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ABSTRACT:

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

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

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

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

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

Level of Evidence: Diagnostic Level II.

INTRODUCTION:

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

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

Moreover, the levels of ESR and CRP may be normal in patients with PJI caused by slow growing organisms such as *Proprionibacterium acnes*[4,5]. In fact the document introducing the MSIS criteria for PJI explicitly states that the levels of some of these markers may be normal in the presence of PJI caused by slow growing organisms that do not elicit physiological inflammation and cautions clinicians in interpreting the level of serological markers in these situations [6].

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

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

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

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

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

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

MATERIALS AND METHODS:

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

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

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

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

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

Statistical Analysis

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

tests were calculated along with their 95% confidence intervals. All statistical analyses were performed using GraphPad Prism, version 7.0a, GraphPad software Inc. California, USA.

Source of Funding: This study was funded in part by a grant from the Orthopaedic Research and Education Foundation (OREF).

RESULTS:

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

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

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 (2-328 mg/L) in PJI patients, 9.2 mg/L (1-27 mg/L) in the reimplantation group, and 47 mg/L (1-179 mg/L) in patients with infection in sites other than a joint (Figure 4), (Table 3).

Using the MSIS thresholds (Table 1), serum CRP and ESR had a sensitivity of 79% (95% Confidence interval [CI]: 66-88%) and 74% (95% CI: 60-84%) and a specificity of 80% (95% CI: 72-86%) and 78% (95% CI: 70-85%), respectively. The sensitivity and specificity of ESR and CRP combined was 84% (95% CI: 76-90%) and 47% (95% CI: 36-58%), respectively**.** Using the calculated threshold for D-dimer (850 ng/mL), Serum D-dimer test had a better sensitivity at 89% (95% CI: 77-95%) and a better specificity at 93% (95% CI: 86-96%) for diagnosing PJI (Table 4). D-dimer was also useful in predicting the presence of infection at the time of reimplantation. Five patients had elevated D-dimer at the time of reimplantation. Of these patients who were reimplanted, two had a positive culture (*Propionibacterium acnes* in one and *Staphylococcus epidermidis* in the other one*)* from intraoperative specimens (Patients #9 and #14 in Table 5). Both of these patients subsequently failed due to infection. It is interesting to note that the corresponding CRP and ESR levels were falsely negative in both of these patients (CRP: 8 and 1 mg/L and ESR: 20 and 9 mm/hr). We are closely following the other three patients with "false positive" D-dimer at the time of reimplantation.

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

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

DISCUSSION:

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

Clinicians are familiar with serum D-dimer as it has been used, albeit with disappointing performance, in screening patients for venous thromboembolism (VTE). [21–23] In recent years

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

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

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

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

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

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

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

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Figure Legend:

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

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

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

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

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

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PJI is present when one of the major criteria or three out of five minor criteria exist		
Major Criteria	1) Two positive periprosthetic cultures with phenotypically identical microorganism **OR** 2) A sinus tract communicating with the joint	
Minor Criteria		Recommended Threshold
	1) Elevated serum CRP **AND** ESR	10 mg/L 30 mm/hr
	2) Elevated SF WBC count **OR** Changes in the leukocyte esterase strip	3,000 cells/μL + 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 (×400)
	5) A single positive culture	

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

	Group A (N=23)	Group B (N=86)	Group C (N=57)	Group D (N=29)	Group E (N=50)	*p*-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	

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

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

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

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

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

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

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.

Culture results	Count
Methicillin-sensitive Staphylococcus aureus	12
Staphylococcus epidermidis	9
Methicillin-resistant Staphylococcus aureus	4
Propionibacterium acnes	3
Streptococcus agalactiae Group B	2
Polymicrobial	2
Anaerobic gram positive cocci	1
Klebsiella pneumoniae	1
Streptococcus sanguinis	1
Enterobacter cloacae	1
Streptococcus mutans	1
Serratia marcescens	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).

Patient number	CRP (mg/L)	ESR (mm/hr)	D-dimer (ng/mL)
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.

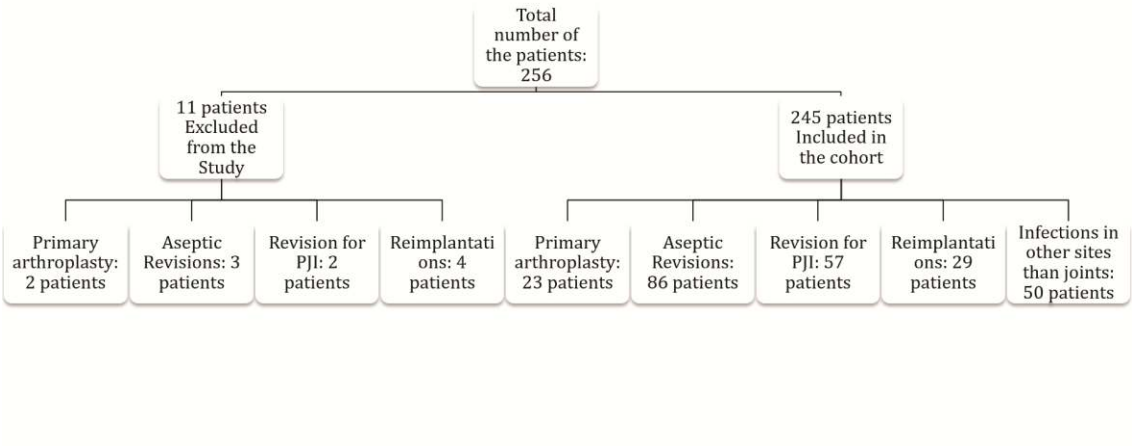

Figure 2.

