Subclinical Abnormal Coagulation in Periprosthetic Joint Infection: A Retrospective Cohort Study

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Research article

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Abstract

Background: Periprosthetic joint infection (PJI) is a serious complication of total joint arthroplasty and often indicate disastrous outcomes. However, the change of coagulation profile in PJI patients has not been explored up to now. Therefore, we performed a single-center retrospective cohort study to determine: 1) the coagulation profile in PJI patients 2) the diagnostic efficacy of coagulation profile for PJI diagnosis based on the MSIS criteria.

Methods: Between 2016 January and 2018 December, a total of 371 patients receiving joint revisions were included in this cohort study. The corresponding medical records were scrutinized to establish the final diagnosis of PJI according to the 2014 MSIS criteria. The difference of coagulation profile between PJI and aseptic loosening patients was analyzed. Moreover, receiver operating characteristic curves were used to determine the proper sensitivity and specificity of coagulation makers.

Results: The levels of APTT, D-dimer, plasma fibrinogen, INR and Platelet Count in PJI group were significantly higher than that in non-PJI group (P<0.05). The AUCs of plasma APTT, plasma D-dimer, plasma fibrinogen and platelet count for PJI diagnosis were 0.625 (95%CI: (0.543, 0.706)), 0.731 (95%CI: (0.656, 0.806)), 0.831 (95%CI: (0.771, 0.890)) and 0.733 (95%CI: (0.660, 0.805)), respectively. Moreover, the coagulation profile was combined by logistic model and the corresponding AUC was 0.865 (95%CI: (0.812, 0.918)).

Conclusions: Despite relatively normal coagulation profile, PJI patients suffer from subclinical abnormal coagulation compared to non-PJI patients. The coagulation profile (APTT, INR, plasma fibrinogen, platelet count, D-dimer) in PJI patients is different from that in non-PJI patients significantly. And the coagulation profile can play a role in PJI diagnosis.

Introduction:

Total joint arthroplasty (TJA) is a successful surgery during the last century because it relieves pain and improves the quality of life for patients with advanced joint diseases[1]. Periprosthetic joint infection (PJI), indicating unfavorable outcomes, is one of the most disastrous complications after total joint arthroplasty (TJA) [2]. And coagulation system is a complex system and abnormal coagulation in perioperative TJA patients is often associated with serious complications such as deep venous thrombosis (DVT), surgical site infection (SSI), deep infection and increased blood loss [3]. Moreover, coagulopathic patients often have delays in surgery and cause aggravated anxiety to both surgeons and patients [3].

Application of coagulation profile in the diagnosis of PJI is emerging recently. Many studies reveal that the levels of plasma fibrinogen and D-dimer in PJI patients are higher than that in non-PJI patients and these markers can play a role in PJI diagnosis[4–6]. Besides, D-dimer was introduced into the 2018 ICM criteria by Parvizi[7–9]. Plasma fibrinogen and D-dimer are indicators of coagulation and fibrinolytic system, respectively. The abnormal fibrinogen and D-dimer in PJI patients may indicate the presence of
abnormal coagulation. In [8], Arjun Saxena e.t suggested that PJI can cause abnormal coagulation and more than one half of patients with PJI may have abnormal coagulation even without being exposed to anticoagulation agents. But the abnormal coagulation in his study was defined when INR > 1.12. However, this definition can lead to bias because INR only reflect extrinsic pathway of coagulation cascade and corresponding intrinsic pathway wasn't evaluated in this study[8]. Besides, several studies also revealed that the use of plasma fibrinogen and D-dimer for the diagnosis of PJI[10, 9, 11, 12]. Recently, the use of platelet count for PJI diagnosis was proposed by Pei F[11]. Despite that these studies suggested the change of coagulation profile in PJI patients, these studies only reflected limited aspects of coagulation system. A comprehensive coagulation profile in PJI patients haven't been explored and built up to now.

