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**Comparison of several biomarkers (MMP-2, MMP-9, the MMP-9 inhibitor TIMP-1, CTX-II, calprotectin, and COMP) in the synovial fluid and serum of patients with and without septic arthritis**

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It is critical to diagnosis septic arthritis (SA) in a timely fashion in order to reduce the risk of irreversible cartilage damage, which has important functional sequelae [1,2]. However, direct Gram stain of synovial fluid is positive in only 25% to 50% of SA cases, and the bacteriological results remain negative in approximately 20% of SA cases [3]. Therefore, readily available and specific biomarkers are needed to help clinicians to decide for hospitalization and antibiotic treatment. This study assessed whether the following serum and synovial biomarkers could distinguish between patients with SA versus non-SA: metalloproteinase MMP-2, MMP-9, tissue inhibitor of MMP (TIMP-1), cartilage oligomeric matrix protein (COMP), C-terminal telopeptide of type II collagen (CTX-II), and calprotectin (CALP).

Serum samples and aspirated synovial fluid samples were prospectively collected from 21 patients with SA. SA was defined as the identification of microorganisms from synovial fluid or blood cultures: *Staphylococcus aureus*, n=13; *Streptococcus*, n=4; *Enterobacteria*, n=3; and coagulase-negative *Staphylococcus*, n=1. We also collected samples from 18 patients with a suspicion of SA who had acutely swollen joints due to other causes: chondrocalcinosis, n=9; gout, n=2; rheumatoid arthritis, n=2; spondyloarthritis, n=1; osteoarthritis, n=3; and hemarthrosis, n=1. TIMP-1, MMP-2, MMP-9, CTX-II, CALP, and COMP levels were measured in synovial fluid and serum using commercial enzyme-linked immunosorbent assay (ELISA) kits and compared between the groups.

The characteristics of the study population are shown in Table 1. Univariate analysis showed that the following were significantly higher in the SA group versus the non-SA group (Table 2): serum TIMP-1 ( $p<0.01$ ), synovial MMP-9 ( $p<0.01$ ); serum ( $p<0.05$ ) and synovial CTX-II ( $p<0.01$ ); and serum ( $p<0.05$ ) and synovial CALP ( $p<0.05$ ). The AUCs for diagnosing SA based on synovial MMP-9, serum TIMP-1, synovial CTX-II, and serum and synovial CALP were 0.84, 0.79, 0.81, 0.7, and 0.72, respectively. When serum TIMP-1 and synovial CTX-II were combined and thresholds of 286.5ng/mL and 873ng/mL were used, respectively, the sensitivity was 75% and the specificity was 94% for diagnosing SA. This combination correctly classified patients in 86% of cases. Synovial MMP-9 substantially correlated with C-reactive protein ( $r=0.61$ ), whole blood white blood cell count [WBC] ( $r=0.46$ ), synovial WBC ( $r=0.66$ ) and the polymorphonuclear cell percentage ( $r=0.51$ ) in synovial fluid. Serum TIMP-1 and synovial CTX-II did not correlate with each other ( $r=0.1$ ) or with CRP ( $r=0.4$  and  $r=0.25$ , respectively) or synovial WBC ( $r=-0.04$  and  $r=0.27$ , respectively).

