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Could serum procalcitonin play a role in an emergency setting for patients with pyogenic spondylodiscitis?

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Abstract. – OBJECTIVE: Spinal infections, represent quite rare but often severe conditions. However, due to symptoms' non-specificity and the lack of specific laboratory tests, diagnosis is often delayed with serious consequences for the patient's outcomes. The present investigation aimed at evaluating the role of procalcitonin (PCT) and other clinical features on the risk stratification and the clinical outcomes in spondylodiscitis patients treated in our Emergency Department.

PATIENTS AND METHODS: The present investigation represents a single-center retrospective study. Clinical records of consecutive patients admitted to our Emergency Department from 1 January 2015 to 31 March 2021 were evaluated and patients with spondylodiscitis diagnosis in this period were recruited. Our primary outcome was the degree of autonomy of patients following the acute event. Our secondary outcome was the resolution of the infection.

RESULTS: In the study period, a total of 345 patients were evaluated. Among these, 165 met the inclusion criteria, and constituted the study cohort. Concerning the primary outcome, we observed that the most significant predictive factors for being non-autonomous were elevated serum creatinine (> 1.05 mg/dl), Blood Urea Nitrogen (BUN) > 23 mg/dl, Lactate dehydrogenase > 228 U/L, PCT > 0.11 ng/mL. Patients with higher PCT (PCT > 0.11 ng/mL) and higher BUN (BUN > 23 mg/dl) had higher odds of infection persistence (the Odd Ratio, OR, were respectively 3.78 for PCT and 3.14 for BUN).

CONCLUSIONS: PCT assay may play a role in diagnosing spondylodiscitis in an emergency setting. A PCT value > 0.11 ng/mL should be considered as a red flag, a predictor of worse clinical outcomes and persistence of infection.

Key Words:
Procalcitonin, Spondylodiscitis, Vertebral Osteomyelitis, Spinal Infections, Low back pain.

Introduction

Spinal infections, such as Spondylodiscitis (SD) and Vertebral Osteomyelitis (VO), represent quite rare but often severe conditions in the emergency department (ED)[1]. SD was defined as an infection of the intervertebral disc, while when the infection involves the contiguous vertebral end plates a VO takes place[2]. The most frequent pathogens that cause pyogenic SD are Gram-positive and Gram-negative (principally *S. aureus* and *Enterobacteriaceae*)[3]. Most patients affected by SD have severe back pain with or without fever; neurological deficits could occur in cases of epidural spinal abscess with radicular or medullary compression[4]. Neutrophilic leukocytosis and elevation of inflammation parameters, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are common; procalcitonin (PCT) dosage is not routinely performed in the SD diagnostic set up but in recent years some studies[5] have reported its role. However, due to symptoms' non-specificity and the lack of specific laboratory tests, diagnosis is often delayed with serious consequences for the patient's outcome[6,7]. Spinal Magnetic Resonance Images (MRI) with hyperintense signal in T2 weighted, Short Tau Inversion Recovery (STIR), or T1 weighted gadolinium contrast-enhanced

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sequences represent the best radiological method to suspect an SD, even if the images must be evaluated by an expert neuroradiologist for the possibility of false positives caused by degenerative diseases of the intervertebral disc, post-traumatic epidural hematomas or neoplastic localizations[8,9].

Generally, SD or VO are conservatively managed with specific antibiotic therapy and immobilization with a rigid brace, but sometimes surgical treatment is required. However, solid management guidelines are still missing in the literature[4].

The present investigation aimed at performing a retrospective analysis of patients with suspect SD or VO diagnosed in the ED, to evaluate the role of PCT and other clinical features on the risk stratification and the clinical outcomes.

Material and Methods

Study Setting and Design

The present investigation represents a single-center retrospective study conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[10]. Clinical records of consecutive patients admitted to our Emergency Department (ED) from 1 January 2015 to 31 March 2021 were evaluated and patients with a diagnosis of SD or VO in this period were recruited.

Inclusion and Exclusion Criteria

All patients with a diagnosis of pyogenic SD or VO treated during the study period were potentially included in the study. Were excluded: patients with malignancy, patients with known immunological deficits, patients with tuberculous or mycotic infection, and pregnant women.

Outcomes

Our primary outcome was the degree of autonomy of patients following the acute event measured through instrumental activities daily living (IADL) and Activity of Daily Living (ADL) scales[11]. Our secondary outcome was the resolution of the infection or its persistence. The infection resolution for a given patient was defined by the inflammation index normalization, the presence of radiological fusion of the involved level, and the absence of pain. The absence of one or more of the above-mentioned criteria was considered as persistence of infection.

Institutional Database and Data Collection

All patients with a diagnosis of SD or VO treated in the ED of our institution, were managed using a standardized data collection system. The following demographic and clinical data were collected, reviewed, and tabulated: age, gender, clinical history, Charlson Comorbidity Index (CCI), diabetes and chronic kidney disease, neurological status (Frankel grade), fever, pain, level involved, and need for hospitalization.

The following laboratory tests were recorded: Hemoglobin (Hb) value, White Blood Cells count (WBC), CRP (at the first access and 7 days after the first ED dosage), PCT (at the first access and 7 days after the first ED dosage), lactate-dehydrogenase (LDH), glycemia, creatinine.

