-induced hypotension (Table 1). The PCT value was positive (> 0.5 ng/mL), in 54 (75 %) of cases. Forty two (58.3 %) patients developed AKI; 19 (26.4 %) stage 1, 12 (16.7 %) stage 2 and 11 (15.3 %) stage 3. The PCT levels in the group with AKI were significantly higher than in the group without AKI (p = 0.004) (Table 2).

AKI occurred in 18 (41 %) patients with sepsis; 3 (100 %) with sepsis-induced hypotension, 13 (93 %) with septic shock and 8 (73 %) with severe sepsis. Thirty-seven cases (88,1 %) presented a PCT value > 0.5 ng/mL). The PCT ranges were distributed as follows: < 0.5 ng/mL) in 5 (11.9%), > 0.5 - 2 ng/mL in 8 (21.6 %), 2.1 - 10 ng/mL in 13 (35.1 %) and PCT>10 ng/mL in 14 (37.8 %).

In the binary logistic regression analysis adjusted for age, gender, subtype of sepsis, site of infection, level of leukocytes, serum creatinine and the presence of positive PCT at hospital admission, it was observed a direct relationship between the creatinine level at admission (OR 37.551, 95 % CI 3.175 – 444.171, *p* = 0.004,) the diagnosis of septic shock (OR 16.593, 95% CI 1.753 – 157.090, *p* = 0.014,) and positive PCT on admission (OR 5.994, 95 % CI 1.505 – 23.873, *p* = 0.011), with the

**Table 1.** Demographic and clinical characteristics.

| | n= 72 |
|---|---|
| Male gender | 35 (48,6) |
| Age in years (range) | 50,9 (18-79) |
| 18-30 years (%) | 12 (16,7) |
| 31-64 years, (%) | 40 (55,6) |
| =65 years (%) | 20 (27,8) |
| **Site of infection (%)** | |
| Lung | 36 (50,0) |
| Urinary | 15 (20,8) |
| Gastrointestinal | 8 (11,1) |
| Multi-organ | 6 (8,3) |
| Nervous system | 4 (5,6) |
| Soft tissues | 2 (2,8) |
| Heart | 1 (1,4) |
| **Distribution of diagnoses of sepsis (%)** | |
| Sepsis | 44 (61,1) |
| Severe sepsis | 11 (15,3) |
| Sepsis-induced hypotension | 3 (4,2) |
| Septic shock | 14 (19,4) |
| **PCT value on admission and its ranges. n (%)** | |
| PCT (negative) < 0.5 | 18 (25) |
| PCT (positive) = 0.5 | 54 (75) |
| PCT = 0.5 - 2 | 18 (25) |
| PCT 2.1 - 10 | 20 (27,8) |
| PCT > 10 | 16 (22,2) |

PCT = Procalcitonin

**Table 2.** Absolute levels of PCT and by ranges according to the presence of AKI.

| | No-AKI n= 30 (%) | AKI n= 42 (%) | |
|---|---|---|---|
| PCT <0,5 ng/ | 13 (43,3) | 5 (11,9) | p= 0,004 |
| PCT 0,5- 2,0 ng/ | 8 (26,6) | 10 (23,8) | |
| PCT 2,1- 10,0 ng/ | 7 (23,3) | 13 (30,9) | |
| PCT >10,0 ng/dl | 2 (0,6) | 14 (46,6) | |

**Table 3.** Adjusted binary logistic regression PCT >0.5 ng/mL at hospital admission and development of AKI. Adjusted for age, gender, sepsis subtype, site of infection and level of leukocytes.

| Variable | OR | CI 95 % | p |
|---|---|---|---|
| Serum creatinine on admission | 37,551 | 3,175 – 444,171 | 0,004 |
| Septic shock | 16,593 | 1,753-157,090 | 0,014 |
| PCT =0.5 ng/mL | 5,994 | 1,505-23,873 | 0,011 |

PCT= procalcitonin

development of AKI (Table 3). The KDIGO stages of AKI were not significantly different according to the subtypes of sepsis and a significant difference between PCT levels and the severity of AKI by KDIGO was not observed.