**Table 1: Clinical characteristics and laboratory data of the study population**

	SA group n = 21	Non-SA group n = 18	p-value
<b>Age, years, mean <math>\pm</math> SD</b>	64.5 $\pm$ 21.1	64.8 $\pm$ 12.6	0.96
<b>Male gender, n (%)</b>	12 (57.1)	8 (44.4)	0.43
<b>Diabetes, n (%)</b>	5 (23.8)	2 (11.1)	0.42
<b>Joint affected</b>	Knee, n (%)	14 (66.7)	15 (83.3)
	Shoulder, n (%)	4 (19)	2 (11.1)
	Hip, n (%)	3 (14.3)	0 (0)
	Elbow, n (%)	0 (0)	1 (5.6)
<b>Max. temperature, °C, mean <math>\pm</math> SD</b>	38.3 $\pm$ 0.7	38.1 $\pm$ 0.7	0.38
<b>Chills, n (%)</b>	7/18 (38.9)	4/18 (22.2)	0.28
<b>Presence of an entry site for infection, n (%)</b>	15/20 (75)	8/18 (44)	0.054
<b>Serum:</b>			
<b>WBC count, /mm<sup>3</sup>, median</b>	10 770 [8250-13 260]	8230 [4900-11 400]	0.03*
<b>CRP, mg/L, median [Q1-Q3]</b>	209 [122-256]	90 [35-184]	0.06
<b>Radiological signs of SA, n (%)</b>	7/18 (38.9)	1/17 (5.9)	0.04
<b>Synovial fluid:</b>			
<b>Turbid, n (%)</b>	13/19 (68.4)	2/17 (11.8)	0.001*
<b>WBC count &gt; 50 000/mm<sup>3</sup>, n (%)</b>	7/16 (43.7)	3/18 (16.7)	0.09
<b>PMN, %, median [Q1-Q3]</b>	90 [89-93]	89 [84-90]	0.17

Values are expressed as mean  $\pm$  standard deviation (SD) or median [Q1-Q3] for continuous variables and n (%) for categorical variables. \* < 0.05

SA: septic arthritis, CRP: C-reactive protein, WBC: white blood cell, PMN: polymorphonuclear cell

**Table 2: Measurement of the biomarkers according to diagnosis (septic or non-septic arthritis)**

\*: *p*-value < 0.05, Mean ± SD: mean and standard deviation, AUC: area under the curve, CI: confidence interval, MMP: metalloproteinase, TIMP: metalloproteinase inhibitor, CTX: C-terminal telopeptide of collagen, COMP: cartilage oligomeric matrix protein.

<b>Marker level</b>	<b>Septic arthritis (n=21)</b>	<b>Non-septic arthritis (n=18)</b>	<b>p-value</b>
<b>MMP-2 serum, mean ± SD, ng/mL</b>	90 ± 35.6	77.1 ± 26.5	0.2
<b>MMP-2 synovial fluid, mean ± SD, ng/mL</b>	248.5 ± 131	241.8 ± 109.4	0.7
<b>MMP-9 serum, mean ± SD, ng/mL</b>	2856 ± 1997	2190 ± 1920	0.2
<b>MMP-9 synovial fluid, mean ± SD, µg/L</b>	49.6 ± 26.3	20.7 ± 16.5	0.002*
<b>TIMP-1 serum, mean ± SD, ng/mL</b>	320.6 ± 169	170.8 ± 69.2	0.003*
<b>TIMP-1 synovial fluid, mean ± SD, ng/mL</b>	947 ± 315	948.1 ± 377.1	0.7
<b>CTX-II serum, mean ± SD, ng/mL</b>	1036.9 ± 549.2	653.5 ± 268	0.03*
<b>CTX-II synovial fluid, mean ± SD, ng/mL</b>	1069.9 ± 540.3	673.5 ± 335.5	0.004*
<b>COMP serum, mean ± SD, ng/mL</b>	304.4 ± 216.1	271.4 ± 157.3	0.8
<b>COMP synovial fluid, mean ± SD, ng/mL</b>	4210 ± 3523	6098 ± 4161	0.2
<b>CALP serum, mean ± SD, mg/mL</b>	2.5 ± 1.4	1.6 ± 1	0.04*
<b>CALP synovial fluid, mean ± SD, µg/mL</b>	1270.9 ± 605.3	798.1 ± 604.8	0.03*

To our knowledge, this is the first study to assess the performance of numerous potentially useful markers in synovial fluid and serum samples of patients with suspected SA. Synovial CTX-II is especially interesting because it appears to add new information regarding cartilage degradation, along with inflammatory host response biomarkers like synovial WBC or CRP.

This preliminary study demonstrates that two biomarkers, serum TIMP-1 and synovial CTX-II, merit further assessment in terms of their diagnostic and prognostic value in a larger cohort of patients with suspected SA.

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