We also recorded any interventional diagnostic or therapeutic procedure (percutaneous or open biopsy, neurological decompression, or spinal fusion).

Patients' Management

During the first access to ED, patients with a suspected diagnosis of SD or VO underwent the execution of 2 pairs of blood cultures, blood tests, and joint evaluation with a spinal surgeon and infectious disease specialist. Spinal radiographs and gadolinium contrast-enhanced MRI are usually done to confirm the diagnosis and establish the level of infection. In patients who cannot perform MRI, a Computer Tomography (CT) scan allows for indirect signs of infection, such as erosion of the vertebral plates or the presence of epidural abscesses.

If blood cultures resulted negative, an attempt at etiological diagnosis by CT-guided percutaneous biopsy was performed. Patients with negative percutaneous biopsy or with neurological deficits were candidates for open biopsy surgery and neurological decompression. Patients who presented a positive blood culture or in whom it was possible to make an etiological diagnosis through biopsy, were treated with specific antibiotic therapy. Patients without an etiological diagnosis were instead treated with broad-spectrum empirical therapy.

Clinical and Radiological Follow-Up

As the standard of care in our institution, each patient with SD or VO was systematically clinically, laboratory (kidney and hepatic function, WBC, CRP), and radiologically (Traditional Spinal X-ray and Gadolinium contrast-enhanced MRI) monitored at 1, 3, 6 and 12 months after

diagnosis and then once a year. All patients were treated with antibiotic therapy for a variable period according to the indications of an infectious disease specialist. Patients were interviewed to assess the patient's outcomes after the treatment. IADL and ADL scales were used. We divided the patients into 3 groups according to the summary score recorded after 1 year of follow-up. A score ranging from 0 to 2 was considered completely dependent; all patients with a summary score ranging from 3 to 6 were considered partially dependent; while patients who presented a summary score ranging from 7 to 8 were considered completely independent[11].

Statistical Analysis

Continuous variables are reported as median [interquartile range]. Categorical variables are reported as absolute numbers (%). Statistical univariate comparison for primary and secondary outcomes was assessed by Mann-Whitney U test for continuous variables, and Chi-square test (with Fisher's test, if appropriate) for categorical variables. Significant factors in the univariate analysis were entered in a multivariate logistic regression model to identify independent predictors of prespecified outcomes.

To improve the model accuracy and the parameter estimation we categorized all the continuous variables into dichotomous parameters (i.e., low/high). For each variable, we obtained the optimal dividing cut-off by Youden's index, performing a ROC curve analysis for the association with the defined outcomes. Multivariate models excluded the single items composing any derived variable, both to avoid model overfitting and parameter overestimation. For this reason, all multivariate models included considered a sum of comorbidities ≥ 3 and excluded both the single comorbidities and the CCI.

The significance was established for a two-sided p-value <0.05. Only one decimal digit was reported and rounded up. Data were analyzed by SPSS v. 25 (IBM Corp., Armonk, NY, USA) and MedCalc v18® (MedCalc Software Ltd., Ostend, Belgium).

Results

In the study period, a total of 345 patients were evaluated in our ED for suspect SD or VO. Among these, 165 received a confirmed diagnosis of SD or VO and met the inclusion criteria and constituted the study cohort.

In the cohort, 106 (64.2 %) were male and the median age was 69 years (Table I). Overall, 26 (15.7%) had previous vertebral surgery, while 139 did not. The most relevant demographic and clinical data concerning the cohort of patients are resumed in Table I.

Factors Associated with Autonomy in Daily Life Activities

Our primary outcome was the degree of autonomy of patients following the acute event (Table II). Overall, 98 patients (59.4%) were still non-autonomous in ADL at 12 months follow-up evaluation.

In univariate analysis, we observed that the most significant predictive factors for being non-autonomous were elevated serum creatinine (> 1.05 mg/dl), BUN > 23 mg/dl, LDH > 228 mU/ml, PCT > 0.11 ng/mL, and pain at clinical presentation, whereas the execution of a biopsy and the shift to specific antibiotic therapy after isolation of the involved microorganism resulted to be protective against being non-autonomous.

After adjusting for significant covariates, the multivariate analysis confirmed that BUN value > 23 mg/dl, a PCT > 0.11 ng/mL, and the shift to specific antibiotic therapy as independent predictors of this primary outcome. In particular, the Odds Ratio (OR) to be non-autonomous was 4.73 if BUN > 23 mg/dl [1.80-12.42], and 3.68 if PCT > 0.11 ng/mL [1.61-8.37]. Conversely, the shift to specific antibiotic therapy resulted to be protective against being non-autonomous with an adjusted Odd Ratio (OR) of 0.32 [0.13-0.77]. Receiver Operating Characteristics (ROC) analysis of emergency PCT and CRP with respect to persistence of infection at 1 year since the ED access, and autonomy in daily life activities were reported in Figure 1. Multivariate adjusted cumulative proportion of patients autonomous in daily life activities, since ED admission according to PCT value > 11 ng/mL at the time of ED evaluation was reported in Figure 2.

