Clinical Rheumatology (2019) 38:2265–2273
https://doi.org/10.1007/s10067-019-04542-0

ORIGINAL ARTICLE

Value of serum procalcitonin for the diagnosis of bacterial septic arthritis in daily practice in rheumatology

Mickaël Chouk[1] · Frank Verhoeven[1] · Maxime Sondag[1] · Xavier Guillot[2] · Clément Prati[1] · Daniel Wendling[1]

Received: 12 January 2019 / Revised: 25 March 2019 / Accepted: 1 April 2019 / Published online: 16 April 2019

Abstract

Introduction/objectives Septic arthritis is a diagnostic and therapeutic emergency because of a high morbidity and mortality. Nevertheless, the etiologic diagnosis is often difficult. The aim of our study was to determine if serum procalcitonin was a discriminatory biomarker in case of arthritis of undetermined etiology.

Method Patients were separated in five groups: gouty arthritis, calcium pyrophosphate deposition arthritis, osteoarthritis or post-traumatic arthritis ("mechanical" arthritis), chronic inflammatory rheumatic arthritis, and septic arthritis. Levels of serum white blood cells, C-reactive protein and procalcitonin were measured.

Results Ninety-eight patients were included: 18 in the "gout" group, 26 in the "calcium pyrophosphate deposition arthritis" group, 16 in the mechanical group, 18 in the "chronic inflammatory rheumatic" group, and 20 in the "sepsis" group. The area under the receiver operating characteristic curve of white blood cells, C-reactive protein, and procalcitonin levels to diagnose a septic arthritis were 0.69 (IC95% 0.55–0.83), 0.82 (IC95% 0.73–0.91), and 0.87 (IC95% 0.76–0.98) respectively. For a cutoff of 0.5 ng/ml, procalcitonin sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio were 65%, 91%, 65%, 91%, 7.2, and 0.4, respectively. Serum C-reactive protein and procalcitonin levels were correlated, were not different in sepsis or gout groups, and were higher in non-septic arthritis with poly-arthritis than with mono-arthritis ($p < 0.05$).

Conclusions Serum procalcitonin is a useful biomarker in arthritis management with diagnosis performances higher than those of other biomarkers (white blood cells, C-reactive protein).

Key Points

- *Diagnostic performances of serum procalcitonin level in septic arthritis are higher than those of serum C-reactive protein or white blood cells levels.*
- *Serum procalcitonin levels are not different in septic arthritis or gouty arthritis.*
- *Serum procalcitonin levels are higher in non-septic arthritis with poly-arthritis than with mono-arthritis.*

Keywords Arthritis · Chronic inflammatory rheumatism · Crystal arthropathies · Procalcitonin · Sepsis

Introduction

The distinction between a septic arthritis and a non-septic arthritis is a major issue. Indeed, septic arthritis is a diagnostic and therapeutic emergency because of a high morbidity and mortality [1, 2]. Unfortunately, the etiologic diagnosis is often difficult because these two entities are close in terms of clinical (fever, local inflammation) and biological (high levels of C-reactive protein (CRP) and white blood cells (WBC)) features [3]. The gold standard to identify a septic origin is the isolation of a pathogenic microorganism, but blood or synovial fluid Gram stains have poor yields, and blood or synovial fluid cultures, or even microbial genome research by polymerase chain reaction (PCR) although faster than cultures, take times [4, 5]. Moreover, a prior initiation of antibiotics can make negative the microbiologic samples. Finally, radiologic abnormalities are often deferred in septic arthritis, not allowing the clinician an early diagnosis [3]. A sensitive and specific biomarker, usable in daily practice, would be a great help for the rheumatologist. Of course, the perfect biomarker does not exist, but it is essential to be aware of the diagnosis performances of the biomarkers we use every day, so that we

✉ Mickaël Chouk
mchouk@chu-besancon.fr

[1] CHRU Jean Minjoz, Service de Rhumatologie, 3 Boulevard Alexandre Fleming, 25000 Besancon, France

[2] CHRU Félix Guyon, Service de Rhumatologie, 97400 Saint-Denis, France

could use them in a diagnostic procedure of good quality and relevance. The diagnostic performance of biomarkers could be evaluated by the area under the corresponding receiver operating characteristic (ROC) curve analysis for example. Some studies suggest using procalcitonin (PCT) to guide us in the etiological diagnosis of arthritis, because of its great diagnostic performances.

PCT is a protein product by thyroid C cells, dependent of the *CALC-1* gene [6]. Almost all PCT products by thyroid neuroendocrine cells are converted into calcitonin [7]. So, except in clinical situations rare in rheumatologic practice like medullary thyroid or small-cell lung carcinoma, cardiac shock, and pancreatitis, after major trauma or surgery, PCT is virtually undetectable in blood. To note, PCT can increase in adult-onset Still's disease (AOSD), and ANCA-associated vasculitis, which can be seen in rheumatology [8]. In septic conditions, *CALC-1* gene expression is increased, and PCT production is not limited to thyroid C cells but is possible in the liver, lung, kidney, and adipose tissues [9], that is why there is a major PCT level rise. Interestingly, PCT level is not impacted in kidney failure [10], pathologic condition frequently observed in gout for example. It has already been shown that PCT is an interesting marker in different bacterial infections and that it is correlated not only with bacterial load on the one hand but also with the severity of the infection on the other hand [8].

Some studies were focused in patients affected by an osteoarticular infection [11]. PCT can be an interesting biomarker for daily practice in two nosological areas. First, it can be useful to make the difference between an infection and an inflammatory flare in patients with chronic rheumatism (inflammatory diseases, crystal-induced arthritis or osteoarthritis) and thus allow to introduce a suitable therapy (antibiotic therapy or, on the contrary, increase immunosuppressors/immunomodulators) and avoid unnecessary iatrogenesis. Second, it can guide the diagnostic approach in case of arthritis of undetermined etiology in all patients. We have chosen to focus on this second interest because of a greater frequency in daily practice in rheumatology. The aim of our study was to determine if serum PCT is a discriminating marker, useful for diagnosis in presence of arthritis of undetermined etiology, due to higher diagnostic performance than other inflammatory biomarkers. The secondary aims were to determine whether serum inflammatory markers (WBC, CRP, PCT) correlated to each other according to the etiology of arthritis and whether they differed according to the number of joints affected and the age of the patients.

