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ORIGINAL ARTICLE

The prognostic value of serum procalcitonin in acute obstructive pyelonephritis

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Abstract

Purpose To evaluate the prognostic value of procalcitonin (PCT) in the occurrence of infectious complications in the management of acute obstructive pyelonephritis (AOP) compared with other biological parameters (leucocyte count, C-reactive protein [CRP]).

Methods We conducted a retrospective study including patients who were treated for AOP and performed serum PCT tests in our center between January 1, 2017 and December 31, 2017. Upper urinary tract obstruction was confirmed by either ultrasound or CT urography. Clinical examinations and laboratory tests including leukocyte count, CRP, urine and blood cultures, and serum PCT measurements were performed in the emergency unit. Treatment included early renal decompression using indwelling ureteral stents or nephrostomy and empiric antibiotic therapy. The primary endpoint was occurrence of severe sepsis (SS), a composite criterion including urosepsis and/or septic shock and/or admission to the intensive care unit (ICU) and/or death.

Results A total of 110 patients (median age: 61 years) were included, of whom 56.3% were female. SS occurred in 39 cases (35.4%). Multivariate regression analysis showed that serum PCT (OR 1.08; 95% CI 1.03–1.17; $p = 0.01$), CRP (OR 1.007; 95% CI 1.001–1.015; $p = 0.03$), and diabetes mellitus (OR 5.1; 95% CI 1.27–27.24; $p = 0.04$) were independent predictors for SS. Serum PCT was the biological marker associated with the highest accuracy to predict SS (ROC 0.912 (95% CI 0.861–0.962) and was superior to CRP ($p < 0.001$): the sensitivity and specificity of PCT to predict SS were 95% and 77%, respectively, with a serum PCT cutoff value of 1.12 µg/L.

Conclusions PCT levels > 1.12 µg/L could help physicians to identify high-risk patients who could benefit from early and aggressive management in collaboration with intensive care specialists.

Keywords Urosepsis · Acute obstructive pyelonephritis · Serum procalcitonin · Serum CRP · Leukocyte

Purpose

Serum PCT has emerged as a sensitive biomarker that provides prognostic information in patients with infections and could therefore improve the management of sepsis [1, 2]. Recent studies have demonstrated that PCT can accurately predict sepsis in patients with community-acquired pneumonia [3], acute fever and in elderly patients with suspected infection [4]. Moreover, PCT is strongly correlated with the extent and severity of bacterial infections [5]. However, PCT remains underused in daily urological practice. Few studies have evaluated the interest of PCT in urinary tract infection (UTI). The majority of these studies have been conducted in pediatric populations and included multiple presentations of

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UTIs (cystitis, non-obstructive pyelonephritis) with a wide range of infectious prognoses [6–8].

Acute obstructive pyelonephritis (AOP) is a severe septic pathology that can potentially lead to death. AOP consists of a bacterial infection of the kidney upstream of an obstruction of the ureter that is due to various causes such as lithiasis or any intrinsic/extrinsic compression. Approximately 80% of urosepsis cases are due to obstructive uropathy [9]. To our knowledge, no prior study has evaluated the interest of PCT to predict the occurrence of septic complications in patients with AOP.

Methods

Study population

Patients who were diagnosed with AOP in our tertiary center between January 1, 2017 and December 31, 2017 were considered for inclusion. The included population focused on patients of age ≥ 18 years with AOP who underwent urgent renal decompression with ureteral stent or nephrostomy tube with antibiotics and were tested for serum PCT in the emergency unit. Patients with concomitant infection in another organ, those who did not undergo decompression, and who had no serum PCT were excluded from the analysis.

The study was declared and approved by the Ethics Committee of the Association Française d'Urologie (CERU_2019/019). The study also guaranteed compliance at all times to the Law Jardé on research including humans (18th November 2016, French Government).

Diagnosis and management of acute obstructive pyelonephritis

AOP was diagnosed by physical exam findings including fever > 38 °C, flank pain, costovertebral angle tenderness, and vomiting, although in some cases, symptoms could be atypical. Obstruction was confirmed via CT scan or Ultrasound by dilatation of renal cavities and delayed excretion of iodine in CT urography if performed. All patients underwent laboratory investigations including leukocyte count, CRP, and blood and urine cultures in the emergency unit.

