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# Serum D-Dimer Test Is Promising for the Diagnosis of Periprosthetic Joint Infection and Timing of Reimplantation.

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- 1 **Serum D-dimer is a Promising Test for the Diagnosis of Periprosthetic Joint Infection and**
- 2 **Timing of Reimplantation**

3 **ABSTRACT:**

4 *Background:* Despite the availability of battery of tests, the diagnosis of periprosthetic joint  
5 infection (PJI) continues to be challenging. Introduction of synovial biomarkers has improved  
6 the diagnosis, however, obtaining synovial fluid is invasive, occasionally impossible and carries  
7 the risk of introduction of infection into the joint. There is a desperate need for a serum marker  
8 of PJI. Serum D-dimer is a widely available test that detects fibrinolytic activities that occurs  
9 during infection. We hypothesized that patients with PJI may have a high level of circulating D-  
10 dimer and that the presence of high levels of serum D-dimer may be a sign of persistent infection  
11 in patients awaiting reimplantation.

12 *Methods:* This prospective study was initiated to enroll patients undergoing primary and revision  
13 arthroplasty. Our cohort consists of 245 patients undergoing primary arthroplasty (N=23),  
14 revision for aseptic failure (N=86), revision for PJI (N=57), patients undergoing reimplantation  
15 (N=29), and a group of patients with infection in a different site than the joint (N=50). PJI was  
16 defined using the Musculoskeletal Infection Society criteria. All patients in the study had serum  
17 D-dimer, erythrocyte sedimentation (ESR), and C-reactive protein (CRP) measured  
18 preoperatively.

19 *Results:* The median D-dimer was statistically higher ( $p < 0.0001$ ) in PJI patients  
20 (1,100ng/mL, range: 243-8,487ng/mL) compared to (299ng/mL, range: 106-6,381ng/mL) in  
21 patients with aseptic failure. Using the Youden's index, 850ng/mL was determined as the  
22 optimal threshold for serum D-dimer for diagnosis of PJI. Serum D-dimer outperformed both the  
23 ESR and the serum CRP with a sensitivity of 89% and a specificity of 93%. ESR and CRP had a  
24 sensitivity of 73% and 79% and a specificity of 78% and 80%, respectively. The sensitivity and

25 specificity of ESR and CRP combined was 84%(95%CI:76-90%) and 47%(95%CI:36-58%),  
26 respectively.

27 *Conclusion:* It appears that the serum D-dimer is a promising marker for diagnosis of PJI. This  
28 test may also have a great utility for determining the optimal timing of reimplantation. This study  
29 demonstrates that serum D-dimer can be utilized as a screening test for PJI.

30 **Level of Evidence:** Diagnostic Level II.

31 **INTRODUCTION:**

32 Despite its immense impact on patients and society, the diagnosis of periprosthetic joint infection  
33 (PJI) remains imperfect and often very challenging<sup>1</sup>. Currently an absolute test for diagnosis of  
34 PJI does not exist, compelling the clinicians to rely on a combination of synovial and serological  
35 tests<sup>2</sup>.

36 Due to the lack of an absolute test, the Musculoskeletal Infection Society (MSIS) introduced a  
37 set of diagnostic criteria for PJI that were recently modified by the International Consensus on  
38 Periprosthetic Joint Infection (ICM)<sup>3</sup>. The latter includes major and minor diagnostic criteria.  
39 The minor criteria include the measure of synovial fluid white blood cell count, neutrophil  
40 differential, culture, and leukocyte esterase testing (**Table 1**). Although numerous serum markers  
41 for PJI have been evaluated in the past including interleukin-6 (IL-6) and others <sup>1</sup>, the most widely  
42 used serums tests for diagnosis of PJI are erythrocyte sedimentation rate(ESR) and C-reactive  
43 protein(CRP)<sup>2</sup>. With the exception of a recent synovial biomarker, namely alpha defensin, none  
44 of the tests being used to diagnose PJI were developed for that purpose and their optimal  
45 threshold for diagnosis of PJI remains unknown.<sup>3</sup>

46 Moreover, the levels of ESR and CRP may be normal in patients with PJI caused by slow  
47 growing organisms such as *Propionibacterium acnes*<sup>4,5</sup>. In fact the document introducing the  
48 MSIS criteria for PJI explicitly states that the levels of some of these markers may be normal in  
49 the presence of PJI caused by slow growing organisms that do not elicit physiological  
50 inflammation and cautions clinicians in interpreting the level of serological markers in these  
51 situations <sup>6</sup>.