Materials and methods

Study population

We made a prospective, monocentric study, from April 2016 to July 2018. Inclusion criteria were the following: (1) patient with synovial fluid obtained by aspiration of a joint or (2) patient with an arthritis showed by ultrasound or MRI if synovial fluid was not obtained. Exclusion criteria were the following: (1) etiologic treatment administration (colchicine, antibiotic therapy, non-steroidal anti-inflammatory drug, increasing corticosteroids therapy) during the week before the inclusion in the study, (2) non-joint infection before or concomitant with arthritis, (3) patient under 18 years old, and (4) patient affected by a vasculitis or a AOSD.

Patients were separated in five groups: gouty arthritis ("gout"), calcium pyrophosphate deposition arthritis ("CPPD"), osteoarthritis or post-traumatic arthritis ("mechanical"), chronic inflammatory rheumatic arthritis ("CIR"), and septic arthritis ("sepsis"). Patients were included in the gout group if they fulfilled the American College of Rheumatology (ACR) criteria [12]. Patients were included in the CPPD group if there were calcium pyrophosphate crystals in the synovial fluid and/or calcium pyrophosphate deposition in the X-ray of the affected joint [13]. Patients were included in the mechanical group if the white cells count in the synovial fluid was less than 1000 cells/mm^3. Patients were included in the CIR group if they fulfilled the Assessment of SpondyloArthritis international Society (ASAS) classification criteria for the axial [14] or peripheral [15] spondyloarthritis, if they fulfilled the ACR/European League Against Rheumatism (EULAR) for rheumatoid arthritis [16], or if they did fulfilled *stricto* sensu those criteria but were affected by repeated inflammatory synovial fluid arthritis without an other diagnostic. Patients were included in the sepsis group if they fulfill the Newman's criteria [17]: (a) organism isolated from joint, (b) organism isolated from elsewhere, or (c) no organism isolated but (i) histological or radiological evidence of infection or (ii) turbid fluid aspirated from joint with prior antibiotic therapy. No patient fulfilled the criteria for two or more pathologies in our study. For each group, age, sex, number of affected joint (1 = mono-arthritis, 2 or 3 = oligo-arthritis, 4 or more = poly-arthritis), and the site of arthritis were evaluated.

Biological analysis

Synovial fluid sample

Synovial fluid aspiration was made by a rheumatologist, and samples were sent to the laboratory immediately after the aspiration. Crystal identification was made using polarized light microscopy, and synovial fluid Gram strain was realized. In addition, synovial fluid cultures were performed, and a part was frozen at − 20° to carry out polymerase chain reaction (PCR) in case of negative culture with a high suspicion of septic arthritis.

Blood samples

Venous blood sample were collected the day of the synovial fluid aspiration, or lasted 24 h later, and before any treatment. Analyses were performed on fresh samples. CRP was measured in serum by using latex particle enhanced turbidimetric immunoassay (MULTIGENT CRP Vario, Abbott, Milan, Italy). The limit of quantification provided by the manufacturer was 0.2 mg/l. PCT was measured in serum by using immunofluorescent assay with Time Resolved Amplified Cryptate Emission (TRACE) technology (B·R·A·H·M·S PCT sensitive KRYPTOR, B·R·A·H·M·S GmbH, Hennigsdorf, Germany). The limit of quantification provided by the manufacturer was 0.02 μg/l.

Statistical analysis

Values are presented as means (SD). Data were analyzed by using GraphPad Prism (version 5.3) and SigmaStat (version 4.0) software. Continuous variables were compared using the Mann–Whitney test or by analysis of variance (ANOVA) with the Kruskal–Wallis test. Categorical variables were compared using the χ^2 test. The diagnostic performance of WBC, CRP, and PCT was evaluated by the area under the corresponding receiver operating characteristic (ROC) curve analysis. The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ration, and negative likelihood ratio were examined by a constructed 2×2 table or by analyzing of the ROC curve. The analysis of the relationship between two parameters was determined using the Spearman correlation coefficient. All of the tests were two-tailed, and a p value < 0.05 was considered as statically significant for all analyses.

Ethics statement

Since PCT evaluation is a regular procedure in front of sepsis in emergency room, no specific ethical procedure was required. Nevertheless, informed consent was obtained from each patient.

Results

Clinical patient characteristics

Ninety-eight patients were included in our study: 18 were included in the gout group, 26 in the CPPD group, 16 in the mechanical group, 18 in the CIR group, and 20 in the sepsis group. The clinical features are summarized in Table 1. As expected, the patients were significantly younger in the CIR group compared to the gout ($p < 0.05$) and CPPD ($p < 0.001$) groups. In the sepsis group, *Staphylococcus aureus* was isolated in six patients, *Streptococcus dysgalactiae* in five patients, *Streptococcus pneumoniae* in two patients, *Streptococcus pyogenes* in one patient, *Streptococcus oralis* in one patient, *Streptococcus gallolyticus* in one patient, *Escherichia coli* in one patient, *Pseudomonas aeruginosa* in one patient, *Neisseria meningitidis* in one patient, and no microorganism was isolated in one patient. On all the groups, 74 patients (75.5%) were affected by a mono-arthritis, 16 patients (16.3%) by an oligo-arthritis, and 8 patients (8.2%) by a poly-arthritis. In case of mono-arthritis, knee was affected in 50 patients (67.6%), hip in 8 patients (10.8%), elbow in 4 patients (5.4%), shoulder in 3 patients (4.1%), sacroiliac joint in 3 patients (4.1%), wrist in 2 patients (2.7%), ankle in 2 patients (2.7%), pubic symphysis in 1 patient (1.3%), and facet joint in 1 patient (1.3%).

Biological patient characteristics

Mean blood levels of WBC, CPR, and PCT in each group are summarized in Table 1 and in Fig. 1. As expected, the mean level of WBC was significantly higher in the sepsis group than in the mechanical group ($p < 0.05$). However, there was no difference between the other groups. About CRP level, it was higher in the sepsis group compared to the mechanical ($p < 0.0001$) and CIR ($p < 0.05$) groups. Moreover, it was significantly lower in the mechanical group compared to the gout ($p < 0.001$), CPPD ($p < 0.0001$), and CIR ($p < 0.05$) groups. Interestingly, CRP level was not different between the sepsis, gout, and CPPD groups. At least, PCT level was significantly higher in the sepsis group compared to the mechanical ($p < 0.0001$), CIR ($p < 0.0001$), and CPPD ($p < 0.001$) groups. More specifically in the sepsis group, PCT level in elderly patients (more than 75 years old) trended to be lower than that in younger patients (less than 75 years old), but the difference did not reach the significance (5.5 ± 8.8 ng/ml versus 10.9 ± 34.8 ng/ml, $p = 0.08$). Interestingly, as for CRP level, PCT level was not different between the sepsis and gout groups. In addition, it is important to note that p values were not impacted when we excluded the two patients with the higher PCT level in sepsis group.