To determine the PCT level, 2 mL of blood was centrifuged and the serum was separated and assessed with a rapid, quantitative, electrochemiluminescence immunoassay (ELECSYS® B.R.A.H.M.S PCT, Hennigsdorf, Berlin, Germany). Assay time was approximately 20 min.

A positive urine culture was defined as a bacterial count > 10^5 colony forming units (CFU)/mL. Pyuria was defined as the presence of ≥ 10 white cells per cubic millimeter in a urine specimen. Diagnosis of infection was multiparametric and relied on clinical, biological, and/or imaging observations: fever, increased CRP, nephritis or pyeloureteritis, perirenal fat stranding, abscess.

For all patients, antimicrobials were administered in the emergency unit before obstruction clearance and in patients with systemic symptoms, no later than 1 h after clinical assumption of sepsis. In agreement with national guidelines, all patients were initially treated with an intravenous antimicrobial regimen by a third-generation cephalosporin and aminoglycoside. In patients with risk factors of extended-spectrum beta-lactamase (ESBL) (colonized or infected within the previous 6 months by ESBL-producing microorganisms), empirical treatment with carbapenems + aminoglycoside was administered instead of C3G + aminoglycosides. In all cases, the regimen was to be re-evaluated after the culture-antibiogram test results and administered for 14 days. Early obstruction clearance was performed by ureteral stenting or percutaneous nephrostomy. After obstruction clearance, in the absence of organ failure, patients were hospitalized in the surgical ICU and if they presented persistent hemodynamic instability, they were hospitalized in the ICU.

Endpoints and assessments

The primary endpoint was occurrence of severe sepsis (SS), a composite criterion including the occurrence of septic shock and/or admission to the ICU and/or death. Urosepsis was defined by an increase in the Quick Sequential [Sepsis-related] Organ Failure Assessment (qSOFA) score [6] of 2 points or more: respiratory rate of 22/min or greater, altered mental status, or systolic blood pressure of 100 mmHg or less. Urosepsis could be present on admission or appear secondarily during hospitalization. Septic shock was defined as urosepsis with persisting hypotension requiring vasopressors to maintain mean arterial pressure ≥ 65 mm Hg and a serum lactate level > 2 mmol/L despite adequate volume resuscitation. All causes of death were included. Thirty-day postoperative complications were also recorded.

Data analysis

Demographic data, preoperative clinical information, and perioperative and follow-up variables were extracted from medical files and recorded in a dedicated database. First, descriptive statistics were carried out for the available variables. Quantitative variables were reported in median, interquartile range [IQR], and analyzed by Mann–Whitney test. Categorical variables were described as numbers and percentages and were analyzed by Fisher's exact test and Chi square test. Second, ROC curves were plotted for PCT, WBC, CRP, and diagnostic accuracy was assessed by calculating the areas under the ROC curves (AUC). AUC comparisons were performed by the Delong test. Third, variables with $p<0.20$ were then considered to be included in the multivariate logistic regression model to calculate the adjusted OR and 95% CI. To detect multicollinearity, we calculated the variance inflation factors (VIF) of each variable included in the model. Factors with VIF > 3 were excluded. The area under the ROC curves was also used to evaluate model discrimination. Statistical analyses were performed using R Version 3.5.3 (The R Foundation for Statistical Computing). For all tests, a two-sided $p<0.05$ was considered statistically significant.

Results

Overall, 110 patients treated for AOP and who had a serum PCT test on admission to the emergency unit between January 1, 2017 and December 31, 2017 were included: 71 (64.6%) patients without SS (Group SS−) and 39 (35.4%) patients with SS (Group SS+). In the 39 patients with SS, urosepsis occurred in 29 cases: 17 cases of urosepsis were present on admission to the emergency unit while in 12 cases, urosepsis occurred later during the hospital stay. Septic shock occurred in 10 cases and 4 deaths were recorded, 3 deaths owing to septic shock and 1 death due to heart disease. Table 1 shows the baseline characteristics. Patients in the SS+ group were older (55 years [39.5–68] vs. 72 years [62.5–82]; $p<0.001$). There was higher female patient rate (34 [47.8%] vs. 28 [71.7%]; $p=0.01$). The Charlson score was higher (2 [0–5] vs. 5 [4–7]; $p<0.001$) and prior diabetes mellitus was more frequent (8 [11.2%] vs. 14 [28.2%]; $p=0.002$) compared with patients in the control group.