52 Recently, synovial fluid biomarkers have been shown to be useful in reaching or refuting the  
53 diagnosis of PJI. Synovial fluid alpha defensin, when combined with synovial CRP, has

54 demonstrated a sensitivity of 97% and specificity of 100% for the diagnosis of PJI.<sup>7</sup> There are,  
55 however, many issues with the use of synovial biomarkers for the diagnosis of PJI. Obtaining  
56 synovial fluid is invasive and painful to patients. There are not infrequent occasions when either  
57 inadequate amount of fluid is available to perform all tests or worse, no fluid is retrieved from  
58 the joint. In addition there is a theoretical, yet real, concern for the introduction of infection into  
59 the joint<sup>8</sup> and in difficult aspirations, especially the hip, contamination of the aspirated fluid may  
60 occur leading to false positive results<sup>9</sup>.

61 Another challenge relates to the lack of a reliable and easily accessible test that can help  
62 determine the optimal timing of reimplantation. ESR and CRP are not reliable markers in this  
63 situation as their level is often elevated in the postoperative period<sup>3,10</sup>. Two independent studies  
64 have demonstrated that the level of ESR and CRP at the time of reimplantation is not predictive  
65 of treatment failure<sup>11,12</sup>.

66 The aforementioned issues highlight the need for a reliable serum test that can help diagnose PJI  
67 and possibly determine the optimal timing of reimplantation. We have been in search of such a  
68 test over the past few years. Through a grant bestowed to us by the **\*\*\*Blinded by JBJS\*\*\***, we  
69 have evaluated over 30 serum and synovial markers for this purpose including D-dimer.

70 Numerous studies have shown that systemic and local infections result in fibrinolytic activities<sup>13-</sup>  
71 <sup>15</sup>. D-dimer has been traditionally used as a screening test for detecting deep venous thrombosis  
72 (DVT) but largely abandoned because of its poor performance. More recently, serum D-dimer  
73 has gained attention for its role in predicting poor outcome in sepsis and bacteremia<sup>16,17</sup>. An *in*  
74 *vivo* study on foals with septic arthritis also demonstrated a marked elevation in the level of  
75 synovial fluid D-dimer in these animals<sup>14</sup>.

76 We hypothesized that patients with PJI may have high levels of circulating D-dimer, and that the  
77 presence of high levels of D-dimer may be indicative of persistent infection in patients awaiting  
78 reimplantation.

79

## 80 **MATERIALS AND METHODS:**

81 Upon institutional review board approval, patients who underwent total joint arthroplasty (TJA)  
82 were prospectively enrolled in this study from April 2015 to August 2016. Patients undergoing  
83 primary and revision arthroplasty were included except those with any type of skin ulcer,  
84 hematoma, recent trauma or dislocation (within two weeks), visible ecchymosis, prosthetic heart  
85 valves, and those with a history of hypercoagulation disorders. The patients enrolled in this study  
86 fall under five categories: those undergoing primary total joint arthroplasty (group A), revision  
87 arthroplasty due to aseptic failure (group B), patients undergoing resection arthroplasty and  
88 spacer insertion for the treatment of PJI (group C), patients with treated PJI undergoing  
89 reimplantation surgery (reimplantation) (group D), and finally patients with known infection in a  
90 site other than a joint (group E). None of the patients in groups A-D were thought to have  
91 concurrent infections.

92 Sex, age, joint, and comorbid conditions including systemic inflammatory disease such as  
93 rheumatoid arthritis, systemic lupus erythematosus, psoriasis, polymyalgia rheumatica,  
94 sarcoidosis, inflammatory bowel disease, gout, hepatitis B and C, lymphocytic leukemia,  
95 myelodysplastic syndrome, multiple myeloma were recorded. Moreover concurrent antibiotic  
96 treatment (not including a single dose of prophylactic perioperative antibiotic), and isolated  
97 organisms were noted for all the patients. A venous blood sample was obtained preoperatively on  
98 the day of surgery and analyzed for serum D-dimer, erythrocyte sedimentation rate (ESR), and



99 C-reactive protein (CRP). PJI was defined using the MSIS criteria<sup>18</sup> (**Table 1**). As part of the  
100 standard protocol at our institution, surgeons obtain at least three intraoperative tissue culture  
101 specimens from patients undergoing revision arthroplasty. Cultures are then incubated for up to  
102 fourteen days. Furthermore, when a pre-operative synovial fluid aspiration is performed, cell  
103 count, neutrophil differential and cultures are requested.

104 Our cohort consists of 245 patients; primary arthroplasty (N=23), aseptic revisions (N=86),  
105 revisions for PJI (N=57), reimplantations (N=29), and those that were clinically diagnosed with  
106 infection in areas other than a joint (N=50), that included 34 cases of urinary tract infections, 9  
107 cases of pneumonia, and 5 cases of upper respiratory infections. Eleven patients were excluded  
108 that included history of trauma within 14 days of the surgery (3 patients), revision for dislocation  
109 (3 patients), presence of extensive ecchymosis (2 patients), presence of prosthetic cardiac valve  
110 (1 patient), and history of deep venous thrombosis (1 patient), and presence of skin ulcer on hand  
111 (1 patient) (Figure 1). Patient demographics are presented in table 2.