In order to comprehensively explore the change of coagulation profile in PJI patients and establish a PJI diagnostic tool based on the preoperative coagulation tests, we conducted a single-center retrospective cohort study to determine 1) the change of coagulation profile in PJI patients 2) the diagnostic efficiency of coagulation profile for PJI based on the MSIS criteria.

Materials And Methods:

Inclusion and exclusion criteria:

Between 2016 January and 2018 December, a total of 371 suspected PJI patients who underwent joint revisions were included in this study as initial patients. The exclusion criteria were as follows: 1) internal fixation implantation 2) patients who were exposed to anticoagulation agents (NSAID, corticosteroid hormone, clopidogrel e.g.) or trauma within 2 weeks before revisions 3) coronary stents or filter implantation 4) periprosthetic fractures 5) prosthetic dislocation. Finally, 332 patients (PJI patients and non-PJI patients) were included in this study. The detailed information on this process was summarized in Figure 1.

Definition:

Suspected PJI was considered when a patient suffered from acute or persistent rest pain, swelling, redness, warmth around the joints, elevated erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) level, or implant failure within 5 years after total joint arthroplasty without any reasonable explanation.

The diagnostic criteria and data collection:

The medical records of these patients were scrutinized and the final diagnosis of PJI was based on the 2014 MSIS criteria (table 4)[13]. Besides, the chart review were performed by the first authors carefully and following data about coagulation profile were extracted: activated partial thromboplastin time (APTT), prothrombin time (PT), international normalized ratio (INR)thrombin time (TT), antithrombin 3
(AT3), prothrombin activity (PTA), plasma D-dimer, plasma fibrinogen and plasma Ca+. Moreover, following information was extracted: the age, sex, body mass index (BMI), ASA scores, the comorbidities of liver diseases, kidney diseases, heart diseases, lung disease, diabetes, and inflammatory joint diseases.

**Statistical analysis:**

The continuous variables were described as means and standard deviations and a t test was used to assess the comparison if normal distribution of continuous variables was detected. Otherwise, rank sum test was used and corresponding medians were calculated. Dichotomous data described as frequencies and percentages were compared by the chi-squared test. P<0.05 indicated statistical significance. Receiver operating characteristic curves (ROC) were used to determine the relationship between the sensitivity and specificity of coagulation profile. Logistic regression was used to build the diagnostic model based on significantly up-regulated coagulation indicators (APTT, plasma fibrinogen, D-dimer, and platelet count). Moreover, Youden's index was used to determine optimal cut-off values. SPSS (IBM; version 26.0) was used to perform all statistical analysis.

**Results:**

1. **Demographic characteristics:**

The median age in the PJI and non-PJI groups was 63 and 61 years, respectively, and no significant differences found between the two groups. Similarly, no significant differences were found in the percentages of females, liver diseases, kidney diseases, lung diseases, heart diseases, smoking and drinking. However, the level of BMI and the percentage of hip circumference were significantly different between the PJI and non-PJI groups. The details were shown in Table 1.

Table 1

| The Demographic Characteristics of Cases Included in This Study. |
| characteristics               | PJI group(n=181) | non-PJI group(n=151) | P value |
|------------------------------|------------------|----------------------|---------|
| Age**                        | 63(53,71)        | 61(52,70)            | 0.202   |
| Female (n,%                  | 91, 50.28%       | 86, 59.95%           | 0.225   |
| Hip (n,%                     | 96, 53.04%       | 116, 76.82%          | P<0.001 |
| BMI**                        | 25.05(22.52,27.84) | 21.49(16.0,24.92)   | 0.002*  |
| ASA(n,%)                     |                  |                      |         |
| 1                            | 3, 1.66%         | 5, 3.31%             | 0.476   |
| 2                            | 145, 80.11%      | 117, 77.48           | 0.559   |
| 3                            | 22, 12.15%       | 18, 11.92%           | 0.948   |
| 4                            | 2, 1.10%         | 0,                   | 0.503   |
| Liver disease (n,%           | 3, 1.66%         | 3, 1.99%             | 1       |
| Kidney disease (n,%          | 1, 0.55%         | 2, 1.32%             | 0.593   |
| Heart disease (n,%           | 7, 3.87%         | 6, 3.97%             | 0.960   |
| Lung disease (n,%            | 3, 1.66%         | 5, 3.31%             | 0.476   |
| DM (n,%                      | 28, 15.47%       | 14, 9.27%            | 0.091   |
| Inflammatory joint diseases (n,% | 17, 9.39%       | 15, 9.93%           | 0.868   |