Diagnostic performance of inflammatory biomarkers

Diagnostic performance of WBC, CRP, and PCT levels to diagnose a septic arthritis was evaluated by ROC curves (Fig. 2). The area under the ROC curve (AUROC) of WBC level was 0.69 (IC95% 0.55–0.83), that of CRP level was 0.82 (IC95% 0.73–0.91), and that of PCT level was 0.87 (IC95% 0.76–0.98). Since PCT levels are not different between the "sepsis" and "gout" groups, and given the positive correlation between PCT and CRP in gout, we have also made the ROC curve of WBC, CRP and PTC levels to diagnose a gouty arthritis, to avoid any doubts about PCT as a discriminatory biomarker in case of septic arthritis (Figure 2). The AUROC

Table 1 Clinical and biological characteristics of the population

Characteristics	Gout ($n = 18$)	CPPD ($n = 26$)	Mechanical ($n = 16$)	CIR ($n = 18$)	Sepsis ($n = 20$)
Age (years)	73.7 ± 12.1	74.3 ± 14.5	62.6 ± 18.4	47.4 ± 19.4	63.6 ± 22.4
Male gender, *n* (%)	14 (77.8)	10 (38.5)	11 (68.8)	8 (44.4)	8 (40.0)
Mono-arthritis, *n* (%)	7 (38.9)	22 (84.6)	16 (100)	12 (66.7)	17 (85.0)
Oligo-arthritis, *n* (%)	7 (38.9)	4 (15.4)	0 (0)	2 (11.1)	3 (15.0)
Poly-arthritis, *n* (%)	4 (22.2)	0 (0)	0 (0)	4 (22.2)	0 (0)
WBC (G/l)	8.8 ± 2.8	9.6 ± 3.0	7.6 ± 2.3	9.2 ± 3.4	12.8 ± 6.7
CRP (mg/l)	114.0 ± 110.6	131.3 ± 82.9	15.5 ± 24.6	93.3 ± 85.2	243.2 ± 150.4
PCT (ng/ml)	0.24 ± 0.23	0.24 ± 0.32	0.11 ± 0.06	0.15 ± 0.17	8.76 ± 27.16

Values are means (SD)

CPPD calcium pyrophosphate deposition arthritis, *CIR* chronic inflammatory rheumatic arthritis, *Mono-arthritis* one joint affected, *Oligo-arthritis* two or three joints affected, *Poly-arthritis* four or more joints affected, *WBC* white blood cells, *CRP* C-reactive protein, *PCT* procalcitonin