112 Patients were followed closely for a minimum of 6 months, the nature of complications and  
113 reason for readmission or reoperation were recorded.

114

### 115 *Statistical Analysis*

116 Descriptive statistics were used to report all the laboratory values. The results of the diagnostic  
117 tests were compared between the groups using Mann-Whitney test considering a  $p$ -value $<0.005$   
118 as a significance of difference between the groups. The optimal threshold for D-dimer as a  
119 diagnostic test for PJI was determined by Youden's J statistic ( $J = \text{Sensitivity} + \text{Specificity} - 1$ )  
120 based on its correspondence with the diagnosis. The sensitivity and specificity of the diagnostic

121 tests were calculated along with their 95% confidence intervals. All statistical analyses were  
122 performed using GraphPad Prism, version 7.0a, GraphPad software Inc. California, USA.  
123 Source of Funding: This study was funded in part by a grant from the Orthopaedic Research and  
124 Education Foundation (OREF).

125

## 126 **RESULTS:**

127 Serum D-dimer was significantly higher in patients with PJI; median D-dimer was 1,110 ng/mL  
128 (range: 243-8,487 ng/mL) in patients with PJI versus 299 ng/mL (range: 106-2,571 ng/mL) in  
129 patients without infection undergoing aseptic revision ( $p$ -value $<0.0001$ ). The mean D-dimer was  
130 212.5 ng/mL (range: 150-430 ng/mL) in the primary arthroplasty cohort, 399.9 ng/mL (range:  
131 106-2,571 ng/mL) in the aseptic revision arthroplasty cohort, 1,634 ng/mL (range: 243-8,487  
132 ng/mL) in PJI patients, 806.7 ng/mL (range: 170-6,381 ng/mL) in the reimplantation group, and  
133 451 ng/mL (range: 150-1,420 ng/mL) in patients with infection in sites other than a joint (Figure  
134 2).

135 The median ESR and CRP were also significantly higher in patients with PJI; the median ESR  
136 was 46 mm/hr (range, 7 to 127 mm/hr) in patients with PJI undergoing resection compared to 15  
137 mm/hr (range, 1 to 89 mm/hr) in patients undergoing revision due to aseptic failure ( $p$  $<0.0001$ )  
138 and for CRP the median was 37 mg/L (range, 2 to 328 mg/L) in the PJI group vs. 3 mg/L (range,  
139 1 to 81 mg/L) in the non-infected cases ( $p$  $<0.0001$ ). The mean ESR was 15.3 mm/hr (1-36  
140 mm/hr) in the primary arthroplasty cohort, 19.2 mm/hr (2-89 mm/hr) in the aseptic revision  
141 arthroplasty cohort, 75.2 mm/hr (7-120 mm/hr) in PJI patients (patients who underwent revision  
142 arthroplasty due to infection), 32.4 mm/hr (4-69 mm/hr) in the reimplantation group, and 72 (35-  
143 121 mm/hr) in patients with infection in sites other than a joint (Figure 3). The mean CRP was

144 4.2 mg/L (1-20 mg/L) in the primary group, 8.2 mg/L (1-81 mg/L) in aseptic revisions, 56 mg/L  
145 (2-328 mg/L) in PJI patients, 9.2 mg/L (1-27 mg/L) in the reimplantation group, and 47 mg/L (1-  
146 179 mg/L) in patients with infection in sites other than a joint (Figure 4), (Table 3).

147

148 Using the MSIS thresholds (Table 1), serum CRP and ESR had a sensitivity of 79% (95%  
149 Confidence interval [CI]: 66-88%) and 74% (95% CI: 60-84%) and a specificity of 80% (95%  
150 CI: 72-86%) and 78% (95% CI: 70-85%), respectively. The sensitivity and specificity of ESR  
151 and CRP combined was 84% (95% CI: 76-90%) and 47% (95% CI: 36-58%), respectively.

152 Using the calculated threshold for D-dimer (850 ng/mL), Serum D-dimer test had a better  
153 sensitivity at 89% (95% CI: 77-95%) and a better specificity at 93% (95% CI: 86-96%) for  
154 diagnosing PJI (Table 4). D-dimer was also useful in predicting the presence of infection at the  
155 time of reimplantation. Five patients had elevated D-dimer at the time of reimplantation. Of these  
156 patients who were reimplanted, two had a positive culture (*Propionibacterium acnes* in one and  
157 *Staphylococcus epidermidis* in the other one) from intraoperative specimens (Patients #9 and #14  
158 in Table 5). Both of these patients subsequently failed due to infection. It is interesting to note  
159 that the corresponding CRP and ESR levels were falsely negative in both of these patients (CRP:  
160 8 and 1 mg/L and ESR: 20 and 9 mm/hr). We are closely following the other three patients with  
161 “false positive” D-dimer at the time of reimplantation.