Factors Associated with the Persistence of the Infection (Non-Resolution)

As a secondary outcome, we evaluated the clinical resolution of the infection or its persistence. Overall, 93 (56.4%) patients had a clinical resolution after the index event.

In the univariate analysis, several variables resulted being associated with the resolution of the infection (Table III). However, after adjusting for significant covariates, the multivariate anal-

Table I. Descriptive table of the patients enrolled in the study cohort. Among them, 26 (15.7%) had previous spine surgery.

	All patients (n = 165)	Previous vetebral surgery (n = 26)	No previous surgery (n = 139)	*p*-value
Sex (Male)	106 (64.2 %)	13 (50.0 %)	93 (66.9 %)	0.105
Age (years)	69	64.5	69	0.128
Clinical presentation				
Pain	117 (70.9 %)	19 (73.1 %)	98 (70.5 %)	0.790
Fever	64 (38.8 %)	8 (30.8 %)	56 (40.3 %)	0.355
Neurological deficit	10 (6.1 %)	1 (3.8 %)	9 (6.5 %)	0.586
Sensory deficit	8 (4.8 %)	1 (3.8 %)	7 (5.0 %)	1.000
Pneumonia	10 (6.1 %)	0 (0.0 %)	10 (7.2 %)	0.365
Sepsis	33 (20.0 %)	2 (7.7 %)	31 (22.3 %)	0.062
Localization				
Cervical	11 (6.7 %)	1 (3.8 %)	10 (7.2 %)	1.000
Dorsal	50 (30.3 %)	4 (15.4 %)	46 (33.1 %)	0.057
Lumbar	108 (65.5 %)	22 (84.6 %)	86 (61.9 %)	**0.018**
Microbiological data:				
Abscess	75 (45.5%)	19 (73.1 %)	56 (40.3 %)	**0.002**
Positive blood cultures	66 (40.0 %)	6 (23.1 %)	60 (43.2 %)	**0.048**
Need for biopsy	97 (58.8 %)	23 (88.5 %)	74 (53.2 %)	< **0.001**
Type of biopsy				
No biopsy	68 (41.2 %)	3 (11.5 %)	65 (46.8 %)	
Percutaneous	61 (37.0 %)	13 (50.0 %)	48 (34.5 %)	**0.003**
Open	36 (21.8 %)	10 (38.5 %)	26 (18.7 %)	
Surgery	33 (20.0 %)	10 (38.5 %)	23 (16.5 %)	**0.016**
Antibiotic resistance				
No bacterial growth	90 (54.5 %)	18 (69.2 %)	72 (51.8 %)	**0.229**
No	30 (18.2 %)	4 (15.4 %)	26 (18.7 %)	
Yes	45 (27.3 %)	4 (15.4 %)	41 (29.5 %)	
Shift to specific antibiotic therapy	98 (59.4 %)	14 (53.8 %)	84 (60.4 %)	0.532
Necessity of corset	98 (59.4 %)	18 (69.2 %)	80 (57.6 %)	0.259
Laboratory				
Hemoglogin (g/dL)	12.3	12.75	12.20	0.302
WBC ($\times 10^{\wedge 9}$)	8.71	8.61	8.74	0.936
Creatinine (mg/dL)	0.89	0.81	0.89	0.267
BUN	19	18.50	20	0.322
Blood Glucose	106	103.5	108	0.202
LDH	191	176.5	197	0.043
Admission ED procalcitonin	0.15	0.1	0.16	0.258
Max procalcitonin in a week	0.06	0.05	0.07	0.428
First CRP	67.5	47.15	68.20	0.137
Max CRP in a week	67.5	47.15	68.20	0.120
Comorbidities				
Charlson Comorbidity Index ≥ 3				
Arterial hypertension	52 (31.5 %)	8 (30.8 %)	44 (31.7 %)	0.929
Coronary artery disease	17 (10.3 %)	2 (7.7 %)	15 (10.8 %)	1.000
Heart failure	9 (5.5 %)	0 (0.0 %)	9 (6.5 %)	0.357
Peripheral artery disease	16 (9.7 %)	1 (3.8 %)	15 (10.8 %)	0.472
Previous stroke or TIA	10 (6.1 %)	0 (0.0 %)	10 (7.2 %)	0.365
Dementia	2 (1.2 %)	0 (0.0 %)	2 (1.4 %)	1.000
COPD	8 (4.8 %)	0 (0.0 %)	8 (5.8 %)	0.359
Connective tissue disease	4 (2.4 %)	0 (0.0 %)	4 (2.9 %)	1.000
Hepatic disease	5 (3.0 %)	0 (0.0 %)	5 (3.6 %)	1.000
Cirrhosis	3 (1.8 %)	0 (0.0 %)	3 (2.2 %)	1.000
Diabetes	33 (20.0 %)	2 (7.7 %)	31 (22.3 %)	0.062
Hemiplegia	3 (1.8 %)	0 (0.0 %)	3 (2.2 %)	1.000
Chronic kidney disease	16 (9.7 %)	2 (7.7 %)	14 (10.1 %)	1.000
Active malignancy	24 (14.5 %)	1 (3.8 %)	23 (16.5 %)	0.129
Metastasis	6 (3.6 %)	0 (0.0 %)	6 (4.3 %)	0.591
Hematologic malignancies	4 (2.4 %)	0 (0.0 %)	4 (2.9 %)	1.000
HIV	3 (1.8 %)	1 (3.8 %)	2 (1.4 %)	0.404
Outcomes				
LOS (days)	21.39	28.50	20.97	0.111
Resolution of infection	93 (56.4 %)	20 (76.9 %)	73 (52.5 %)	**0.018**
Non autonomous in ADL	98 (59.4 %)	13 (50.0 %)	85 (61.2 %)	0.291
Ward admission > 30 days/ death	64 (38.8 %)	13 (50.0 %)	51 (36.7 %)	0.206
Death	11 (6.7 %)	1 (3.8 %)	10 (7.2 %)	1.000

