ORIGINAL INVESTIGATION

Reliability of serum procalcitonin concentration for the diagnosis of sepsis in elderly patient with chronic kidney disease

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Background and aims. Sepsis is complicated by high mortality in hospitalized patients. Procalcitonin (PCT) is a validated tool in the diagnosis of sepsis in both adults and aged patients. Several studies demonstrated the reliability of PCT in adults with chronic kidney disease (CKD), but this has not been studied in the geriatric population. Thus, we aimed at evaluating the reliability of PCT in a group of elderly patients with CKD.
Methods. 382 subjects (mean age, 78.9 years) were consecutively enrolled and stratified in two groups at the time of the admission based on the absence or presence of CKD, defined as estimated Glomerular Filtration Rate (e-GFR) less than 60 ml/min/1.73 m^2. These two groups were further divided according to the presence (SEPSIS/NO CKD, n = 41; SEPSIS/CKD, n = 45) or absence of sepsis (NO SEPSIS/NO CKD, n = 147; NO SEPSIS/CKD, n = 149), and the serum PCT was analyzed.
Results. PCT was highly sensitive and specific in patients presenting with sepsis and no CKD. The mean serum PCT concentration in the group SEPSIS/CKD was significantly higher than in NO SEPSIS/CKD (21.00 [5.83 to 97.00] ng/ml *vs* 0.90 [0.24 to 1.32] ng/ml, $p < 0.001$). However, the PCT threshold value was 1.7 ng/ml (sensitivity 91.1%, specificity 88.6%) as compared with the currently used threshold value of 0.5 ng/ml (sensitivity 93.3%, specificity 30.2% in our population study).
Conclusions. Our study confirms the diagnostic reliability of PCT for the diagnosis of sepsis in elderly patients with CKD. Nevertheless, we suggest to apply a cut-off of 1.7 ng/ml in this population.

Key words: Circulating procalcitonin, Chronic kidney disease, Sepsis

INTRODUCTION

Sepsis is defined as a systemic inflammatory response secondary to an acute infection [1]. The incidence of sepsis and sepsis-related mortality has increased over the past 30 years, particularly in elderly people and it is now the 10th leading cause of death in the United States [2 3]. Approximately 750,000 people per year are affected by severe sepsis, and more than 50% of the affected population is over 65 years old [4]. Since the aging population is increasing worldwide, the incidence of sepsis is expected to raise in the future. In aged patients, the atypical symptoms and presentation can make sepsis difficult to diagnose clinically, leading to a delay in both diagnosis and initiation of therapy, thus resulting in increased mortality [5-8]. Assessment of procalcitonin (PCT) level in serum may be helpful in rapid diagnosis of sepsis [9]. PCT is the precursor of calcitonin produced by thyroid C cells circulating in the blood at very low concentrations (< 0.05 ng/ml) in healthy subjects; during bacterial infections, PCT production increases rapidly in all parenchyma [10 11]. PCT production is stimulated by both cytokines and bacterial endotoxin or lipopolysaccharide [12]. The utility of PCR is not only due to the

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rapid increase in the serum concentrations, but also to the rapid cleavage in case of an effective empirical treatment [6 10 11]. In patients with chronic kidney disease (CKD), PCT levels are higher than in subjects with normal renal function, and it is demonstrated that these levels are reduced after hemodialysis [13]. Thus, it is conceivable that a standard cut-off of 0.5 ng/ml could be less specific. We designed the present study to evaluate the diagnostic validity of PCT in the diagnosis of sepsis in geriatric patients presenting with CKD.

PATIENTS AND METHODS

The study was conducted at the Department of Medicina Interna Universitaria, "Ospedali Riuniti" in Foggia (Italy). We recruited 382 consecutive patients aged 65 or older. The exclusion criteria were the following: age < 65 years, active cancer, musculoskeletal trauma or recent surgery. Two groups were formed according to diagnosis of CKD (NO CKD; CKD). CKD was defined as estimated Glomerular Filtration Rate (e-GFR) less than 60 ml/min/1.73 m^2 at the time of admission.