*P<0.05

**values were given as the medians with the IQR in the paratheses.

2. The difference of the coagulation profile between PJI group and non-PJI group.

As shown in table 2, the levels of APTT, D-dimer, plasma fibrinogen, INR and platelet Count in PJI group were significantly higher than that in non-PJI group. There is no significant difference between the two groups in the values of PT, TT and AT3. The APTT level in PJI group was 38s and 36s in non-PJI group(P<0.001). The D-dimer in PJI group was 1.52 and 0.74 in non-PJI group(P<0.001). The plasma fibrinogen in PJI group was 4.99 and 3.22 in non-PJI group(P<0.001). The platelet count in PJI group was 275.27 and 226.65 in non-PJI group(P<0.001). The corresponding clinical reference values in our laboratory were listed in table 2.
The Difference of Coagulation Markers Between PJI Group and non-PJI Group.

|                     | PJI group       | non-PJI group   | P value |
|---------------------|-----------------|-----------------|---------|
| **APTT***(s)**      | 38(35.0,41.7)   | 36(33.6,38.85)  | P<0.001 |
| **PT***(s)**        | 13.4(12.8,14.0) | 13.3(12.85,13.75)| 0.10    |
| **INR**             | 1.04(0.98,1.10) | 1.02(0.97,1.07) | 0.02    |
| **TT***(s)**        | 15.8(15.2,16.6) | 16(15.3,16.6)   | 0.65    |
| **AT3 (%)**         | 87(76,101)      | 89.65(77,99)    | 0.51    |
| **ACT (s)**         | 94.5(86,104)    | 97(89.5,105)    | 0.10    |
| **Plasma Ca+**      | 2.2(2.11,2.29)  | 2.2(2.12,2.27)  | 0.67    |
| **Platelet count**  | 275.27±74.55    | 226.65±64.88    | P<0.001 |
| **D-dimer (μg/mL)** | 1.52(0.88,2.38) | 0.74(0.45,1.43) | P<0.001 |
| **Plasma fibrinogen** | 4.99(4.12,5.79) | 3.22(2.82,3.95) | P<0.001 |
| **ESR (mm/hr)**     | 36(22,62)       | 10(5.5,16)      | P<0.001 |
| **CRP (mg/dl)**     | 1.93(0.9,3.9)   | 0.316(0.1,0.60) | P<0.001 |

*Values are given as median with the IQR in the parentheses.

+values are given as means with the 95%CI.

**P<0.05

3. The diagnostic efficiency of coagulation profile for PJI diagnosis based on the MSIS criteria

The diagnostic efficiency of coagulation profile was evaluated and depicted in ROC curves (Fig.2). The AUCs of APTT, D-dimer, plasma fibrinogen and platelet count were 0.625(95%CI: (0.543,0.706)),0.731(95%CI:(0.656,0.806)),0.831(95%CI:(0.771,0.890)),0.733(95%CI:(0.660,0.805)), respectively. The optimal cut-off value of APTT for PJI diagnosis was 37.25 and the corresponding sensitivity and specificity were 0.637 and 0.637 respectively. The optimal predictive cutoff value of D-dimer was 0.745 and the corresponding sensitivity and specificity were 0.853 and 0.537 respectively. The optimal cut-off value of platelet count for PJI diagnosis was 245, and the corresponding sensitivity and specificity were 0.676 and 0.712 respectively. The optimal cut-off value of plasma fibrinogen for PJI diagnosis was 4.13 and the corresponding specificity and sensitivity were 0.755 and 0.825 respectively.
Moreover, the coagulation profile was combined by logistic model (appendix 1) and the corresponding AUC was 0.865(95%CI:(0.812,0.918)). The details about the diagnostic efficiency of coagulation profile and serum markers for PJI diagnosis were summarized in Table 3.