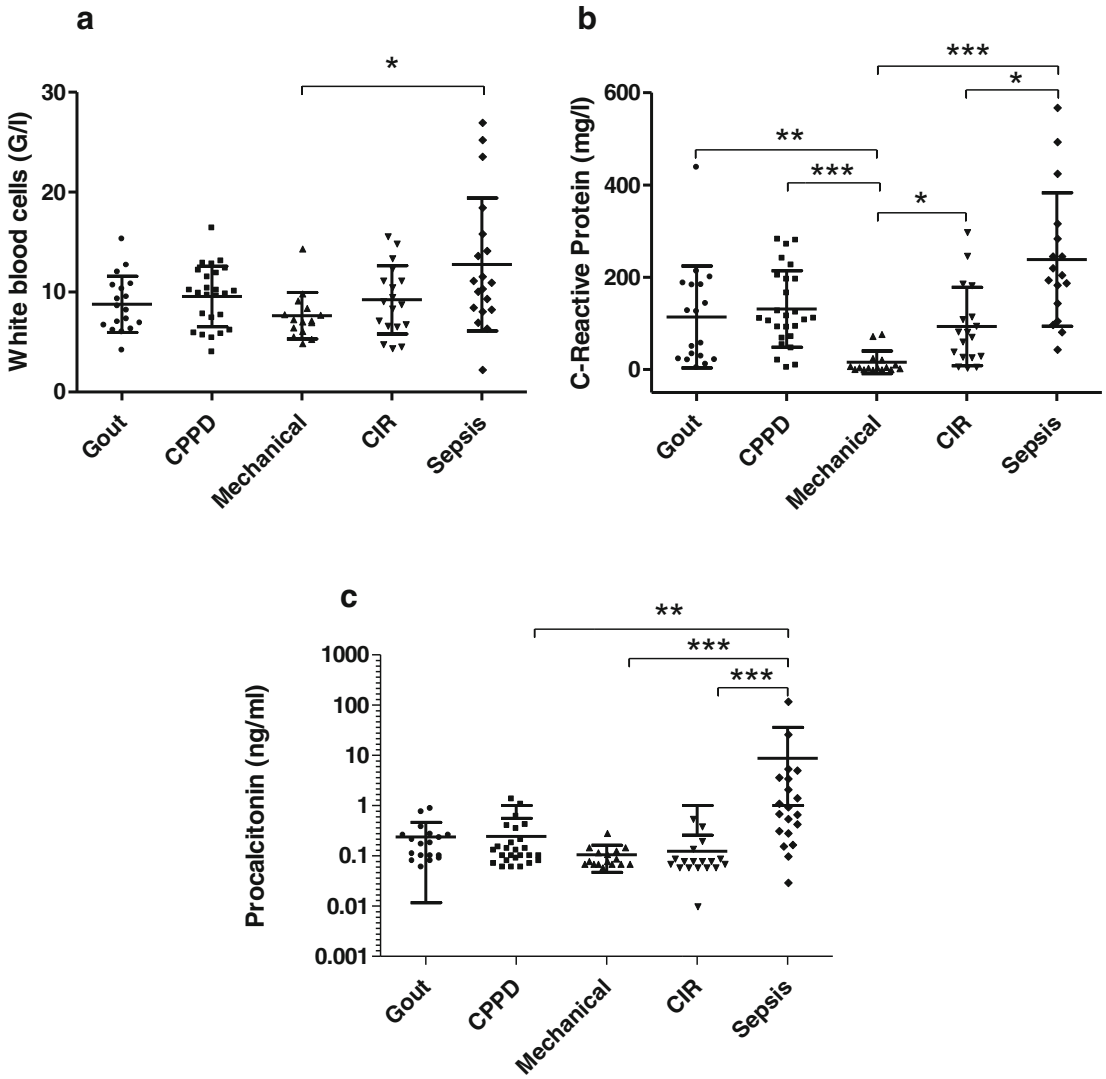

Fig. 1 Biological characteristics of patients. Mean (SD) levels of white blood cells (**a**), C-reactive protein (**b**), and procalcitonin (**c**) in groups "gout" ($n = 18$), "CPPD" ($n = 26$), "mechanical" ($n = 16$), "CIR" ($n = 18$), and "sepsis" ($n = 20$). To note, a logarithmic scale was used in **c**. CPPD calcium pyrophosphate deposition arthritis, CIR chronic inflammatory rheumatic arthritis. *$p < 0.05$; **$p < 0.001$; ***$p < 0.0001$. Statistical analysis: ANOVA (Kruskal–Wallis test). Only significant differences are shown

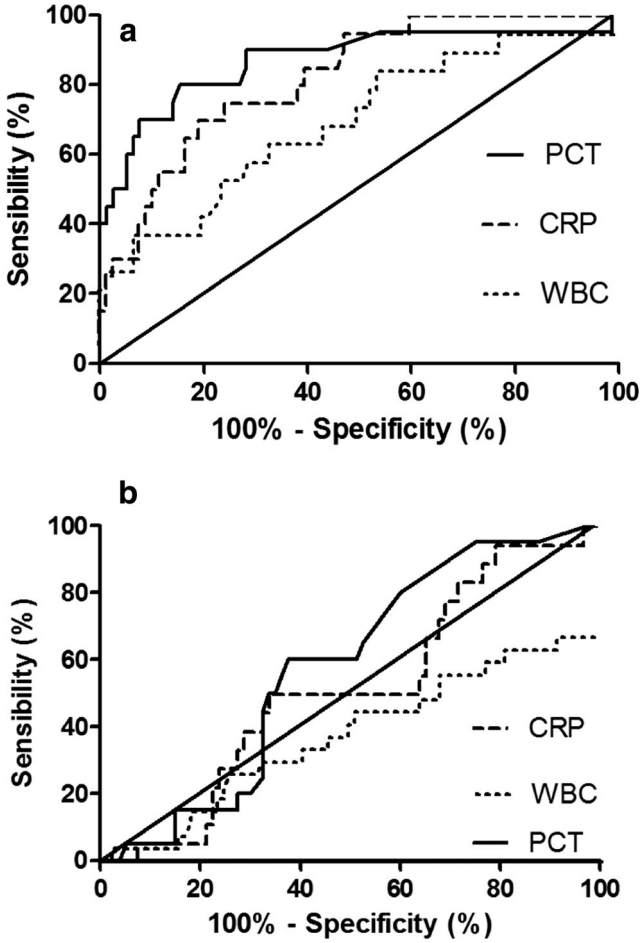

Fig. 2 (**a**) ROC curves of white blood cells, C-Reactive Protein and procalcitonin levels to diagnose a septic arthritis. Sepsis group: $n = 20$, Non-sepsis group: $n = 78$. (**b**) ROC curves of white blood cells, C-Reactive Protein and procalcitonin levels to diagnose a gouty arthritis. Gout group: $n = 18$, Non-gout group: $n = 80$. PCT procalcitonin, CRP C-reactive protein, WBC white blood cells

of WBC level was 0.56 (IC95% 0.42–0.70), that of CRP level was 0.52 (IC95% 0.38-0.65), and that of PCT level was 0.58 (IC95% 0.46–0.70) to diagnose a gouty arthritis.

About PCT performances, the sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio to diagnose a septic arthritis for a cutoff of 0.2 and 0.5 ng/ml are recapitulated in Table 2.

Table 2 Diagnosis performances of procalcitonin with cutoff of 0.2 and 0.5 ng/ml

	Sensibility	Specificity	PPV	NPV	LR+	LR−
Cutoff of 0.2 ng/ml	80.0	74.4	44.4	93.5	3.1	0.3
Cutoff of 0.5 ng/ml	65.0	91.0	65.0	91.0	7.2	0.4

Diagnostic performance of procalcitonin level to distinguish a septic arthritis from a non-septic arthritis for a cutoff of 0.2 and 0.5 ng/ml

PPV positive predictive value, *NPV* negative predictive value, *LR+* positive likelihood ratio, *LR−* negative likelihood ratio

Correlations between inflammatory biomarkers

We studied the correlations between the inflammatory biomarkers, according to the different pathologies (Table 3). There was a correlation between CRP and PCT levels when the sepsis group was excluded ($r = 0.453$, $p < 0.0001$) or not ($r = 0.577$, $p < 0.0001$) to the all other groups of arthritis. More specifically, PCT level was correlated to CRP level only in the gout ($r = 0.618$, $p < 0.05$) and sepsis ($r = 0.505$, $p < 0.05$) groups. Conversely, there was no correlation between WBC and PCT levels.

Impact of the number of affected joint and the age of patient on inflammatory biomarkers

We wanted to know if the number of affected joint (Fig. 3) and the age of patient could impact the different inflammatory biomarkers, whatever the cause of the arthritis, mistakenly evoking a septic involvement if the levels of these biomarkers rise. When excluding the sepsis group, WBC levels were not different if there were mono-, oligo-, or poly-arthritis. Conversely, CRP and PCT levels, which are positively correlated, were both significantly higher in poly-articular than in mono-articular arthritis ($p < 0.05$).

Moreover, when excluding the sepsis group, there was a positive correlation between PCT level and the age of patient ($r = 0.358$, $p < 0.001$), PCT level increasing in elderly patients.