Patients of both groups were divided according to the absence or the presence of sepsis (NO SEPSIS/NO CKD; SEPSIS/NO CKD; NO SEPSIS/CKD; SEPSIS/CKD). SEPSIS was defined as the presence of Systemic Inflammatory Response Syndrome (SIRS) plus suspect or proven infection with radiologic or blood culture. SIRS diagnosis was defined by the presence of two or more of the following criteria: white blood cells (WBC) > 12000/mm^3 or < 4000/mm^3, heart rate > 90 beats per minute, body temperature < 36°C or > 38°C, respiratory rate > 20 breaths per minute or a $PaCO_2$ < 32 mmHg [14].

Patients included in the NO SEPSIS groups who presented with febrile episodes or leukocytosis during hospitalization were excluded.

At the hospital admission time laboratory tests such as WBC count, erythrocyte sedimentation rate (ESR), serum ferritin, C-reactive protein (CRP), uric acid and creatinine were assessed. PCT was measured by electrochemiluminescence, and the standard cut-off value was established at 0.5 ng/ml, according to the most recent literature [15-17].

STATISTICAL ANALYSIS

Comparison between continuous variables was performed using Student's T-test or Mann Whitney's test and expressed as mean ± standard deviation of the mean (SD) or median (Interquartile Range, IR). Nominal and categorical variables were analyzed by the Chi-Square test and expressed as *n* (%). The impact of CKD as well as sepsis presence on the circulating levels of PCT was analyzed by two-way analysis of variance (ANOVA), using CKD as row factor and sepsis as column factor. For the diagnosis of sepsis, PCT sensitivity and specificity were calculated by receiver operating characteristic curve (ROC) analysis. Statistical tests were performed using SPSS 20 software analysis. Power analysis was performed by the GPower Software.

RESULTS

We enrolled 382 consecutive patients divided in two group based on renal function: patients without CKD (NO CKD group, n = 188) and patients with CKD (CKD group, n = 194). The patients were divided according to the sepsis diagnosis: 296 (77%) without sepsis and 86 (23%) with sepsis. Baseline characteristic are summarized in Table I. There were no significant differences among septic and no septic patients as regards age, serum ferritin, as well as creatinine and e-GFR. The percentage of women was significantly higher in the non-sepsis group ($p < 0.03$). The prevalence of co-morbidities in the enrolled patients is summarized in Table II. The percentage of patients presenting with ≥ 3 co-morbidities was not different among the CKD and NO CKD groups. The most common comorbidities in both groups were hypertension, chronic obstructive pulmonary disease (COPD) and diabetes mellitus.

The mean value of WBC and ESR, as well as the median value of CRP and PCT were significantly higher in the groups with sepsis than in no septic (Tab. I). The two-way ANOVA showed that the presence of CKD ($F = 5.072$, $p < 0.0001$) or sepsis ($F = 6.09$, $p < 0.0001$), as well as the interaction between these two variables ($F = 4.339$, $p < 0.0001$) influenced serum PCT values. Post-hoc analysis demonstrated that, while there were no significant differences in circulating PCT from CKD and NO CKD groups without sepsis, septic patients with CKD presented with higher PCT levels as compared to those with NO CKD (Fig. 1).

The sensibility and specificity in the NO CKD group using normal PCT cut-off (< 0.5) were respectively 95.1% and 87.8% (AUC 0.987) (Tab. III). Very interestingly, the sensibility and specificity using normal PCT cut-off (< 0.5) were 93.3% and 30.2% respectively in the CKD group.

We performed receiver operating characteristic curve (ROC) analysis to establish PCT value with better sensitivity and specificity for the diagnosis of sepsis in the CKD group. Results showed a cut-off value of 1.7 ng/ml with sensitivity 91.1% and specificity 88.6% with Area Under the Curve (AUC) 0.932 (Fig. 2, Tab. III). The

Table I. Baseline characteristics of elderly patients without and with chronic kidney disease (CKD). Data are presented as mean ± standard deviation, median (interquartile range) or *n* (percentage) as appropriate. Statistical differences were assessed by student's t-test for numerical variables and chi-square test for categorical variables.