**Table 3**

| The Diagnostic Values of Tested Indicators in Suspected PJI Patients. |
|---|---|---|---|---|
| Indicator          | AUC (95%CI)       | Yonden's index | optimal cut-off | Sensitivity | Specificity |
| APTT               | 0.625(0.543,0.706) | 0.275          | 37.25           | 0.637       | 0.637       |
| Plasma fibrinogen  | 0.831(0.771,0.890) | 0.580          | 4.13            | 0.755       | 0.825       |
| D-dimer            | 0.731(0.656,0.806) | 0.390          | 0.7450          | 0.853       | 0.537       |
| Platelet count     | 0.733(0.660,0.805) | 0.389          | 245             | 0.676       | 0.712       |
| ESR                | 0.843(0.787,0.900) | 0.600          | 26.5            | 0.725       | 0.875       |
| CRP                | 0.824(0.761,0.887) | 0.629          | 0.789           | 0.804       | 0.825       |
| Combined Coagulation model | 0.865(0.812,0.918) | 0.619          | 0.476           | 0.794       | 0.825       |

**Discussion:**

In this study, we found that the coagulation profile in PJI patients was different from that in non-PJI patients and PJI patients can suffer from subclinical abnormal coagulation profile. In consistent with previous reports, some coagulation markers such as plasma D-dimer and fibrinogen show promising PJI diagnostic values. Besides, we also revealed a few new markers (APTT, INR and platelet count) for PJI diagnosis from the coagulation profile in PJI patients. Then we build a logistic model based on these 3 markers and the ROC analysis suggested this model was promising in PJI diagnosis.

PJI indicating that infection occurs to the prosthesis and surrounding tissues is one of the most disastrous complications after TJA and its pathogens are known to impair their host by secreting endotoxin and exotoxin which can stimulate CD8+ T cells and antigen-presenting cells (APC) to produce various cytokines[8]. These cytokines (IL-1, TNFα, and IL-6) can disrupt normal coagulation cascade and subsequently cause abnormal coagulation profile[14–16]. However, a review of literature suggests that the coagulation profile in PJI patients remain unknown. This study evaluated the change of coagulation profile in PJI patients.

In the presence of chronic infection, large amounts of endothelial cells can be disrupted and following cytokines and tissue factors will be released into the blood. Then coagulation system and following
fibrinogen system can be activated[17]. Eventually, the body will delete excessive coagulation factors such as antithrombotic factors, TFPI (tissue factor pathway inhibitor) for hemostasis[18, 19]. Then, following coagulopathy may appear in PJI patients.

The levels of APTT, INR, D-dimer, plasma fibrinogen, platelet count in the PJI group is significantly higher than that in non-PJI group. Despite relatively higher levels of APTT and INR, the levels of these two markers is still within clinical reference values. It suggests that PJI patients are suffering from subclinical abnormal coagulation. The levels of APTT and INR in PJI group is significantly higher than that in non-PJI group but the level of TT between the two groups is comparative. This condition reveals that the change of coagulation cascade in PJI group is mainly ascribed to the change of intrinsic pathway and extrinsic pathway instead of the common pathway (Fig. 3). Therefore, the coagulation factors participating in the two pathways of coagulation may be different between the two groups. However, this hypothesis needs approving further. And subsequent studies should focus on the change of coagulation factors in PJI patients.