Discussion

Our study has shown that serum PCT level could be an interesting biomarker to guide diagnosis in case of arthritis without clearly defined etiology, due to higher diagnostic performances than other inflammatory biomarkers used in daily practice. Our results are consistent with those of two previous meta-analysis [11, 18]. In our study, we observed an AUROC for PCT of 0.87, a sensibility of 65.0%, a specificity of 91.0%, a positive predictive value of 65.0%, a negative predictive value of 91.0%, a positive likelihood ratio of 7.2, and a negative likelihood ratio of 0.4. The meta-analysis of Shen et al. [18] and of Zhao et al. [11] has included almost the same studies and especially two studies with a pediatric population, in contrary to us. Nevertheless, the diagnosis performances of PCT, when taking into account only to studies focus on the cutoff of 0.5 ng/ml, are very close to our, respectively, AUROC of 0.66 and 0.78, sensibility of 46.0% and 49.0%, specificity of 91.0% and 96.0%, positive likelihood ratio of 4.84 and 13.59, and a negative likelihood ratio of 0.6 and 0.53. To note, odds ratio for the septic arthritis diagnosis of PCT is

Table 3 Correlation between procalcitonin, with blood cells and C-reactive protein levels in different pathologies

	Correlations PCT/WCB	Correlations PCT/CRP
Gout ($n = 18$)	$r = 0.046$ NS	$r = 0.618$*
CPPD ($n = 26$)	$r = -0.062$ NS	$r = 0.345$ NS
Mechanical ($n = 16$)	$r = 0.168$ NS	$r = 0.371$ NS
CIR ($n = 18$)	$r = -0.072$ NS	$r = 0.383$ NS
Sepsis ($n = 20$)	$r = 0.188$ NS	$r = 0.505$*
Total without sepsis ($n = 78$)	$r = 0.034$ NS	$r = 0.453$***
Total ($n = 98$)	$r = 0.175$ NS	$r = 0.577$***

Statistical analysis: Spearman coefficient

CPPD calcium pyrophosphate deposition arthritis, *CIR* chronic inflammatory rheumatic arthritis, *PCT* procalcitonin, *WBC* white blood cells, *CRP* C-reactive protein, *NS* non-significant

*$p < 0.05$; ***$p < 0.0001$

considerably higher in European studies than in non-European studies: 41.14 (IC95% 10.93–154.88) versus 15.73 (IC95% 6.38–38.78) [11], with some diagnosis performances slightly closer to ours (AUROC of 0.90, sensibility of 56.0%, specificity of 97.0%, positive likelihood ratio of 18.6, negative likelihood ratio of 0.45).

Various cutoff of PCT are used to diagnose septic arthritis. The more used cutoff is 0.5 ng/ml. Some studies propose to decrease the cutoff to 0.2–0.3 ng/ml [8, 11, 18] or, on the contrary, to increase this cutoff to 0.66 [19]. We think that the cutoff of 0.5 ng/ml is a good compromise between the two others proposed in the literature. A biological criterion to help for diagnosis must be specific enough to not induce a useless iatrogeny (unnecessary antibiotic therapy in this case), what is not possible with the cutoff of 0.2 ng/ml with a specificity of 74.4% only. Likewise, increasing the cutoff to 0.66 ng/ml can improve specificity compared to the cutoff of 0.5 ng/ml (94.9% versus 91.0%), but the sensibility will substantially decrease (60.0% versus 65.0%), making the daily practical use of this biomarker less useful.

In some cases, PCT level can increase without a septic cause, making the use of cutoff of 0.5 ng/ml subject to interpretation.

First, in some inflammatory diseases like AOSD [20, 21], ANCA-associated vasculitis [20, 22–24] or Kawasaki disease [25], PCT level can rise even if there is no infection. In contrast, another study has objectified no increased PCT levels in ANCA-associated vasculitis [26]. Some authors recommended to use the cutoff of 1.4 and 1.0 ng/ml in ANCA-associated vasculitis and AOSD respectively [8]. That is why we did not included patients affected by these diseases in our study.

Second, we have shown that the number of affected joint could increase PCT levels in case of non-septic arthritis. In our study, the PCT level was significantly higher in poly-articular than in mono-articular arthritis. A study confirm a trend to a correlation, but without significance, between the PCT level and the Disease Activity Score 28 and the Ankylosing Spondylitis Disease Activity Score [27], even if these scores are composites, so not taking into account only of the number of affected joint. To note, other several studies have demonstrated a correlation between the PCT level and the severity of sepsis [8], but it was not studies about septic arthritis.

Third, we also have shown that the age of patients could increase the PCT level in non-septic arthritis. To our knowledge, this fact was never described in literature. Conversely, in "septic" group, the oldest patients (more than 75 years old) trend to have lower PCT levels than those younger (less than 75 years old). This difference was not significant, probably because of a low number of patients. Nevertheless, in studies including specifically elderly patients, authors concluded that PCT levels were lower in elderly patients in case of sepsis and that PCT sensibility was lower [28–30]. However, these studies were not conducted on patients with septic arthritis specifically. The different course of PCT level according to different clinical situations shows us that other studies are necessary to decipher the precise physiopathological mechanisms underlying the production of this protein, especially in particular populations such as the elderly patients.

Fourth, data are contrasting for gouty arthritis. Zhang et al. did not observed any differences in PCT levels between patients with fever and a flare of chronic gouty arthritis and those with a infection [31]. Conversely, Choi et al. have shown that PCT was a good biomarker to distinguish a gouty from a septic arthritis [32]. However, in these studies, only approximately 3% of the patients in the "infection" group were affected by a septic arthritis, and the other patients were affected by an infection of another organ. Interestingly, Liu et al. have observed that PCT levels were higher in gouty patient who presented tophus compared to those who did not, although there is no correlation between PCT and uric acid levels [27]. Moreover, they observed a higher PCT level in the gout group compared to the rheumatoid arthritis and ankylosing spondylitis groups. These results are not congruent with ours, but we have included less patients in the CIR group than in the study of Liu et al. Anyhow, in our study, there was no difference in mean PCT