	NO CKD			CKD		
Characteristics	**NO Sepsis n. 147**	**Sepsis n. 41**	***P value***	**NO Sepsis n. 149**	**Sepsis n. 45**	***P value***
Age, years	77.7 (± 7.9)	78.0 (± 8.2)	0.84	80.3 (± 7.7)	79.6 (± 8.4)	0.60
Sex, F	74 (50.3%)	13 (31.7%)	0.03	84 (56.4%)	20 (44.4%)	0.46
ESR, mm/h	48.8 (± 31.4)	77.6 (± 26.0)	< 0.001	56.7 (± 32)	69.7 (± 33)	0.02
CRP, mg/l	45 (7.00 to 97.50)	124 (66.0 to 187.9)	< 0.001	32.2 (7.5 to 109.8)	188 (82.6 to 260.8)	< 0.001
Ferritin, ng/ml	380.4 (± 42.6)	295.4 (± 56.2)	0.23	379.4 (± 81)	371 (± 47)	0.96
WBC, /ul	8655 (± 345)	14053 (± 6768)	< 0.001	10131 (± 747.9)	15521 (± 1031.1)	< 0.001
Creatinine, mg/dl	0.78 (± 0.21)	0.81 (± 0.19)	0.32	2.0 (± 1.3)	1.9 (± 0.8)	0.67
e-GFR, ml/min/1.73^2	95.99 (± 30.3)	94.98 (± 26.5)	0.85	36.69 (± 14.2)	36.21 (± 11.98)	0.84
Comorbidities ≥ 3 (n. patients)	64 (43.5%)	17 (41.5%)	0.81	103 (69.1%)	34 (75.6%)	0.41
PCT, ng/ml	0.07 (0.05 to 0.30)	8.5 (2.80 to 16.23)	< 0.001	0.90 (0.24 to 1.32)	21.00 (5.83 to 97.00)	< 0.001

Abbreviations: F: female; ESR: erythrocyte sedimentation rate; CRP: C protein reactive; WBC: white blood cell; PCT: procalcitonin.

Table II. Prevalence of co-morbidities of elderly patients without and with chronic kidney disease (CKD). Data are presented as *n* (percentage). Statistical differences were assessed by chi-square test.

	NO CKD			CKD		
Characteristics	**NO Sepsis n. 147**	**Sepsis n. 41**	***P value***	**NO Sepsis n. 149**	**Sepsis n. 45**	***P value***
Hypertension, *n*	86 (58.5%)	25 (61.0%)	0.86	104 (69.8%)	29 (64.4%)	0.58
Diabetes, *n*	45 (30.6%)	12 (29.3%)	0.98	75 (50.3%)	25 (55.6%)	0.61
Heart failure, *n*	29 (19.7%)	8 (19.5%)	0.99	54 (36.2%)	9 (20%)	0.05
Atrial fibrillation, *n*	31 (21.1%)	6 (14.6%)	0.50	51 (34.2%)	14 (31.1%)	0.86
Ictus, *n*	17 (11.6%)	4 (9.8%)	0.74	15 (10.1%)	6 (13.3%)	0.71
IHCD, *n*	24 (16.3%)	9 (22.0%)	0.49	43 (28.9%)	11 (24.4%)	0.70
Cirrhosis, *n*	11 (7.5%)	3 (7.3%)	0.97	11 (7.4%)	4 (8.9%)	0.82
COPD, *n*	46 (31.3%)	23 (56.1%)	0.001	58 (38.9%)	13 (28.9%)	0.29

Abbreviations: COPD, chronic obstructive pulmonary disease; IHCD, ischemic heart chronic disease.

analysis performed by Gpower software indicated 0.99 statistical power.