162 Seventeen patients in our cohort required reoperations (Table 5). 15 patients underwent revision  
163 surgery for infection; of which, 10 patients subsequently were reimplanted. Among these 10  
164 patients, D-dimer decreased below its threshold level in 7 patients at the time of reimplantation.  
165 The culture results of the PJI patients are provided in table 6. The rate of culture negative PJI in  
166 the cohort was 33% (19/57). The false negative rate for D-dimer in this subgroup was 5% (1/19)

167 whereas it was 47% (9/19) for CRP and 52% (10/19) for ESR (Table 7). The data relating to  
168 patients with infection in sites other than a joint was very interesting. All 50 patients (100%) had  
169 elevated ESR (>30 mm/hr), 42 patients (84%) had elevated CRP (>10 mg/L), and the D-dimer  
170 was elevated above 850 ng/dL in 6 patients (12%).

171

## 172 **DISCUSSION:**

173 This is, to our knowledge, the first study that evaluates the role of serum D-dimer as a diagnostic  
174 test for PJI and predicting the presence of infection in patients awaiting reimplantation. In the  
175 given cohort that we assembled over the past two years, D-dimer was more accurate than ESR  
176 and CRP, even when combined, in diagnosing PJI and also predicting the presence of infection at  
177 the time of reimplantation. Out of five patients with “elevated” D-dimer at the time of  
178 reimplantation, two patients had a positive culture from the samples taken during reimplantation.  
179 ESR and CRP were both normal in these two patients. Both of these patients subsequently failed  
180 due to infection. Thus, we believe that the sensitivity and specificity of D-dimer is likely higher  
181 than calculated in this cohort as some of the patients with “positive” D-dimer who were  
182 classified as non-infected, may indeed have infection by slow growing organisms that did not  
183 elicit physiological inflammation and failed to meet the MSIS criteria for PJI. The MSIS  
184 workgroup proposing the PJI definition cautioned clinicians about such a possibility, when  
185 organisms like *P. acnes* causing PJI may not elicit adequate inflammation and all minor criteria  
186 may be negative<sup>19,20</sup>. Thus, using the MSIS criteria for these patients may have adversely  
187 affected the performance of D-dimer.

188 Clinicians are familiar with serum D-dimer as it has been used, albeit with disappointing  
189 performance, in screening patients for venous thromboembolism (VTE).<sup>21-23</sup> In recent years

190 evidence has been emerging to suggest that the D-dimer levels are likely to rise in the setting of  
191 systemic inflammation and infection, especially in a joint.<sup>14,16,17</sup> Busso et al.<sup>24</sup> explained how  
192 D-dimer levels are elevated in patients with rheumatoid arthritis. Inflamed synovium secretes a  
193 significant amount of fibrin and degradation of these proteins subsequently leads to an increased  
194 concentration of serum and synovial fluid D-dimer.<sup>24</sup> Studies have also shown that coagulation  
195 factors that are formed following activation of the coagulation cascade can have  
196 proinflammatory effects.<sup>25,26</sup> Inducible tissue factor expression has been reported in endothelial  
197 cells and monocytes following *in vitro* augmentation with proinflammatory factors, such as  
198 cytokines (IL-1, IL-6, and tumor necrosis factor [TNF]).<sup>27</sup> Furthermore, several studies have  
199 shown that fibrin(ogen) itself can mediate and enhance the inflammatory response<sup>28-30</sup>. In fact  
200 an older study by Ribera et al.<sup>14</sup> demonstrated that the concentration of synovial fluid D-dimer  
201 increased several folds in foals with septic joint disease, endorsing the fact that D-dimer is  
202 involved in mediating inflammation/infection in the joint. The increased fibrinolytic activity and  
203 generation of byproducts such as D-dimer are believed to localize the infecting organisms or  
204 inflammatory cells and thus prevent their systemic damage. The byproduct of this fibrinolytic  
205 activity also “leaks” into the circulation and can thus be measured.

206 Serum D-dimer levels has been shown to be a significant prognostic factor in patients with  
207 systemic sepsis. Rodelo et al.<sup>31</sup> reported that higher levels of D-dimer are associated with an  
208 increased 28-day mortality in patients with sepsis and emphasized the prognostic role of D-dimer  
209 for septic patients.