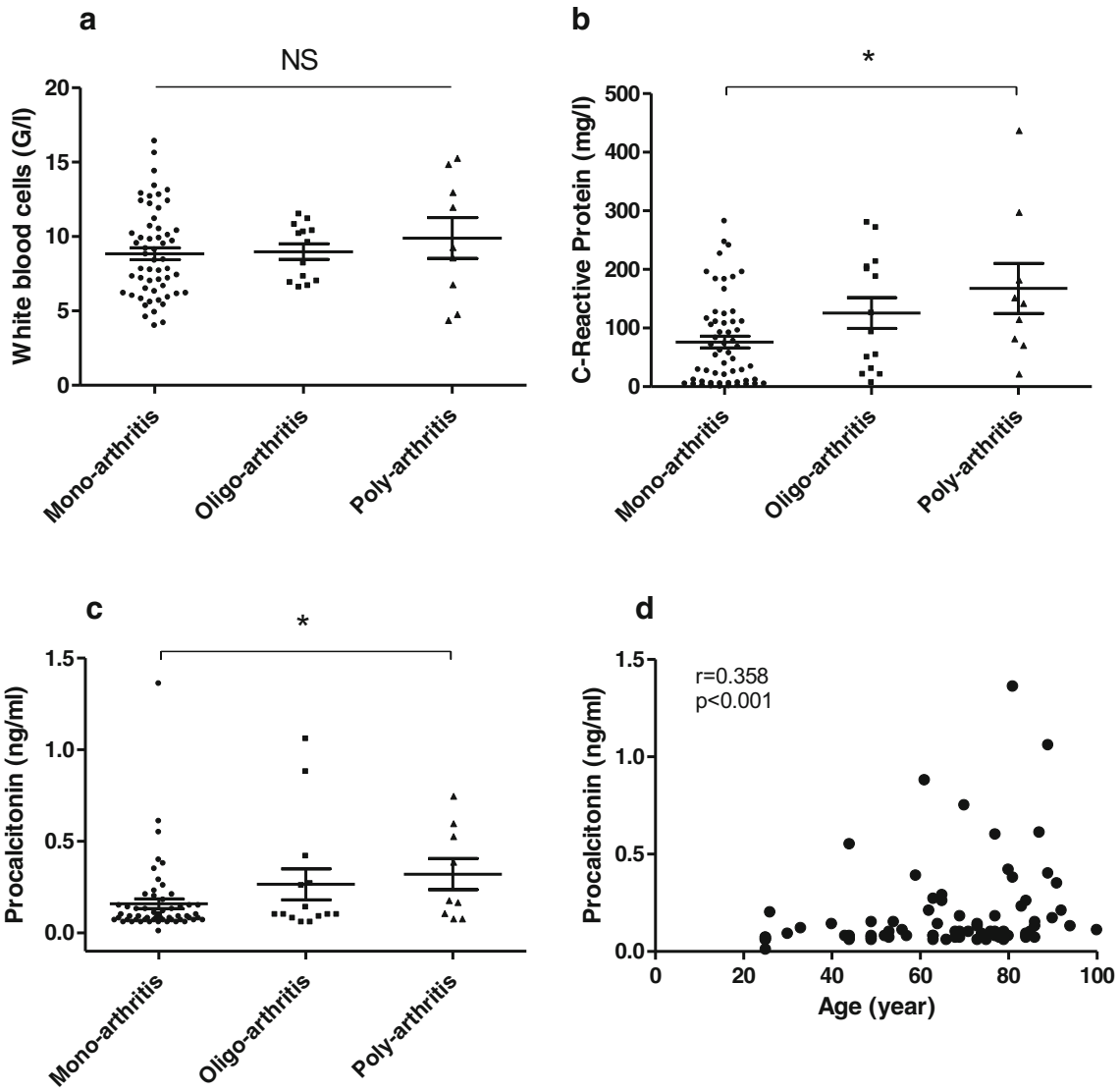

Fig. 3 Impact of the number of affected joint and the age on inflammatory biomarkers without septic arthritis. (**a**) Levels of white blood cells in mono-arthritis ($n = 56$), oligo-arthritis ($n = 13$), and poly-arthritis ($n = 9$). (**b**) Levels of C-reactive protein in mono-arthritis ($n = 57$), oligo-arthritis ($n = 14$), and poly-arthritis ($n = 9$). (**c**) Levels of de procalcitonin in mono-arthritis ($n = 57$), oligo-arthritis ($n = 13$), and poly-arthritis ($n = 9$). (**d**) Levels of procalcitonin according to age. NS non-significant; *$p < 0.05$. Statistical analysis: ANOVA (Kruskal–Wallis test) and Spearman's coefficient.

levels between gouty and septic arthritis. This can possibly be explained by the fact that interleukin-1 is a cytokine particularly involved in gout [33, 34]. However, PCT production not only is directly induced by microbial endotoxins but can also be indirectly induced not only by many pro-inflammatory cytokines such as interleukin-1 but also by TNFα or interleukin-6 [7, 35, 36]. This may partly explain the increased PCT level in gout, especially with tophus, but does not explain why it does not rise in other pathologies such as rheumatoid arthritis where such cytokines are also involved and even constitute major therapeutic targets.

Our study was limited to evaluate the interest of PCT in serum, this marker being easily dosed in routine and the results being fast. Other works were designed to evaluate the diagnostic performance of PCT in synovial fluid [37–41]. All of these studies conclude that synovial PCT level is higher in septic groups than in "non-septic" groups, except for that of Martinot et al. where the difference does not reach the significance. The study of Talebi-Taher et al. has evaluated an AUROC of 0.65 only, finding a limited interest in this biomarker, while that of Saeed et al. has evaluated an AUROC of 0.82. Lastly, Wang et al. have even concluded to a better diagnosis performance synovial PCT compared to serum PCT levels (AUROC respectively of 0.95 and 0.76).

One of the limitations of our study is the small number of patient, but relatively similar to that of other studies in the literature, despite a long period of inclusion. The small number of patient can make the subgroup analyses open to

interpretation. This can be explained by strict inclusion criteria, like the exclusion of patients who have previously received etiological treatment. Indeed, the majority of patients with arthritis often consult first-line their general practitioner who initiates treatment with antibiotic, colchicine, or anti-inflammatory. It is also not uncommon for patients with chronic rheumatism to self-medicate with colchicine in case of crystals-induced arthritis or with anti-inflammatory drugs in case of CIR. All these patients were therefore not included in the study. Thus, the population in our study does not "closely" reflect the patients in daily practice, but we wanted to avoid confounding factors on PCT levels, although corticosteroids do not seem to affect PCT level, unlike CRP level [42]. Moreover, patients with a concomitant infection were also excluded, while it is known that a sepsis can lead to a crystal-induced arthritis for example. This situation is also common in daily practice, but we wanted to asses specifically the impact of arthritis on PCT level, not the impact of another causes of sepsis, again to avoid confounding factors. Another limitation is the monocentric character. We deliberately chose to restrict inclusions in a single university hospital center so that the different methods of dosing CRP and PCT do not affect the results [11]. We also have included patients with osteoarthritis in which the suspicion of septic arthritis was low. This could increase artificially the diagnostic performances of PCT level. Lastly, the use of Newman's criteria [17] to diagnose a septic arthritis may be a limitation. Indeed, these criteria make it possible to diagnose a septic arthritis without isolating a germ. This was the case for one of our patients only. Nevertheless, for this patient, there was an abscess on MRI and we observed a clear clinical and biological improvement after the introduction of probabilistic antibiotic therapy. Similarly, another patient did not benefit from synovial fluid aspiration because of the positivity of blood cultures, an abscess on MRI, and a clinical and biological improvement after the introduction of an adapted antibiotic therapy. These two patients had a unilateral infectious sacroiliitis.