DISCUSSION

PCT is a validate marker to recognize bacterial sepsis in patients with symptoms and signs of infections [10]. PCT concentration increases in the serum within three to six hours from the development of sepsis without systemic mycoses, localized infection or SIRS. These features make the PCT a great tool for rapid differential diagnosis [13]. A systemic bacterial infection can be excluded, when the serum PCT level is < 0.5 ng/mL in SIRS patients, but it is strongly suggested if PCT > 2.0 ng/mL; a level of ≤ 2.0 ng/mL, indicates the need for re-examination after 6 to 24 hours when bacterial infection or sepsis is suspected [18].

Clinical manifestations of infection or sepsis in the elderly may be atypical compared to young adults. This can make it difficult for early diagnosis especially in the elderly with co-morbidities [8 19]. Results on the reliability of PCT to diagnose infection in aged patients are controversial. Infact, a previous study failed to demonstrate a good efficiency of PCT to detect infection in elderly people admitted to acute geriatric wards; the Authors suggested that the lack of sensitivity may be linked to the low severity of infection or to the aging process *per se*, but neither age nor comorbidity decreases the specificity of PCT [20]. Nevertheless, the ability of PCT to

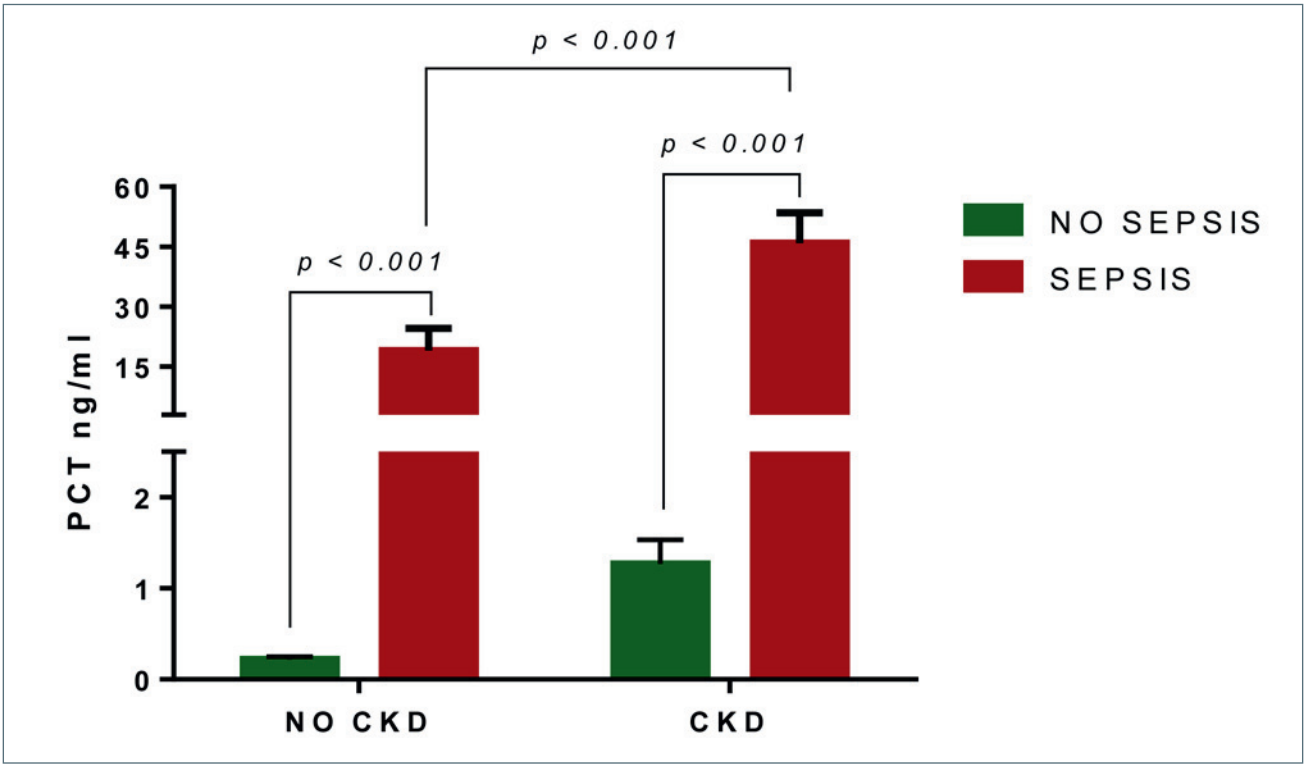

Figure 1. Serum procalcitonin (PCT) levels in all groups of studied patients. Statistical differences were assessed by two-way ANOVA and Tukey's as *post hoc* test. Abbreviations: CKD, chronic kidney disease.

Table III. Stratification of the studied population based on PCT cut off sensibility and specificity for the diagnosis of sepsis. Data are presented as *n* (percentage).