210 This study has several strengths. First, patients were recruited prospectively and unlike most  
211 diagnostic studies that limit their population to patients without concurrent inflammatory  
212 conditions, our cohort was heterogeneous and included patients with inflammatory conditions,

213 metallosis, polyethylene wear, as well as those who were receiving ongoing antibiotic therapy.  
214 We believe that the inclusion of these patients provided a more realistic clinical situation  
215 allowing for the evaluation of D-dimer in clinical settings. As part of our ongoing efforts, we  
216 investigated numerous other serum biomarkers in an animal model of PJI and also in a small  
217 cohort of patients and found that D-dimer outperformed all of the other serum markers of  
218 infection<sup>1</sup>. The second strength of this study is that we included a cohort of “positive control”  
219 patients with infection at sites other than a joint. This allowed us to assess whether D-dimer is  
220 elevated by non-joint related infections. It certainly appeared that D-dimer is a better test than  
221 ESR and CRP in this clinical setting as it was elevated in only 12% of patients compared to ESR  
222 being elevated in 100% and CRP being elevated in 84% of patients. The other strength of this  
223 study is that it evaluated the role of a serum marker for patients undergoing reimplantation,  
224 arguably the most understudied area in orthopedic infections. D-dimer appeared to have an  
225 impressive performance in that setting also. Finally, we used statistical methods to determine the  
226 appropriate threshold for D-dimer for diagnosis of PJI. Although the latter could change with  
227 addition of further data from our institution or others, it is a great starting point and a guide to  
228 clinicians who may wish to use this test.

229 The study suffers some limitations and our findings should be interpreted in light of these  
230 shortcomings. There is no “gold standard” for the diagnosis of PJI, therefore, some of the  
231 patients that were allocated in the non-infection group might be in fact, infected and the reverse  
232 may also be true. The MSIS criteria for PJI, however, is universally accepted as the best  
233 definition for PJI<sup>3</sup> and was used as the gold standard in this study and the analyses that were  
234 performed. Although patients with systemic inflammatory diseases and those who received  
235 immunosuppressive therapies were not excluded from this study, our cohort contains a few

236 patients with these conditions. In the absence of a large number of patients, we refrain from  
237 making comments regarding the value of D-dimer in evaluating patients for PJI who have  
238 concurrent inflammatory joint disease. We are, in a follow-up study, examining this issue.  
239 Lastly, the lack of frozen section in these patients may be considered as a shortcoming. We do  
240 not routinely perform frozen section or histology in our patients undergoing revision surgery or  
241 reimplantation due to the fact that we believe the latter, at least at our institution, has serious  
242 limitations. Therefore, data related to frozen section or histology was not available for the  
243 comparisons that were performed in this study.

244 This study, for the first time, demonstrates the real value of serum D-dimer for diagnosis of PJI  
245 and in determining the presence of infection in patients undergoing reimplantation. Based on the  
246 findings of this study, we believe that serum D-dimer, an inexpensive and universally available  
247 test, should be added to the work-up of patients for PJI. Elevated D-dimer for patients  
248 undergoing reimplantation should be taken seriously as it could be an indication of persistent  
249 infection.

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341

342 **Figure Legend:**

343 **Figure 1.** Number of included and excluded patients in each study group.

344 **Figure 2.** D-dimer levels in the study groups. The red line determines the calculated threshold  
345 for diagnosis of PJI (850 ng/mL). Group A: Primary arthroplasties, Group B: Aseptic revisions,  
346 Group C: Revisions for infection, Group D: Reimplantations, and Group E: Patients with  
347 infection in sites other than a joint. One of the patients in Group C had a D-dimer of 8,487  
348 ng/mL that is not represented in the graph.

349  
350 **Figure 3.** ESR levels in the study groups. The red line determines the threshold recommended by  
351 the musculoskeletal infection society (30 mm/hr). Group A: Primary arthroplasties, Group B:  
352 Aseptic revisions, Group C: Revisions for infection, Group D: Reimplantations, and Group E:  
353 Patients with infection in sites other than a joint.

354  
355 **Figure 4.** CRP levels in the study groups. The red line determines the threshold recommended  
356 by the musculoskeletal infection society (10 mg/L). Group A: Primary arthroplasties, Group B:  
357 Aseptic revisions, Group C: Revisions for infection, Group D: Reimplantations, and Group E:  
358 Patients with infection in sites other than a joint.

359

360 **Table 1.** Definition of PJI according to the musculoskeletal infection society and the threshold  
 361 for the minor diagnostic criteria.