Acute obstructive pyelonephritis management

Table 2 shows the clinical and biochemical characteristics of the 110 cases of AOP. Obstruction by urolithiasis was more frequent in the SS− group (52 [73.2%] vs. 21 (53.8); $p=0.03$). In the SS+ group, the etiologies of AOP were significantly less related to urolithiasis ($p=0.03$), including 1 upper urinary tract urothelial carcinoma, 8 ureteral stent

Table 1 Baseline characteristics

	Group SS − ($n=71$)	Group SS+ ($n=39$)	p
Females, *n* (%)	34 (47.8)	28 (71.7)	0.01
Median (IQR) age, years	55 (39.5–68)	72 (62.5–82)	< 0.001
Median (IQR) body mass index	24.8 (23–27.9)	24 (23–31.1)	0.84
Median (IQR) Charlson score	2 (0–5)	5 (4–7)	< 0.001
Diabetes mellitus, *n* (%)	8 (11.2)	14 (28.2)	0.002

Table 2 Clinical and biochemical characteristics of 110 cases of AOP

	Group SS − ($n=71$)	Group SS+ ($n=39$)	p
Etiology of obstruction			0.03
Urolithiasis, *n* (%)	52 (73.2)	21 (53.8)	
Other cause, *n* (%)	19 (26.8)	18 (46.2)	
Median (IQR) PCT, mg/L	0.27 (0.12–1.01)	16.5 (4.6–43.9)	< 0.001
Median (IQR) CRP, mg/L	84.7 (24.6–176.5)	191.6 (151.8–252)	< 0.001
Median (IQR) WBCs, G/L	14 (8.9–17)	16 (10–22.5)	0.06
Results of urine culture			
Sterile, *n* (%)	19 (26.8)	3 (7.7)	0.01
Polymicrobial, *n* (%)	17 (23.9)	6 (15.4)	0.29
Positive, *n* (%)	35 (49.3)	30 (76.9)	0.004
Results of blood culture			< 0.001
Sterile, *n* (%)	62 (87.3)	21 (53.8)	
Positive, *n* (%)	9 (12.7)	18 (46.2)	
MDR organisms, *n* (%)	5 (7)	8 (20.5)	0.06
Place of hospitalisation:			< 0.001
Surgical unit, *n* (%)	71 (100)	29 (74.4)	
Intensive care unit, *n* (%)	0 (0)	10 (25.6)	
Median (IQR) length of hospitalisation, days	4 (3–5)	6 (5–10)	< 0.001

PCT Procalcitonin, *CRP* C-reactive protein, *WBC* wight blood cell, *MDR* multi-drug resistant obstructions, 3 extrinsic compressions and in 6 cases, the etiologies were not reported. Laboratory analysis showed that CRP ($p < 0.001$) and PCT ($p < 0.001$) levels were significantly higher in the SS+ group, whereas no difference was found in WBC count between both groups ($p = 0.06$).

Positive urine and blood cultures were more frequent in the SS+ group ($p = 0.004$ and $p < 0.001$, respectively). Of the 65 positive urine cultures, the most common causative agents of UTI were *E. coli* (50.7%), *Klebsiella spp.* (20%), and *Proteus mirabilis* (9.2%) without differences between both groups. Multi-drug-resistant organisms were most frequent in the SS+ group (5 [7%] vs. 8 [20.5%]) but the difference was not significant ($p = 0.06$). All of the patients in the SS− group were hospitalized in the surgical unit while 10 patients (25.6%) in SS+ group were hospitalized in the ICU after surgery because they had persistent haemodynamic instability despite adapted treatment (septic shock). Finally, the median (IQR) length of hospitalization was 6 days [5–10] in the SS+ group compared with 4 days [3–5] in control group ($p < 0.001$).