To determine the performance of PCT as a predictive biomarker of AKI, a ROC curve was constructed (Figure 2), which presented an AUC of 0.75 (95 % CI 0.639 – 0.862, $p$ <0.0001), establishing that the cut-off point of PCT 2.565 ng/mL had the best performance, with a sensitivity of 61.9 %, a specificity of 80 %, a PPV of 44.52 %, NPV of 56.18 %, LR+ of 0.80 and a LR- of 0.77.

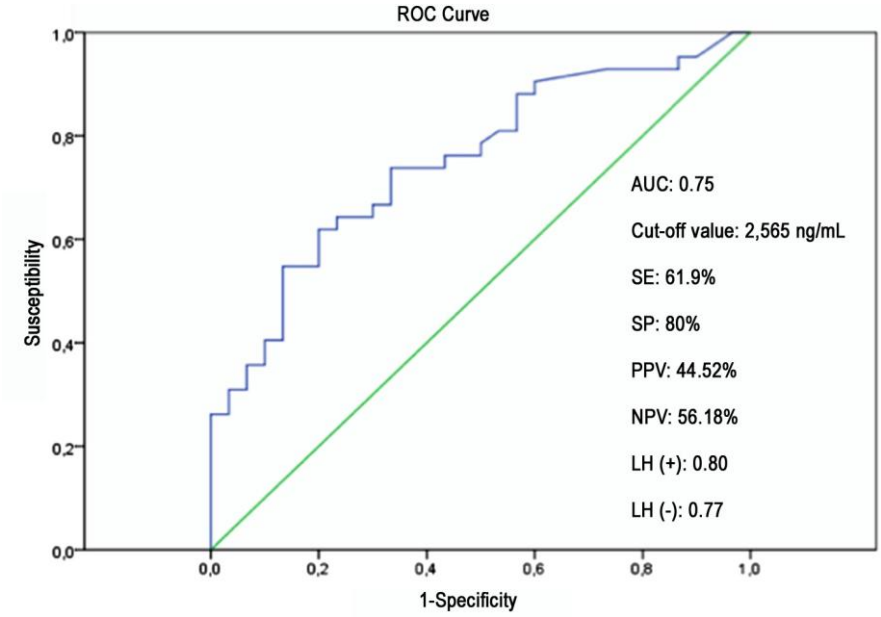
Finally, mortality and requirements for RST were evaluated according to the levels of PCT. Seven (16.7 %) patients with AKI died, while no death was observed in those without AKI (OR 1.2; 95 % CI [1.048 – 1.374] $p$ < 0.05. No significant relationship was observed between the positive PCT value and death (p = 0.1) and requirement of RST (p = 0.1).

## Discussion

In this single-center, prospective, observational and analytical study, it was demonstrated that upon hospital admission with the spectrum of sepsis, PCT can predict the development of AKI. PTC is a prohormone of calcitonin whose value can be increased up to thousand-fold during the sepsis period. The magnitude of its increase correlates with the severity and evolution of the infection.[20]

PCT has proven to be an accurate biomarker of infection and sepsis,[11] it also manifests a severity gradient, that is, the higher PCT levels, the greater severity of the infection.[12]

The possible harmful effect of PCT on the renal parenchyma has been demonstrated in experimental studies. Araujo et al., demonstrated the direct toxic effect of PCT on cultured mesangial cells. The infusion of PCT induced a disruption of the actin cytoskeleton, reducing the viability of mesangial cells by up to 36% and induced significantly greater




AUC = area under de curve, SE= sensitivity, SP= specificity, PPV= positive predictive value, NPV= negative predictive value, LH= likelihood ratio.