362

PJI is present when one of the major criteria or three out of five minor criteria exist		
<b>Major Criteria</b>	1) Two positive periprosthetic cultures with phenotypically identical microorganism <b><u>OR</u></b> 2) A sinus tract communicating with the joint	
<b>Minor Criteria</b>		Recommended Threshold
	1) Elevated serum CRP <b><u>AND</u></b> ESR	10 mg/L 30 mm/hr
	2) Elevated SF WBC count <b><u>OR</u></b> Changes in the leukocyte esterase strip	3,000 cells/ $\mu$ L  + Or ++
	3) Elevated SF PMN%	80%
	4) Positive histological analysis of the periprosthetic tissue	>5 neutrophil per high power field in 5 high power fields ( $\times$ 400)
	5) A single positive culture	

363

364

365 **Table 2.** Demographics of the study groups. Group A: Primary arthroplasty, Group B: Aseptic  
 366 revisions, Group C: First stage of a two stage exchange revision protocol, Group D: Second stage  
 367 of a two stage exchange protocol (reimplantation), Group E: Patients with infections other than  
 368 periprosthetic joint infection.

369

	Group A (N=23)	Group B (N=86)	Group C (N=57)	Group D (N=29)	Group E (N=50)	<i>p</i> -value
Sex	12 Male/11 Female	49 Male/37 Female	24 Male/33 Female	16 Male/13 Female	28 Male/22 Female	>0.05
Age (years)	65.3 (44- 75)	63.6 (51- 81)	59.7 (49- 76)	62.2 (51- 77)	56.2 (44- 78)	
Presence of systemic inflammatory condition	2 patients	5 patient	4 patients	1 patient	2 patients	
Joint	9 Knee/ 14 Hip	40 Knee/46 Hip	35 Knee/ 22 Hip	14 Knee/ 15 Hip	Not applicable	

370

371

372 **Table 3. Comparing laboratory values between two cohorts of patients with infection either**  
 373 **in a joint (Group C) or elsewhere in the body (Group E)**

Table 3.			
	<b>Patients with periprosthetic joint infection (Group C) (N=57)</b>	<b>Patients with infection in sites other than a joint (Group E) (N=50)</b>	<b><i>p</i>-value</b>
<b>D-Dimer (ng/dL)*</b>	1110 (243 to 8,487)	335 (150 to 1,420)	<0.0001
<b>Erythrocyte sedimentation rate (mm/Hr)*</b>	46 (7 to 127)	67 (35 to 121)	0.0016
<b>C-reactive protein (mg/L)*</b>	37 (2 to 328)	42 (1 to 79)	0.9732

381 \*Laboratory values are presented as median and (range).

382

383 Table 4. Performance of the serum tests for diagnosing periprosthetic joint infection. ESR:  
384 Erythrocyte Sedimentation Rate, CRP: C-reactive Protein.

385

	<b>ESR</b>	<b>CRP</b>	<b>D-Dimer</b>
<b>TN</b>	110	112	128
<b>FN</b>	15	12	6
<b>FP</b>	30	28	10
<b>TP</b>	42	45	51
<b>Sensitivity</b>	73.68%	78.95%	89.47%
<b>SE of Sensitivity</b>	5.83%	5.40%	4.06%
<b>Specificity</b>	78.57%	80.00%	92.75%
<b>SE of Specificity</b>	3.47%	3.38%	2.21%
<b>PPV</b>	58.33%	61.64%	83.61%
<b>SE of PPV</b>	5.81%	5.69%	4.74%
<b>NPV</b>	88.00%	90.32%	95.52%
<b>SE of NPV</b>	2.91%	2.66%	1.79%
<b>+LR</b>	3.43	3.94	12.34
<b>-LR</b>	0.33	0.26	0.11

386

387 TN: True Negative, FN: False Negative, FP: False positive, TP: True Positive, SE: Standard  
388 Error, PPV: Positive Predictive Value, NPV: Negative Predictive Value, +LR: Positive  
389 Likelihood Ratio, -LR: Negative Likelihood Ratio