PCT compared with other parameters to predict SS

Multivariate regression analysis using all variables with $p < 0.20$ from the univariate analysis showed that PCT serum levels (adjusted OR 1.08; 95% CI 1.03–1.17; $p = 0.01$), CRP serum levels (adjusted OR 1.007; 95% CI 1.001–1.015; $p = 0.03$), and diabetes mellitus (adjusted OR 5.1; 95% CI 1.27–27.24; $p = 0.04$) were independent predictors of SS (Table 3).

In order to assess the overall discriminatory ability of each biological marker for SS, we calculated ROC curves (Fig. 1). PCT had the highest diagnostic accuracy to predict SS with an area under the curve of 0.912 (95% CI 0.861–0.962) in the overall population and was superior to the CRP and WBC counts ($p < 0.001$). The maximum sensitivity and specificity of serum PCT corresponded to a serum PCT of 1.12 µg/L and were, respectively, 95% and 77% in the overall cohort. The sensitivity, specificity, positive,

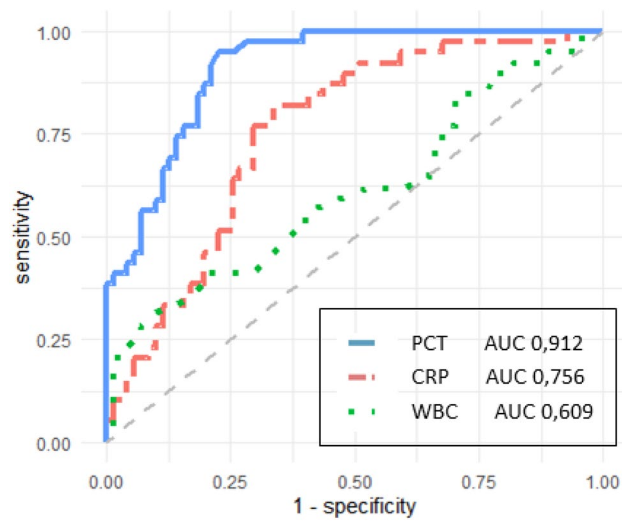

Fig. 1 Receiver operating characteristic (ROC) curve analysis comparing Procalcitonin, C-reactive protein, and white blood cells in the overall cohort. *PCT* Procalcitonin, *CRP* C-reactive protein, *WBC* wight blood cell

Table 3 Multivariate logistic regression analysis of variables associated with urosepsis

	Group SS − ($n = 71$)	Group SS+ ($n = 39$)	p univariate	p multivariate	VIF
Females, *n* (%)	34 (47.8)	28 (71.7)	**0.01**	0.74	1.33
Median (IQR) age, years	55 (39.5–68)	72 (62.5–82)	**< 0.001**	0.32	1.16
Diabetes mellitus, *n* (%)	8 (11.2)	14 (28.2)	**0.002**	**0.04**	1.31
Etiology of obstruction					
Urolithiasis, *n* (%)	52 (73.2)	21 (53.8)	**0.03**	0.14	1.19
Other cause, *n* (%)	19 (26.8)	18 (46.2)			
Median (IQR) PCT, mg/L	0.27 (0.12–1.01)	16.5 (4.6–43.9)	**< 0.001**	**0.01**	1.62
Median (IQR) CRP, mg/L	84.7 (24.6–176.5)	191.6 (151.8–252)	**< 0.001**	**0.03**	1.28
Median (IQR) WBCs, G/L	14 (8.9–17)	16 (10–22.5)	0.06	0.21	1.04
Positive urine culture, *n* (%)	35 (49.3)	30 (76.9)	**0.004**	0.14	1.18
Positive blood culture, *n* (%)	9 (12.7)	18 (46.2)	**< 0.001**	0.20	1.43
MDR organisms, *n* (%)	5 (7)	8 (20.5)	0.06	0.07	2.04

"Group SS–" stands for "severe sepsis negative" = control group

"Group SS+" stands for "severe sepsis positive" = test group

Charlson score was excluded from multivariate analysis: VIF > 3

Area under the ROC curve: 0.92

Hosmer and Lemeshow goodness of fit (GOF) test: $p = 0.27$

PCT Procalcitonin, *CRP* C-reactive protein, *WBC* wight blood cell, *MDR* multi-drug resistant and negative predictive value for each biological marker is reported in Table 4.