Table II. Factors associated with reduced or absent autonomy in the activities of daily life (ADL) in the study cohort patients.

	Non autonomous in ADL (n = 98)	Autonomous in ADL (n = 67)	*p*-value	Odds Ratio (95% CI)	Multivariate *p*-value
Sex (Male)	61 (62.2%)	45 (67.2%)	0.516		
Previous surgery	13 (13.3%)	13 (19.4%)	0.291		
Age (years)	69	67	0.078		
Clinical presentation					
Pain	63 (64.3%)	54 (80.6%)	**0.021**	0.67 (0.29-1.67)	0.384
Fever	38 (38.8%)	26 (38.8%)	0.997		
Neurological deficit	4 (4.1%)	6 (9.0%)	0.203		
Sensory deficit	3 (3.1%)	5 (7.5%)	0.201		
Associated Pneumonia	6 (6.1%)	4 (6.0%)	1.000		
Associated Sepsis	22 (22.4%)	11 (16.4%)	0.337		
Localization					
Cervical	7 (7.1%)	4 (6.0 %)	0.765		
Dorsal	30 (30.6%)	20 (29.9%)	0.917		
Lumbar	64 (65.3%)	44 (65.7%)	0.961		
Microbiological data					
Abscess	42 (42.9%)	33 (49.3%)	0.418		
Positive blood cultures	35 (35.7%)	31 (46.3%)	0.175		
Need for biopsy	46 (46.9%)	51 (76.1%)	**< 0.001**	0.66 (0.27-1.64)	0.385
Type of biopsy					
No biopsy	52 (53.1%)	16 (23.9%)	**0.001**		
Percutaneous	29 (29.6%)	32 (47.8%)			
Open	17 (17.3%)	19 (28.4%)			
Surgery	16 (16.3%)	17 (25.4%)	0.157		
Antibiotic resistance					
No bacterial growth	59 (60.2%)	31 (46.3%)	0.207		
No	16 (16.3%)	14 (20.9%)			
Yes	23 (23.5%)	22 (32.8%)			
Shift to specific antibiotic therapy	47 (48.0%)	51 (76.1%)	**< 0.001**	**0.32 (0.13-0.77)**	**0.011**
Need for corset	48 (49.0%)	50 (74.6%)	**0.001**	0.70 (0.29-1.66)	0.455
Laboratory					
Hemoglogin	12.2	12.4	0.989		
WBC	9.08	8.56	0.166		
Creatinine	0.90	0.81	**0.034**		
Creatinine > 1.05 mg/dL	29 (29.6%)	13 (19.4%)	0.140	0.49 (0.18-1.33)	0.207
BUN	21	19	**0.005**		
BUN > 23	42 (42.9%)	13 (19.4%)	**0.002**	**4.73 (1.80-12.42)**	**0.002**
Blood glucose	106.5	106	0.339		
LDH	208	176	**< 0.001**		
LDH > 228	46 (46.9%)	13 (19.4%)	**< 0.001**	1.85 (0.70-4.86)	0.211
Admission ED PCT	0.18	0.11			
Max PCT in a week	0.12	0.05	**< 0.001**		
Admission PCT > 0.11	51 (52.0%)	14 (20.9%)	**< 0.001**	**3.68 (1.61-8.37)**	**0.002**
Admission CRP	69.5	61.2	0.140		
Max CRP	72.4	63.5			

Continued

ysis revealed that only a PCT > 0.11 ng/mL, a BUN > 23 mg/dL, the need for a biopsy, and the diagnosis of sepsis were independently associated with the clinical resolution. The different factors were either associated with the clinical resolution or the non-resolution (persistence of infection). As expected, patients with higher PCT (PCT > 0.11 ng/mL) and higher BUN (BUN > 23 mg/dl)

Table II. ***(Continued).*** Factors associated with reduced or absent autonomy in the activities of daily life (ADL) in the study cohort patients.