	NO CKD group		CKD group	
PCT Cut-off	**NO Sepsis n. 147**	**Sepsis n. 41**	**NO Sepsis n. 149**	**Sepsis n. 45**
< 0.5, ng/ml	87.8% (129)	4.9% (2)	30.2% (45)	6.7% (3)
≥ 0.5, ng/ml	12.2% (18)	95.1% (39)	69.8% (104)	93.3% (42)
	100% (147)	100% (41)	100% (149)	100% (45)
< 1.7, ng/ml	98.6% (145)	9.8% (4)	88.6% (132)	8.9% (4)
≥ 1.7, ng/ml	1.4% (2)	90.2% (37)	11.4% (17)	91.1% (41)
	100% (147)	100% (41)	100% (149)	100% (45)

Abbreviations: CKD, chronic kidney disease.

differentiate sepsis from localized infections or SIRS in elderly patients was demonstrated effective in another report [21].

Chronic kidney disease (CKD) is a substantial concern in the elderly, with both an increasing incidence of treated kidney failure with dialysis as well as a high prevalence of earlier stages of CKD [22]. Different results are reported for the reliability of PCT in CKD. A previous study concluded that PCT is not a reliably sensitive or specific diagnostic test for bacterial infection in patients with renal impairment when using a single threshold, although at a threshold of 0.5 ng/mL, it does have a reasonable specificity for predicting bacterial infections and a reasonable negative predictive value for predicting bacteremia [23].

Moreover, in patients with CKD a low diagnostic reliability of the current standard PCT cut-off values was shown, and a higher threshold (0.75 ng/ml) was proposed [13]. PCT levels can also increase during organ perfusion or after a severe cardiogenic shock [24,25].

To date, there have been poor data about the diagnostic reliability of the PCT in elderly patients with CKD.