**Figure 2.** ROC curve for PCT as a predictor of AKI.

apoptosis when compared with controls.[17] These results could explain the direct toxic effect of PCT on the kidney.

The performance of some acute phase reactants and the incidence of AKI were evaluated in a prospective cohort of 1316 patients with suspected or proven infection. A PCT value of 1.575 ng/mL showed to be predictive of AKI, with an AUC 0.823 higher than the other acute phase reactants.[21] It is possible that the reported PCT value is different from that found in our study (2.56 ng/mL) due to the larger number of patients.

However, it has been suggested that the increased levels of PCT in AKI may be due to its decreased elimination by the kidney. Nakamura et al., evaluated the performance of PCT levels in the diagnosis of sepsis in patients with and without renal failure, finding a negative correlation between the levels of PCT and renal function[22] and suggesting that the kidney could be one of the organs responsible for the elimination of PCT. However, this has not been confirmed by others. Although the molecular weight of PCT is 13,600 Da, and therefore it is ultrafiltrable, it does not appear to accumulate in renal failure.[13,14]

Other biomarkers of AKI, such as urinary interleukin-18 (IL18), urinary liver-type fatty acid binding protein (LFABP), neutrophil gelatinase-associated lipocalin (NGAL) and the quotient of the multiplication of [TIMP-2]•[IGFBP7], have been studied with controversial results. In the meta-analysis, urinary IL-18 and LFABP have a moderate performance as predictors of AKI, with an AUC of 0.70[23] and AUC 0.72,[24] respectively. Also in a meta-analysis conducted to determine the performance of NGAL as a predictor of AKI in sepsis, the AUC of the plasma and urinary NGAL was 0.86 and 0.90, respectively.[25]

The only biomarker accepted by the FDA and the most accurate predictor of AKI, is the quotient of the multiplication of tubular cell arrest proteins, the tissue inhibitor of metalloproteinase 2 (TIMP-2) and the insulin-like growth factor-binding protein 7 (IGFBP-7); [TIMP 2]•[IGFBP7], which has shown one of the best predictive performances, with an AUC 0.87 when the quotient is > 2.[26]

However, the high cost and limited availability of these biomarkers have restricted their widespread use in developing countries. Because of its accessibility and low cost, PC could be a good option as a predictor of AKI in patients with sepsis in these countries. The fact that PCT increases in other pathologies associated with AKI, such as contrast-induced nephropathy[27] and acute pancreatitis,[28] suggests that it could be used as a marker of AKI in these entities.

Our analysis has several limitations that must be taken into account when interpreting the results. First, the number of participants is small; second, the retrospective nature could have omitted important data for analysis that were not captured; third, for the diagnosis of AKI we used only serum creatinine values, which may underestimate the true incidence of the pathology; fourth, we did not compare the performance of PCT with another biomarker of AKI. Finally, the single-center design limits its external validation.

## Conclusion

PCT appears to be useful as a biomarker of AKI in adult patients with sepsis spectrum. Its availability and low cost make it a good option for the timely identification of AKI with PCT and positively influence the clinical evolution.

## Conflict of interest

The authors declare they do not have any conflict of interest.

## Funding

None.

## Ethical responsibilities

### Protection of people and animals

The authors declare that no experiments were performed on human beings or animals for this research.

### Data confidentiality

The authors declare that they have followed the protocols of their workplace on the publication of patient data.

### Right to privacy and informed consent

The authors declare that patient data do not appear in this article.

## Contribution of the authors

Jonathan S. Chavez Iñiguez participated in the design and implementation of the study, statistical analysis and writing of the manuscript. Luis Arnoldo Muñoz-Nevárez participated in the design and implementation of the study. Evelyn Fabiola Morraz-Mejía, Rodolfo Alejandro Moreno-Alvarado, Marisol López-Ceja and José Manuel Montalbán-Castellanos participated in the implementation of the study and data collection. Guillermo García-García participated in the design of the study and writing of the manuscript.

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