390

**Table 5. Patients that required reoperation in our study cohort. N/A: not available.**

Name	Date of Procedure	Primary	Aseptic Revision	Revision for PJI	Reimplantation	CRP (mg/L)	ESR (mm/Hr)	D-dimer (ng/mL)	Intraoperative Cultures
Patient #1	8/19/2015			X		145	120	3,051	MSSA
	4/8/2016			X		16	40	3,664	MSSA
	6/22/2016				X	9	69	170	NEGATIVE
Patient #2	1/27/2016			X		179	105	959	STAPHYLOCOCCUS AUREUS
	4/22/2016				X	6	18	579	NEGATIVE
Patient #3	4/24/2016			X		328	83	978	MSSA
	7/18/2016				X	20	29	762	NEGATIVE
Patient #4	2/9/2016			X		21	33	2,536	STAPHYLOCOCCUS EPIDERMIDIS
	4/12/2016			X		4	22	973	NEGATIVE
Patient #5	4/27/2016			X		122	1270	930	MSSA
	7/13/2016				X	11	14	548	NEGATIVE
Patient #6	3/30/2016			X		43	60	1,228	STAPHYLOCOCCUS EPIDERMIDIS
	5/25/2016			X		77	47	1,502	MSSA
Patient #7	5/31/2016			X		3	14	910	NEGATIVE
	7/19/2016				X	7	29	637	NEGATIVE
Patient #8	6/6/2016		X			14	44	298	N/A
	6/28/2016			X		137	89	776	MSSA
Patient #9	2/2/2016			X		25	60	1,101	STAPHYLOCOCCUS EPIDERMIDIS
	4/12/2016				X	8	20	1,038	STAPHYLOCOCCUS EPIDERMIDIS
Patient #10	3/25/2016			X		26	34	2,060	GROUP B STREPTOCOCCUS
	6/17/2016				X	6	12	614	NEGATIVE
Patient #11	5/26/2015			X		8	7	1,110	P.ACNES
	3/22/2016			X		35	73	928	NEGATIVE
Patient #12	4/27/2015	X				1	11	271	N/A
	3/14/2016		X			1	13	311	N/A
Patient #13	3/1/2016			X		65	36	2,038	NEGATIVE
	5/27/2016				X	11	27	2,113	NEGATIVE
Patient #14	10/23/2015			X		109	48	8,487	STREP SANGUINIS
	3/11/2016				X	1	9	6,381	P.ACNES
Patient #15	3/23/2016			X		127	86	1,483	MSSA
	6/10/2016				X	6	30	877	NEGATIVE
Patient #16	6/3/2015			X		47	69	995	NEGATIVE
	6/29/2016			X		37	45	1,391	MRSA
Patient #17	6/7/2016				X	4	47	204	NEGATIVE
	7/26/2016			X		34	120	521	SERRATIA MARCESCENS



**Table 6.** Culture results in patients who underwent revision surgery due to periprosthetic joint infection.

<b>Culture results</b>	<b>Count</b>
<i>Methicillin-sensitive Staphylococcus aureus</i>	12
<i>Staphylococcus epidermidis</i>	9
<i>Methicillin-resistant Staphylococcus aureus</i>	4
<i>Propionibacterium acnes</i>	3
<i>Streptococcus agalactiae Group B</i>	2
<i>Polymicrobial</i>	2
<i>Anaerobic gram positive cocci</i>	1
<i>Klebsiella pneumoniae</i>	1
<i>Streptococcus sanguinis</i>	1
<i>Enterobacter cloacae</i>	1
<i>Streptococcus mutans</i>	1
<i>Serratia marcescens</i>	1
Negative Cultures	19

**Table 7.** Periprosthetic joint infections with negative culture. The false-negative laboratory values are marked in yellow (Thresholds are based on the Musculoskeletal Infection Society diagnostic criteria for periprosthetic joint infection. D-dimer's threshold [850 ng/mL] is calculated based on the results of this study).

<b>Patient number</b>	<b>CRP (mg/L)</b>	<b>ESR (mm/hr)</b>	<b>D-dimer (ng/mL)</b>
1	57	80	911
2	37	13	1906
3	32	13	2166
4	10	29	1106
5	89	94	2577
6	78	93	2258
7	5	25	999
8	65	36	2038
9	6	21	929
10	35	73	928
11	4	22	973
12	8	10	923
13	13	66	2631
14	8	17	770
15	3	14	910
16	31	36	1265
17	2	10	243
18	2	31	4733
19	8	31	1681

Figure 1.

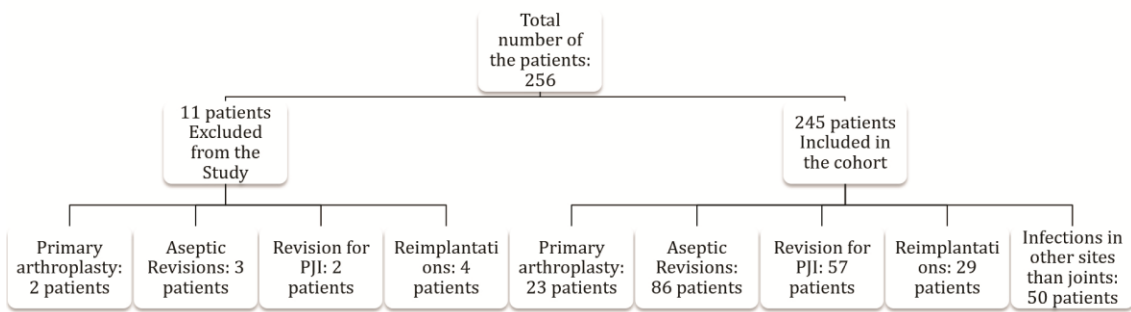


Figure 2.