To conclude, serum PCT is an interesting biomarker to help the rheumatologist in the diagnostic and therapeutic management of a patient affected by arthritis, with higher diagnostic performance than other serum inflammatory markers. It can be used in daily practice, and the result is obtained quickly. On the other hand, it is only an additional help, a part of the diagnostic procedure. In no way, it should supplant a clinical examination of good quality. Similarly, although its diagnostic performance is higher than other biomarkers also daily used (WBC, CRP), its balance cost financial/diagnostic performance must be weighed wisely in the current economic context.

Acknowledgments The authors thank Mr. Marc Puyraveau, statistician, for his help about statistical analyses.

Compliance with ethical standards

Since PCT evaluation is a regular procedure in front of sepsis in emergency room, no specific ethical procedure was required. Nevertheless, informed consent was obtained from each patient.

Disclosures None.

References

1. Sharff KA, Richards EP, Townes JM (2013) Clinical management of septic arthritis. Curr Rheumatol Rep 15:332. https://doi.org/10.1007/s11926-013-0332-4
2. Ferrand J, El Samad Y, Brunschweiler B et al (2016) Morbimortality in adult patients with septic arthritis: a three-year hospital-based study. BMC Infect Dis 16:239. https://doi.org/10.1186/s12879-016-1540-0
3. Margaretten ME, Kohlwes J, Moore D, Bent S (2007) Does this adult patient have septic arthritis? JAMA 297:1478–1488. https://doi.org/10.1001/jama.297.13.1478
4. Mathew AJ, Ravindran V (2014) Infections and arthritis. Best Pract Res Clin Rheumatol 28:935–959. https://doi.org/10.1016/j.berh.2015.04.009
5. Kim H, Kim J, Ihm C (2010) The usefulness of multiplex PCR for the identification of bacteria in joint infection. J Clin Lab Anal 24:175–181. https://doi.org/10.1002/jcla.20384
6. Whicher J, Bienvenu J, Monneret G (2001) Procalcitonin as an acute phase marker. Ann Clin Biochem 38:483–493. https://doi.org/10.1177/000456320103800505
7. Maruna P, Nedelníková K, Gürlich R (2000) Physiology and genetics of procalcitonin. Physiol Res 49(Suppl 1):S57–S61
8. Shaikh MM, Hermans LE, van Laar JM (2015) Is serum procalcitonin measurement a useful addition to a rheumatologist's repertoire? A review of its diagnostic role in systemic inflammatory diseases and joint infections. Rheumatol Oxf Engl 54:231–240. https://doi.org/10.1093/rheumatology/keu416
9. Linscheid P, Seboek D, Nylen ES, Langer I, Schlatter M, Becker KL, Keller U, Müller B (2003) In vitro and in vivo calcitonin I gene expression in parenchymal cells: a novel product of human adipose tissue. Endocrinology 144:5578–5584. https://doi.org/10.1210/en.2003-0854
10. Meisner M, Lohs T, Huettemann E, Schmidt J, Hueller M, Reinhart K (2001) The plasma elimination rate and urinary secretion of procalcitonin in patients with normal and impaired renal function. Eur J Anaesthesiol 18:79–87
11. Zhao J, Zhang S, Zhang L, Dong X, Li J, Wang Y, Yao Y (2017) Serum procalcitonin levels as a diagnostic marker for septic arthritis: a meta-analysis. Am J Emerg Med 35:1166–1171. https://doi.org/10.1016/j.ajem.2017.06.014
12. Wallace SL, Robinson H, Masi AT, Decker JL, Mccarty DJ, Yü T'F (1977) Preliminary criteria for the classification of the acute arthritis of primary gout. Arthritis Rheum 20:895–900
13. Zhang W, Doherty M, Bardin T, Barskova V, Guerne PA, Jansen TL, Leeb BF, Perez-Ruiz F, Pimentao J, Punzi L, Richette P, Sivera F, Uhlig T, Watt I, Pascual E (2011) European League Against Rheumatism recommendations for calcium pyrophosphate deposition. Part I: terminology and diagnosis. Ann Rheum Dis 70:563–570. https://doi.org/10.1136/ard.2010.139105
14. Rudwaleit M, Landewé R, van der Heijde D et al (2009) The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including