	Non autonomous in ADL (n = 98)	Autonomous in ADL (n = 67)	*p*-value	Odds Ratio (95% CI)	Multivariate *p*-value
Comorbidities					
Charlson's Comorbidity index ≥ 3	37 (55.2)	56 (57.1)	0.807		
Arterial hypertension	31 (31.6%)	21 (31.3%)	0.969		
Coronary artery disease	5 (5.1%)	12 (17.9%)	**0.008**		
Heart failure	6 (6.1%)	3 (4.5%)	0.740		
Peripheral artery disease	6 (6.1%)	10 (14.9%)	0.063		
Previous stroke or TIA	7 (7.1%)	3 (4.5%)	0.741		
Dementia	2 (2.0%)	0 (0.0%)	0.515		
COPD	6 (6.1%)	2 (3.0%)	0.475		
Connective tissue disease	3 (3.1%)	1 (1.5%)	0.647		
Hepatic disease	3 (3.1%)	2 (3.0%)	1.000		
Cirrhosis	3 (3.1%)	0 (0.0%)	0.272		
Diabetes	22 (22.4%)	11 (16.4%)	0.337		
Hemiplegia	2 (2.0%)	1 (1.5%)	1.000		
Chronic kidney disease	11 (11.2%)	5 (7.5%)	0.416		
Active malignancy	17 (17.3%)	7 (10.4%)	0.209		
Metastasis	6 (6.1%)	0 (0.0%)	0.082		
Hematologic malignancies	4 (4.1%)	0 (0.0%)	0.147		
HIV	1 (1.0%)	2 (3.0%)	0.567		
Outcomes					
LOS (days)	19.01	23.47	0.111		
Ward admission >3 0 days or death	41 (41.8%)	23 (34.2%)	0.330		
Resolution of infection	34 (34.7%)	59 (88.1%)	< **0.001**		

Multivariate model Chi-square = 0.252; -2 log-likelihood 175.012. Chi-square (Hosmer and Lemeshow) = 11.829, $p = 0.106$.

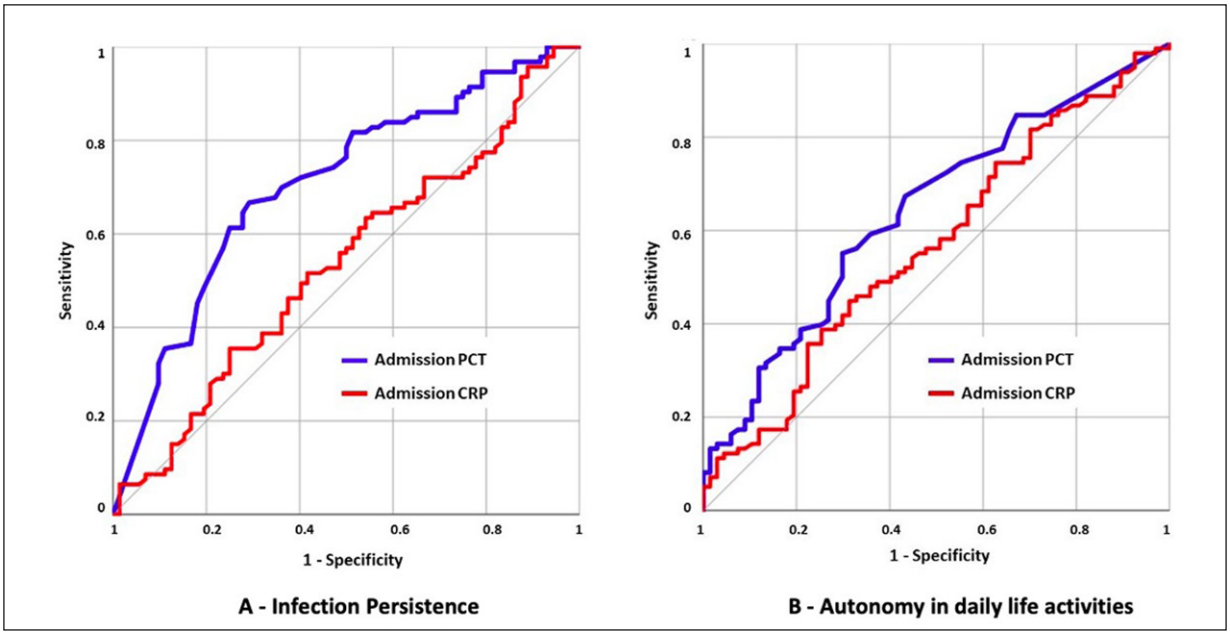

Figure 1. Receiver Operating Characteristics (ROC) Analysis of Emergency Department Procalcitonin (PCT) and C-reactive protein (CRP) with respect to Persistance of infection at 1 year since the ED access, and autonomy in daily life activities (ADL). **A**, ROC area under curve (AUC) for infection persistence was 0.706 (0.626-0.786) for PCT ($p<0.001$) and 0.535 (0.446-0.624) for CRP ($p=0.445$). **B**, ROC AUC for autonomy in daily life activities at 1 year was 0.642 (0.557-0.727) for PCT ($p=0.002$) and 0.568 (0.479-0.657) for CRP ($p=0.140$).