Thirty-day postoperative complications

Thirty-day postoperative complications were observed in 11 patients (15.5%) in the SS− group and in 27 patients (69.2%) in the SS+ group ($p < 0.001$): grade 1 ($p = 0.02$) and grade 2 ($p < 0.001$) complications were most frequent in the SS+ group ($n = 8$: 2 blood transfusions, 2 pulmonary embolisms, 1 acute pulmonary oedema, 1 atrial fibrillation, 1 renal abscess that did not require drainage, 1 epileptic seizure) compared with the control group ($n = 1$, corresponding to 1 blood transfusion) (Table 5). Major complications (grade 3) were observed in six cases (15.3%) in the SS+ group and included 2 cases of renal failure requiring dialysis and 4 deaths (3 deaths secondary to septic shock and 1 death from heart disease).

Table 5 Overall 30-day postoperative complications classified according to Clavien–Dindo grading system

Grade	Group SS − ($n = 71$)	Group SS+ ($n = 39$)	p
1, n (%)	10 (14)	13 (33.3)	0.02
2, n (%)	1 (1.4)	8 (20.5)	< 0.001
≥ 3, n (%)	0 (0)	6 (15.3)	0.001

Discussion

In this study, we demonstrated the correlation between serum PCT and septic shock and/or admission to an ICU and/or death in AOP. In this retrospective monocentric study of AOP, PCT > 1.12 µg/L proved to be the most reliable biological marker to identify high-risk patients who would benefit from early and aggressive management in collaboration with intensive care and infectious disease specialists. PCT was associated with prolonged hospitalization and higher postoperative complications classified according to the Clavien–Dindo grading system [10–12]. In our study, serum PCT even predicted worse outcomes in 12 patients who initially had no clinical/biological signs of severity but who subsequently required transfer to the ICU owing to delayed septic shock despite antimicrobials and emergency obstruction clearance.

Several studies have evaluated the diagnostic accuracy of PCT for sepsis of various infection sites with contradicting conclusions following comparable results [1–12]. Tang et al. concluded that there was no clear use for PCT in diagnosing sepsis (area under the SROC curve of 0.78, sensitivity: 71%, specificity: 70%) [13]. However, their inclusion may be biased by specifically excluding sepsis originating from certain types of common infection sites [13]. In contrast, Wacker et al. concluded that PCT was useful for the diagnosis of sepsis (area under the ROC curve 0.85, sensitivity: 77%, specificity: 79%) [1]. Previous results are supported by a recent meta-analysis where the diagnostic accuracy of PCT for sepsis was evaluated in different subgroups of hospitalized adult patients with suspected infection or sepsis [14]. Overall, at a cut-off level of 0.5 ng/mL, PCT had a fair diagnostic accuracy for bacteremia with an area under the ROC curve of 0.79 [14].

Few studies have been conducted to identify predictive factors of urosepsis in patients with UTI [15, 16] and to

Table 4 Area under the curve of receiver operating characteristic plot analysis and diagnostic accuracy

	AUC (CI)	p	Se	Sp	LH+	LH-	Youden
PCT	0.912 (0.861–0.962)						
> 0.01 µg/L			1	0.05	1.05	0	0.05
> 0.50 µg/L			1	0.57	2.32	0	0.57
> 1.12 µg/L			0.95	0.77	4.13	0.06	0.72
CRP	0.756 (0.665–0.847)	$p < 0.001$					
> 5 mg/L			0.97	0.07	1.04	0.42	0.04
> 50 mg/L			0.94	0.38	1.51	0.15	0.58
> 121.4 mg/L			0.82	0.66	2.41	0.27	0.71
WBC count	0.609 (0.493–0.724)	$p < 0.001$					
> 1.8 G/L			1	0.01	1.01	0	0.36
> 10 G/L			0.32	0.71	1.10	0.95	0.46
> 20.5 G/L			0.31	0.92	3.87	0.75	0.70