uncertainty appraisal. Ann Rheum Dis 68:770–776. https://doi.org/10.1136/ard.2009.108217
15. Rudwaleit M, van der Heijde D, Landewé R et al (2011) The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis 70:25–31. https://doi.org/10.1136/ard.2010.133645
16. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MD, Combe B, Costenbader KH, Dougados M, Emery P, Ferraccioli G, Hazes JM, Hobbs K, Huizinga TW, Kavanaugh A, Kay J, Kvien TK, Laing T, Mease P, Menard HA, Moreland LW, Naden RL, Pincus T, Smolen JS, Stanislawska-Biernat E, Symmons D, Tak PP, Upchurch KS, Vencovsky J, Wolfe F, Hawker G (2010) 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 69:1580–1588. https://doi.org/10.1136/ard.2010.138461
17. Newman JH (1976) Review of septic arthritis throughout the antibiotic era. Ann Rheum Dis 35:198–205
18. Shen C-J, Wu M-S, Lin K-H, Lin WL, Chen HC, Wu JY, Lee MCH, Lee CC (2013) The use of procalcitonin in the diagnosis of bone and joint infection: a systemic review and meta-analysis. Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol 32:807–814. https://doi.org/10.1007/s10096-012-1812-6
19. Paosong S, Narongroeknawin P, Pakchotanon R et al (2015) Serum procalcitonin as a diagnostic aid in patients with acute bacterial septic arthritis. Int J Rheum Dis 18:352–359. https://doi.org/10.1111/1756-185X.12496
20. Scirè CA, Cavagna L, Perotti C, Bruschi E, Caporali R, Montecucco C (2006) Diagnostic value of procalcitonin measurement in febrile patients with systemic autoimmune diseases. Clin Exp Rheumatol 24:123–128
21. Chen D-Y, Chen Y-M, Ho W-L, Chen HH, Shen GH, Lan JL (2009) Diagnostic value of procalcitonin for differentiation between bacterial infection and non-infectious inflammation in febrile patients with active adult-onset Still's disease. Ann Rheum Dis 68:1074–1075. https://doi.org/10.1136/ard.2008.098335
22. Schwenger V, Sis J, Breitbart A, Andrassy K (1998) CRP levels in autoimmune disease can be specified by measurement of procalcitonin. Infection 26:274–276
23. Moosig F, Csernok E, Reinhold-Keller E, Schmitt W, Gross WL (1998) Elevated procalcitonin levels in active Wegener's granulomatosis. J Rheumatol 25:1531–1533
24. Zycinska K, Wardyn KA, Zielonka TM et al (2008) Procalcitonin as an indicator of systemic response to infection in active pulmonary Wegener's granulomacytosis. J Physiol Pharmacol Off J Pol Physiol Soc 59(Suppl 6):839–844
25. Okada Y, Minakami H, Tomomasa T et al (2004) Serum procalcitonin concentration in patients with Kawasaki disease. J Infect 48:199–205
26. Herrmann K, Schinke S, Csernok E, Moosig F, Holle JU (2015) Diagnostic value of procalcitonin in ANCA-associated vasculitis (AAV) to differentiate between disease activity, infection and drug hypersensitivity. Open Rheumatol J 9:71–76. https://doi.org/10.2174/1874312901409010071
27. Liu W, Sigdel KR, Wang Y, Su Q, Huang Y, Zhang YL, Chen J, Duan L, Shi G (2015) High level serum procalcitonin associated gouty arthritis susceptibility: from a southern Chinese Han population. PLoS One 10:e0132855. https://doi.org/10.1371/journal.pone.0132855
28. Steichen O, Bouvard E, Grateau G, Bailleul S, Capeau J, Lefèvre G (2009) Diagnostic value of procalcitonin in acutely hospitalized elderly patients. Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol 28:1471–1476. https://doi.org/10.1007/s10096-009-0807-4
29. Caterino JM, Scheatzle MD, Forbes ML, D'Antonio JA (2004) Bacteremic elder emergency department patients: procalcitonin and white count. Acad Emerg Med Off J Soc Acad Emerg Med 11:393–396
30. Zhang H, Wang X, Zhang Q, Xia Y, Liu D (2017) Comparison of procalcitonin and high-sensitivity C-reactive protein for the diagnosis of sepsis and septic shock in the oldest old patients. BMC Geriatr 17:173. https://doi.org/10.1186/s12877-017-0566-5
31. Zhang J, Liu J, Long L, Zhou Q, Cheng J, Zhou B (2015) Value of procalcitonin measurement in the diagnosis of bacterial infections in patients with fever and flare of chronic gouty arthritis. Zhonghua Yi Xue Za Zhi 95:2556–2559
32. Choi ST, Song JS (2016) Serum procalcitonin as a useful serologic marker for differential diagnosis between acute gouty attack and bacterial infection. Yonsei Med J 57:1139–1144. https://doi.org/10.3349/ymj.2016.57.5.1139
33. Martinon F (2010) Mechanisms of uric acid crystal-mediated autoinflammation. Immunol Rev 233:218–232. https://doi.org/10.1111/j.0105-2896.2009.00860.x
34. Dalbeth N, Haskard DO (2005) Mechanisms of inflammation in gout. Rheumatol Oxf Engl 44:1090–1096. https://doi.org/10.1093/rheumatology/keh640
35. Becker KL, Nylén ES, White JC, Müller B, Snider RH Jr (2004) Clinical review 167: procalcitonin and the calcitonin gene family of peptides in inflammation, infection, and sepsis: a journey from calcitonin back to its precursors. J Clin Endocrinol Metab 89:1512–1525. https://doi.org/10.1210/jc.2002-021444
36. Kettelhack C, Hohenberger P, Schulze G, Kilpert B, Schlag PM (2000) Induction of systemic serum procalcitonin and cardiocirculatory reactions after isolated limb perfusion with recombinant human tumor necrosis factor-alpha and melphalan. Crit Care Med 28:1040–1046
37. Talebi-Taher M, Shirani F, Nikanjam N, Shekarabi M (2013) Septic versus inflammatory arthritis: discriminating the ability of serum inflammatory markers. Rheumatol Int 33:319–324. https://doi.org/10.1007/s00296-012-2363-y
38. Streit G, Alber D, Toubin MM, Toussirot E, Wendling D (2008) Procalcitonin, C-reactive protein, and complement-3a assays in synovial fluid for diagnosing septic arthritis: preliminary results. Jt Bone Spine Rev Rhum 75:238–239. https://doi.org/10.1016/j.jbspin.2007.07.012
39. Saeed K, Dryden M, Sitjar A, White G (2013) Measuring synovial fluid procalcitonin levels in distinguishing cases of septic arthritis, including prosthetic joints, from other causes of arthritis and aseptic loosening. Infection 41:845–849. https://doi.org/10.1007/s15010-013-0467-2
40. Wang C, Zhong DA, Liao Q et al (2014) Procalcitonin levels in fresh serum and fresh synovial fluid for the differential diagnosis of knee septic arthritis from rheumatoid arthritis, osteoarthritis and gouty arthritis. Exp Ther Med 8:1075–1080. https://doi.org/10.3892/etm.2014.1870
41. Martinot M, Sordet C, Soubrier M, Puéchal X, Saraux A, Lioté F, Guggenbuhl P, Lègre V, Jaulhac B, Maillefert JF, Zeisel M, Coumaros G, Sibilia J (2005) Diagnostic value of serum and synovial procalcitonin in acute arthritis: a prospective study of 42 patients. Clin Exp Rheumatol 23:303–310
42. Christ-Crain M, Müller B (2005) Procalcitonin in bacterial infections–hype, hope, more or less? Swiss Med Wkly 135:451–460. https://doi.org/2005/31/smw-11169