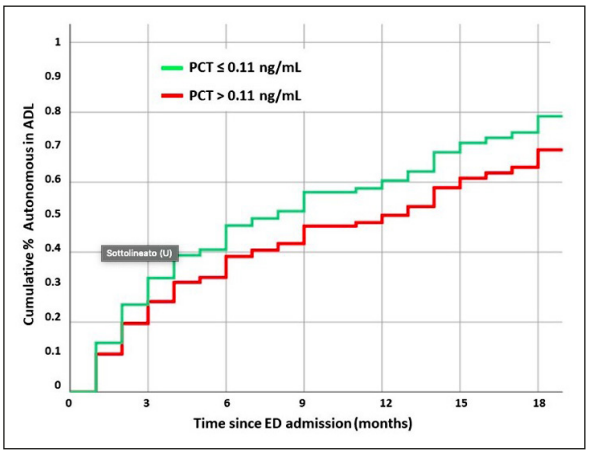

Figure 2. Multivariate adjusted cumulative proportion of patients autonomous in daily life activities since ED admission according to Procalcitonin value > 11 ng/mL at the time of ED evaluation (Cox regression model).

had higher odds of infection persistence (the OR were respectively 3.78 for PCT and 3.14 for BUN, Table III). Conversely, the biopsy was associated with lower odds of infection persistence (OR = 0.23 compared to non-biopsy patients). Similarly, and somewhat contrary to common sense, the presence of associated sepsis was associated with lower odds of infection persistence (OR = 0.11, compared to non-septic patients). Multivariate adjusted cumulative proportion of patients with persisting infection according to the time since ED admission according to Procalcitonin value > 11 ng/mL at the time of ED evaluation is reported in Figure 3.

Discussion

Background

The estimated annual incidence of pyogenic SD in Europe ranges from 0.5 to 2.5 cases per 100,000 inhabitants; however, in the last decades, SD represents an increasing condition. On one hand, this depends on the increase in the global life expectancy of the population; on the other hand, it depends on the improvement of diagnostic and radiological techniques that allow a more accurate and earlier diagnosis[12,13]. This condition is therefore rare, but could require the need for lengthy treatments, with a consequent reduction in the quality of life and negative outcomes[13]. SD seems to be still related to high morbidity and mortality rates despite these being decreasing compared to past years[13].

The pathogenetic mechanisms of SD are heterogeneous: hematogenous spread, direct inoculation (often iatrogenic), and propagation from contiguous sites[13]. Hematogenous spread remains the most frequent cause of infection, so much so that concomitant endocarditis is found in about 12% of patients with SD[14].

Early diagnosis represents one of the goals to be achieved; however, today it still represents a challenge due to the non-specific clinical and laboratory onset. It is possible to observe an average delay of 30-90 days between the onset of the symptoms and SD diagnosis[15]. Furthermore, especially during the present SARS-CoV-2 pandemic, a differential diagnosis with patients presenting with fever in the ED is even more important[16,17].

Back pain is one of the typical symptoms, yet it remains highly non-specific. Fever occurs in less than half of patients, while neutrophilic leukocytosis is present in less than a third of patients with SD[15]. Serum CRP appears to be a good laboratory parameter for assessing the presence of primary SD, as argued by Covino et al[18]; however, its increase is also present in other clinical conditions. In suspicious cases, gadolinium contrast-enhanced MRI remains the most sensitive radiologic technique for SD diagnosis confirmation[8,9].

The etiological diagnosis is essential to set up a specific antibiotic therapy. However, it is often not easy to obtain since blood cultures are negative in half of the cases[7]. CT-guided fine-needle percutaneous biopsy represents the gold standard for etiological diagnosis[7,19]. Open biopsy should be reserved for all cases that require a surgical neurological decompression for spinal cord compression with neurologic symptoms. Nevertheless, the success rates remain low[7]. Spinal fusion (open or percutaneous) should be reserved for patients with spinal instability or progressive deformity[20,21].

The Role of PCT in SD

A reliable biomarker is necessary to rule out septic progression during the management of SD and its early diagnosis. Although the PCT's role in other septic pathologies has been widely debated in the literature[18,22], only a few studies[5] report the usefulness of PCT use in the management of patients with SD.

Jeong et al[5] sustained that PCT seems to be less sensitive than CRP for the diagnosis of spondylodiscitis. They observed that about

Table III. Factors associated with persistence of the infection in the patients.