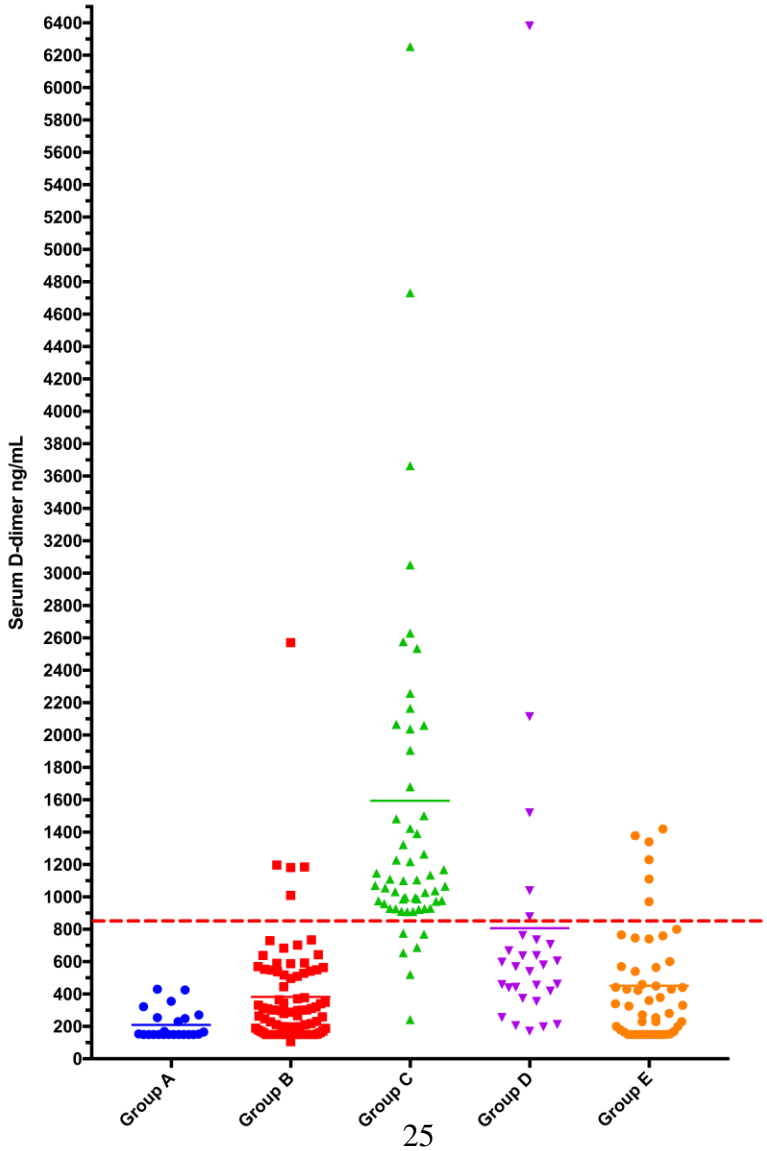

Figure 3.

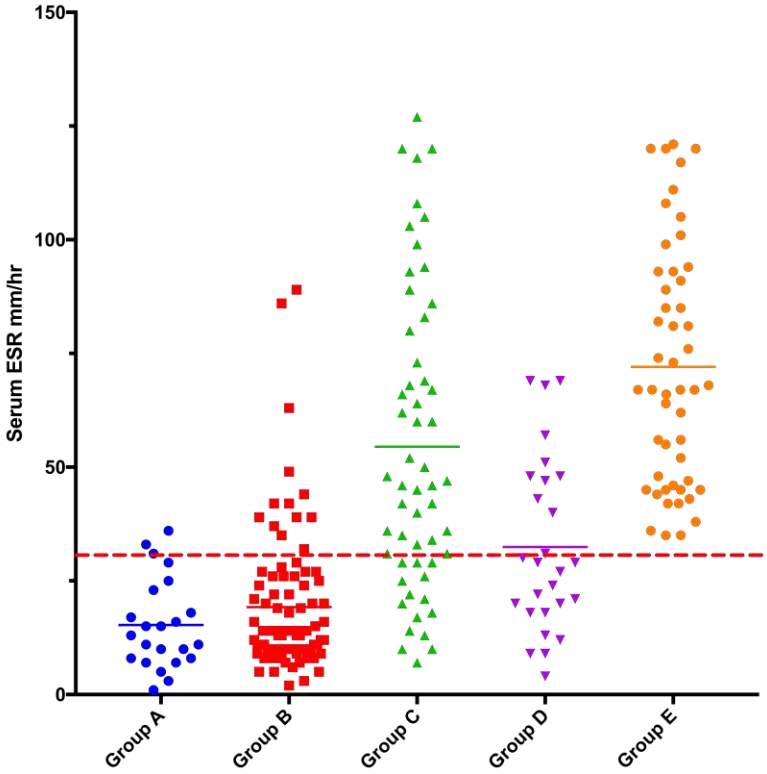

Figure 4.