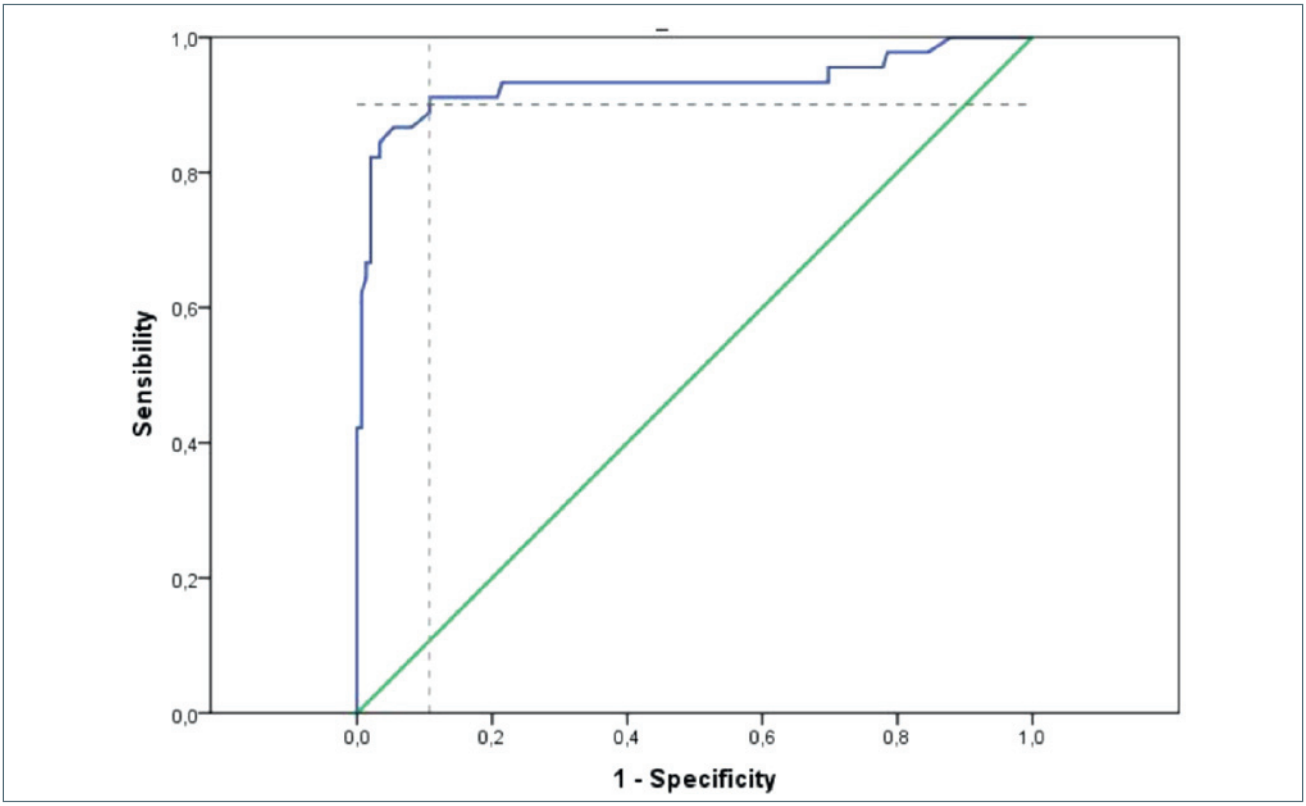

Figure 2. Area under the receiver operating characteristic curve for procalcitonin PCT cut off in the diagnosis of sepsis (AUC 0.932).

The present study confirmed the strong correlation between WBC, ESR, CRP and PCT and inflammation, showing a significant increase in geriatric patients with sepsis. However, there are differences in elderly with CKD as compared with patients with normal renal function. Our results showed that the threshold of 0.5 ng/ml in group with sepsis and renal impairment presents a high sensibility but a poor specificity for the diagnosis of sepsis. This is consistent with previous findings about the impact of renal function on serum PCT [26 27] but not in the elderly, where PCT confirms its sensibility and specificity [21]. Previous studies have shown that co-morbidities and renal impairment are associated with increased levels of cytokines, particularly IL-6, which can contribute to the inflammatory state [28-30]. This could be a possible mechanism linked to higher PCT values in elderly patients with CKD, since this pro-inflammatory cytokine is associated with increased levels of circulating PCT during sepsis [31 32]. We confirmed the significant correlation between several variables in patients with CKD with or without sepsis like WBC, PCR and PCT. We found performing the ROC curve, the value of 1.7 ng/mL as cut-off with best sensitivity and specificity, respectively, of 91.1% and 88.6%.

We are aware of the limitations of our study. First, the type of study (single-center) and small sample size restricted further subgroup analysis. A second limitation is represented by the retrospective analysis. The timing between culture and serum procalcitonin was less exact than may have been ideal due to the retrospective nature of the study. Ideally, in a prospective study, these would have been simultaneous.

In conclusion, our data confirm the diagnostic reliability of PCT in the diagnosis of sepsis in geriatric patients with CKD. However, we suggest to use a threshold value of 1.7 ng/ml, which shown the best sensitivity and specificity. Given the imperfect accuracy, we do not recommend that the PCT test be used in isolation; instead, we suggest that it be interpreted in the context of clinical findings.

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