	Resolution of the infection (n = 93)	Persistence of the infection (n = 72)	*p*-value	Odds Ratio (95% CI)	Multivariate *p*-value
Sex (Male)	62 (66.7 %)	44 (61.1 %)	0.460		
Previous surgery	20 (21.5 %)	6 (8.3 %)	**0.021**	0.39 (0.11-1.36)	0.140
Age (years)	68	71	0.100		
Clinical presentation:					
Pain	74 (79.6%)	43 (59.7%)	**0.005**	1.42 (0.53-3.80)	0.415
Fever	37 (39.8%)	27 (37.5%)	0.765		
Neurological deficit	5 (5.4%)	5 (6.9%)	0.675		
Sensory deficit	5 (5.4%)	3 (4.2%)	0.720		
Associated Pneumonia	5 (5.4%)	5 (6.9%)	0.675		
Associated Sepsis	25 (26.9%)	8 (11.1%)	**0.012**	**0.11 (0.03-0.37)**	**0.001**
Localization:					
Cervical	6 (6.5%)	5 (6.9%)	0.900		
Dorsal	19 (20.4%)	31 (43.1%)	**0.002**	2.65 (0.62-11.37)	0.187
Lumbar	70 (75.3%)	38 (52.8%)	**0.003**	0.55 (0.14-2.27)	0.414
Microbiological data:					
Abscess	52 (55.9%)	23 (31.9%)	**0.002**	1.64 (0.59-4.54)	0.343
Positive blood cultures	47 (50.5%)	19 (26.4%)	**0.002**	0.37 (0.12-1.15)	0.087
Need for biopsy	71 (76.3%)	26 (36.1%)	**< 0.001**	**0.23 (0.08-0.65)**	**0.006**
Type of biopsy:					
No	22 (23.7%)	46 (63.9%)	< 0.001		
Percutaneous	46 (49.5%)	15 (20.8%)			
Open	25 (26.9%)	11 (15.3%)			
Surgery	21 (22.6%)	12 (16.7%)	0.346		
Antibiotic resistance:					
No b. growth	41 (44.1%)	49 (68.1%)	0.006		
No	19 (20.4%)	11 (15.3%)			
Yes	33 (35.5%)	12 (16.7%)			
Shift to specific antibiotic therapy	67 (72.0%)	31 (43.1%)	< 0.001	0.99 (0.31-3.16)	0.985
Need for corset	70 (75.3%)	28 (38.9%)	< 0.001	0.44 (0.17-1.15)	0.097
Laboratory					
Hemoglobin	12.20	12.35	0.721		
WBC	8.89	8.34	0.294		
Creatinine	0.83	0.92	0.004		
Creatinine > 1.05 mg/dL	17 (18.3)	25 (34.7)	**0.016**	1.60 (0.52-4.90)	0.411
BUN	19	22	0.017		
BUN > 23	24 (25.8 %)	31 (43.1%)	**0.020**	**3.14 (1.07-9.18)**	**0.037**
Blood glucose	108	104.5	0.764		
LDH	174	256	< 0.001		
LDH > 228	17 (18.3)	42 (58.3)	< 0.001	2.55 (0.84-7.75)	0.098
ED Admission PCT	0.11	0.21	< 0.001		
Admission PCT > 0.11	26 (28.0)	39 (54.2)	**< 0.001**	**3.78 (1.44-9.94)**	**0.007**
Max PCT value in 1 week	0.05	0.16	< 0.001		
Ed Admission CRP	61.2	69.5	0.445		
CRP in 1 week	33.4	36.45	0.903		
Max CRP	67.9	67.5	0.543		

Continued

80% of examined patients with high PCT levels had at least one concurrent infection in other body regions (e.g., pneumonia, urinary infections, etc.), with established sepsis[5]. In fact, they recommended that patients suffering from SD or VO with elevated PCT should be evaluated for a concomitant infection and an appropriate antibiotic therapy should be started[5]. Some au-

Table III *(Continued)*. Factors associated with persistence of the infection in the patients.

	Resolution of the infection (n = 93)	Persistence of the infection (n = 72)	*p*-value	Odds Ratio (95% CI)	Multivariate *p*-value
Comorbidities:					
Charlson Comorbidity Index ≥ 3	51 (54.8)	42 (58.3)	0.654	1.21 (0.47-3.08)	0.689
Arterial hypertension	27 (29.0%)	25 (34.7%)	0.435		
Coronary artery disease	11 (11.8%)	6 (8.3%)	0.464		
Heart failure	4 (4.3%)	5 (6.9%)	0.506		
Peripheral artery disease	10 (10.8%)	6 (8.3%)	0.602		
Previous stroke or TIA	5 (5.4%)	5 (5.9%)	0.675		
Dementia	1 (1.1%)	1 (1.4%)	1.000		
COPD	2 (2.2%)	6 (8.3%)	0.080		
Connective tissue disease	1 (1.1%)	3 (4.2%)	0.319		
Hepatic disease	2 (2.2%)	3 (4.2%)	0.654		
Cirrhosis	0 (0.0%)	3 (4.2%)	0.081		
Diabetes	21 (22.6%)	12 (16.7%)	0.346		
Hemiplegia	2 (2.2%)	1 (1.4 %)	1.000		
Chronic kidney disease	11 (11.8%)	5 (6.9%)	0.293		
Active malignancy	8 (8.6%)	16 (22.2%)	**0.014**		
Metastasis	0 (0.0%)	6 (8.3%)	**0.006**		
Hematologic malignancies	0 (0.0%)	4 (5.6%)	**0.035**		
HIV	3 (3.2%)	0 (0.0%)	0.258		
Outcomes					
LOS (days)	22.44	17.47	**0.008**		
Ward admission > 30 days/death	36 (38.7%)	28 (38.9%)	0.981		
Death	1 (1.1%)	10 (13.9%)	**0.001**		
Non autonomous	34 (36.6%)	64 (88.9%)	**< 0.001**		

Multivariate model Chi-square = 0.372; -2 log-likelihood 149.393. Chi-square (Hosmer and Lemeshow) = 6.010, $p = 0.646$.