PCT procalcitonin, *CRP* C-reactive protein, *WBC* wight blood cell, *AUC* area under the ROC curve, *Se* sensitivity, *Sp* specificity, *LH+* positive likelihood ratio, *LH−* negative likelihood ratio

p: comparison of ROC curves to test the statistical significance of the difference between the areas under ROC curves with the method of DeLong our knowledge, no prior study has specifically targeted patients with AOP. Van Nieuwkoop et al. found that only PCT was a robust surrogate marker for urosepsis but patients with urolithiasis or hydronephrosis were excluded from the analysis. The AUC of the ROC curve of PCT diagnosing bacteremia was 0.81 (95% CI 0.77–0.85) [17]. A threshold of 1.16 ng/ml was proposed by Julian-Jemenez et al. as having the largest area under the ROC curve at 0.993 and therefore the most relevant in guiding medical decision-making [18]. In the present study which specifically included patients with AOP, the AUC of PCT was 0.91 which corresponded to good discriminative power compared with the previous results.

A strength of our study was that we checked clinical history, blood tests, and imaging for each of the included patients, meaning that all cases were confirmed cases of AOP. Although the initial presentations were clearly in favor of AOP, 21 patients (20%) presented negative urine cultures in the overall cohort. Urine culture results can be of limited significance in AOP in some cases because the urine with the highest infectious load is most often proximal to the obstruction (sensitivity: 30.2%, specificity: 73%) [19]. The gold standard for detection of bacteraemia remains the performance of at least two blood cultures to achieve sufficient sensitivity. In our study, only 27 patients (24.5%) had positive blood cultures, mostly in the urosepsis group ($n = 18$), from the previously reported rates to approximately 30% [20]. In AOP, blood and urine cultures are delayed and therefore unreliable markers of infection.

As in any study, our study has limitations. First, the main limitation is its retrospective design. Second, 21 urine cultures were negative in the overall cohort and microbiological diagnosis of UTI could not be proven. Although we excluded patients with sites of infection other than the urinary tract, it is not entirely possible to rule out the influence of concomitant infections. We did not study preoperative urine culture results because antibiotic therapies were administered before obstruction clearance in the emergency unit and the results would have been associated with a high risk of false-negatives. Third, practitioners were instructed to routinely perform serum PCT assay in all patients with suspected AOP regardless of septic status. However, the final decision to perform serum PCT assay was at the practitioner's discretion and the risk of assaying PCT only in severe patients was high, which can lead to selection bias. Other biological markers such as mid-regional pro-adrenomedullin, lactate dehydrogenase, or presepsin which have proven to be predictive of severe sepsis outcome were not investigated in our study. Since this current study, serum PCT in our center is assessed only in patients who do not present septic status on admission to the emergency unit in order to identify patients who are at high risk of secondarily developing septic complications.

Conclusion

In this monocentric study of consecutive patients with AOP admitted to the emergency unit, serum PCT proved to be the most reliable biological factor to predict immediate or delayed septic shock and/or admission to the ICU and/or death. PCT levels > 1.12 µg/L could help clinicians to identify high-risk patients who would benefit from early and aggressive management in collaboration with intensive care specialists.

Author contributions MB and RB had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. RB: study concept and design. MB, MDB: acquisition of data. MB, BGT, RA, EL, RG, RB: analysis and interpretation of data. MB, RB: drafting of the manuscript. EA, FM, PCS, AA, AG, VD, GK, RG, EL: critical revision of the manuscript for important intellectual content. BGT, MB, RB: statistical analysis.

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Compliance with ethical standards

Conflict of interest The authors have nothing to disclose.

Ethics approval The study was declared and approved by the Ethics Committee of the Association Française d'Urologie (CERU_2019/019). The study also guaranteed compliance at all times to the Law Jardé on research including humans (18th November 2016, French Government).

Informed consent Demographic data, preoperative clinical information, and perioperative and follow-up variables were extracted from medical files and recorded in a dedicated anonymous database. As part of the standard medical care in l'Assistance Publique des Hopitaux de Marseille, France, every patient signed during hospital stay, a written consent for the anonymous use of clinical and biological data. All the urine test, blood test, imaging, and urinary decompression reported in this study were part of the standard care of the included patients and were analyzed retrospectively.

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