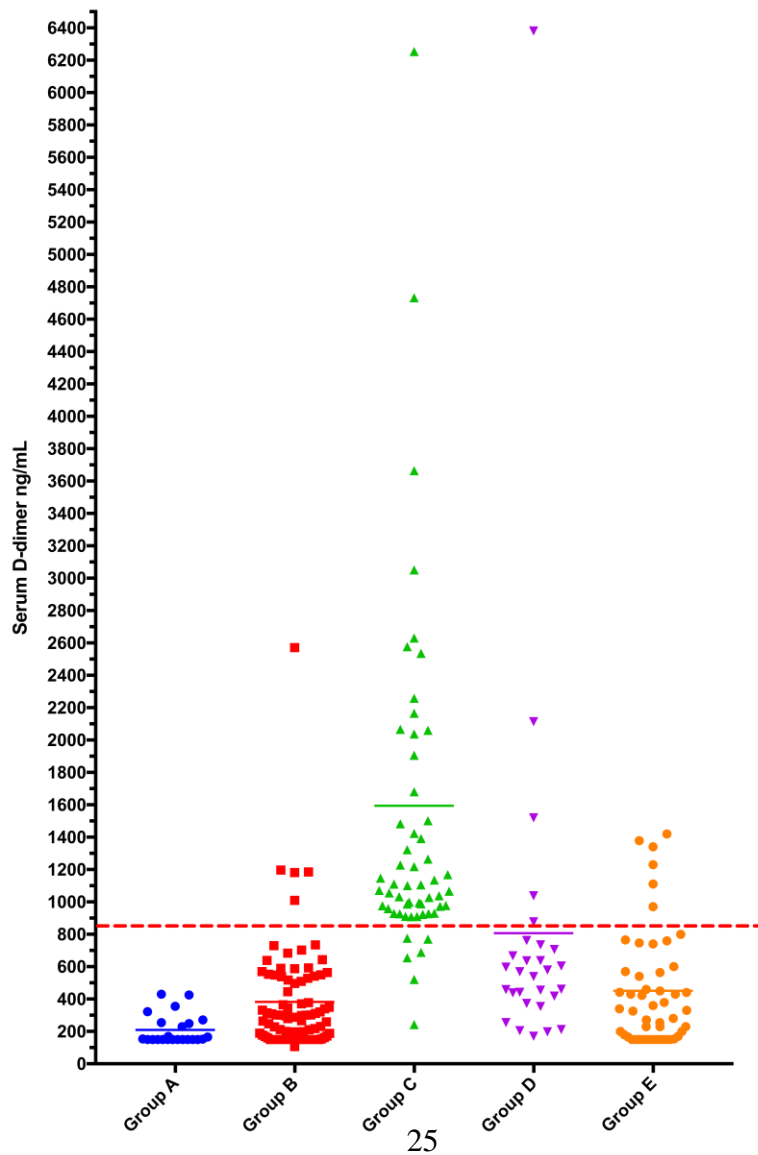


Figure 3.

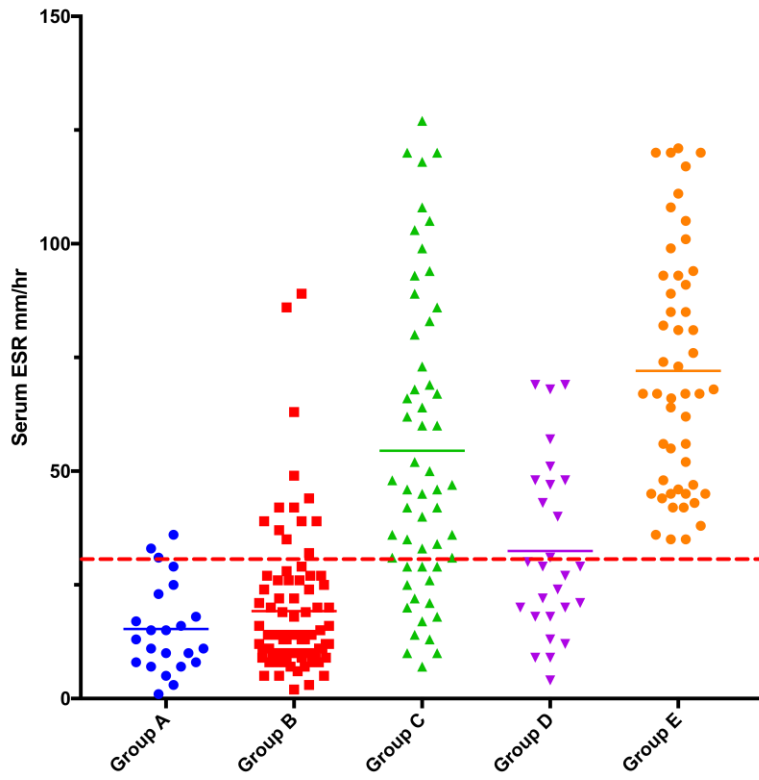


Figure 4.