thors[23-25] sustained that PCT did not represent a useful tool for monitoring the SD progression. Maus et al[24], in their study on 17 patients, found changes in PCT levels only in one patient with a concomitant cardiac pacemaker infection. Yoon et al[25] identified instead PCT as a biomarker to differentiate delayed drug hypersensitivity and systemic bacterial infection. In fact, they found that only in 21% of patients with a diagnosis of SD PCT values were above the cutoff of 0.5 ng/ml[25]. In these patients delayed drug hypersensitivity was detected with a PCT cutoff value of 1.67 ng/ml. Other authors[25,26] argued that the sensitivity of serum PCT in primary SD appears to be low and not useful for the discrimination between a bacterial infection and another aseptic spinal inflammatory disease[26]. The high sensitivity is found only in cases with severe infectious syndrome[25].

Despite the limited evidence in the literature for the utility and specificity of serum PCT assay in SD patients, these results need to be critically interpreted due to the low number of patients analyzed.

Our Results

We collected several clinical and laboratory data concerning our cohort of patients with ED diagnosed SD or VO and observed that several variables were correlated to our primary and

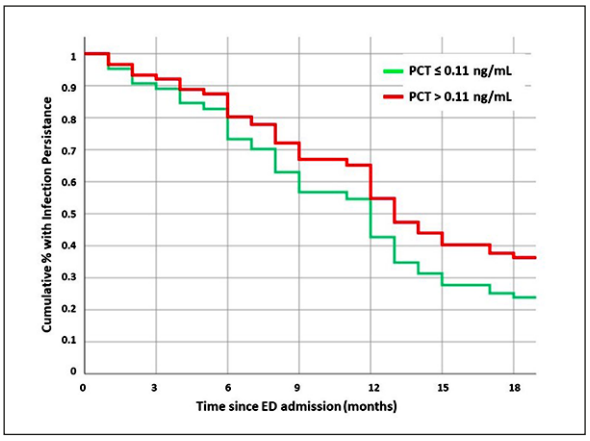

Figure 3. Multivariate adjusted cumulative proportion of patients with persisting infection according to the time since ED admission according to Procalcitonin value > 11 ng/mL at the time of ED evaluation (Cox regression model).

secondary outcomes with statistical significance. Among these variables, the most relevant observations, as obtained with multivariate analysis, were that a value of PCT > 0.11 ng/mL at ED presentation was an independent risk factor for our primary outcome, non-autonomy, with an OR of 3.68 (Table II). Conversely, a shift to specific antibiotic therapy as a result of isolation of the infectious agent resulted to be a protective factor in our cohort of patients, with an OR to be non-autonomous of 0.32 if a shift to specific antibiotic therapy was performed. These data might shed new light on the role of procalcitonin in the early risk stratification of these patients, potentially providing an adjunctive tool to assess patient outcome and quality of life after the acute event. Moreover, the paramount importance of microbiological isolation (either *via* blood cultures or *via* needle-biopsy) and subsequent shift to specific antibiotic therapy was confirmed by our data.

Concerning the secondary outcome, resolution of infection, the role of laboratory markers was significant too. Again, procalcitonin value > 0.11 ng/mL was an independent risk factor for the persistence of the infection (OR of 3.78 for infection persistence if PCT > 0.11), as well as a value of BUN > 23. Interestingly, those patients who were concomitantly septic had an increased probability of resolving the infection (infection persistence OR = 0.11). A possible explanation for the observed phenomenon might be that those patients who presented with sepsis or septic shock received a more aggressive treatment starting from the early phases of stabilization and diagnostic workup in the ED, with more thorough execution of blood cultures and early initiation of broad-spectrum antibiotic therapy, with respect to patients with a more subtle presentation. Nonetheless, more data are needed to confirm this observation.

Limitations

As for any other retrospective study, our work suffers from some limitations. The relatively small sample of patients and the retrospective nature of our evaluation did not allow us to draw some more definitive conclusions concerning the role of procalcitonin in SD and VO. Furthermore, the role of concomitant sepsis is not completely clear. Whether it is a confounding factor or rather a significant aspect in the management of these patients remains unclear. Future research, possibly of a prospective nature, might help in clarifying this matter.

Conclusions

PCT assay may play a role in diagnosing spondylodiscitis in an emergency setting. A PCT value > 0.11 ng/mL should be considered as red flag, a predictor of worse clinical outcomes and persistence of infection. The shift to a targeted antibiotic therapy after the etiological diagnosis is still the main goal of the treatment of spondylodiscitis to obtain remission from the disease and better clinical outcomes.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethical Approval

This study was in accordance with the Ethical Standards of the Institutional and National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the local Institutional Review Board (Approval No.: IRB #005181419).

Informed Consent

Written informed consent for scientific purposes and clinical data collection was obtained according to institutional protocol.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contribution

MC, AG, FF, GM, DAS conceived and designed the study. All authors contributed to the preparation of the materials, the conception of the database and the collection of data. AP, GT, LP and SF performed the data analysis. GT, AP, RV wrote the first draft of the manuscript. MC, LP, and GM corrected and edited the first draft. FCT and SG reviewed the draft. All authors read and approved the final manuscript.

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