The subclinical coagulation change may have potential influence on increased blood loss in PJI patients[20]. Elevated APTT and INR indicate impaired coagulation system and can cause increased joint effusion after revision. This is consistent with our clinical observation that patients after PJI revisions often have larger drainage volume and longer drainage tube retention time than non-PJI patients. However, the larger joint effusion volume can increase the likelihood of PJI recurrence conversely. It can be paradoxical when doctors try to hold the balance between the abnormal coagulation and VTE in PJI patients after revision. Besides, vitamin K and FFP which is often used in the treatment of patients with coagulopathies are associated with severe reactions such as allergy.[21] Therefore, correcting the abnormal coagulation in PJI patients may be a challenging work. And the association between abnormal coagulation profile and the outcomes of PJI need to be explored further.

The level of APTT and INR in PJI patients is significantly higher than that in non-PJI patients. It means that PJI patients suffer from hypocoagulation compared to non-PJI patients. In [8], Parvizi reveled similar results. Despite a fact that most coagulation indictors were still within clinical reference values, we do hold the opinion that the subclinical coagulation profile still causes some abnormalities. The use of regional anesthesia in these patients can increase the risk of epidural or spinal hematoma formation theoretically. And hypocoagulation may impair incision healing after surgery.

In this study, we also evaluated the use of coagulation profile for PJI diagnosis. We found that APTT, platelet count, plasma fibrinogen and D-dimer can play a role in the diagnosis of PJI. The use of D-dimer for the diagnosis of PJI have been introduced into the 2018ICM criteria and the application of plasma fibrinogen and platelet count in PJI diagnosis has also been revealed by several studies[10, 11]. But the accuracy of APTT has not been studied in suspected PJI patients. In our research, we found that plasma fibrinogen performed better than D-dimer and plasma fibrinogen when these markers were evaluated. It is consistent with previous studies and suggests that plasma fibrinogen can be a better marker than D-
dimer[10, 12]. Besides, although platelet count and the level of APTT had inferior diagnostic value compared with CRP, ESR, plasma fibrinogen and D-dimer, they can be useful for the diagnosis of PJI.

To further assess the performance of coagulation profile in PJI diagnosis, a logistic model was built based on significantly up-regulated coagulation indicators in PJI patients (APTT, plasma fibrinogen, D-dimer, and platelet count). And this model performed better than CRP and ESR in the diagnosis of PJI. This result suggested that the coagulation profile can be used as a screening tool in suspected PJI patients because this is a routine test before surgery and the corresponding cost is relatively low. Besides, this test can be performed in most hospitals. It makes this test become a simple screening tool for PJI diagnosis in primary hospital.

This study also has several limitations. First, even though the relationship between the coagulation profile and PJI was revealed by our study, we can't assess the change of certain coagulation factors because of limited medical information. Second, this was a retrospective study performed in a single center so the study design and absent in medical records can lead to selection bias. Besides, it is hard for us to discern the causal link between PJI and abnormal coagulation profiles. Third, some patients with systemic diseases (kidney disease, liver diseases and systemic inflammatory diseases e.g.) were not excluded from this study[22]. These conditions can influence the coagulation profile of PJI patients. However, the heterogeneous cohorts can also provide a more realistic clinical situation for the evaluation of the coagulation profile in PJI patients.

**Conclusions:**

PJI patients suffer from subclinical abnormal coagulation. The coagulation profile in PJI patients is different from that in non-PJI patients and can serve as a method for PJI diagnosis. However, the relationship between the subclinical hypocoagulation and clinical outcomes of PJI patients need to be explored further.

**Abbreviations**

TJA: Total joint arthroplasty

PJI: periprosthetic joint infection

MSIS: Musculoskeletal Infection Society criteria

PT: Prothrombin time

APTT: activated partial thromboplastin time

INR: International normalized ratio

PTA: Prothrombin Activity
Declarations

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Ethics approval and consent to participate

This study was approved by the institutional review board of our hospital (Chinese People's Liberation Army General Hospital).

Consent for publication

We have obtained consent to publish from the participants.

Competing interests

All authors declare that they have no competing interests.
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Conflict of Interest Statement:

Each author certifies that he or she has no commercial associations

Ethical review committee statement:

This study was performed in accordance with the ethical standards in the 1964 Declaration of Helsinki.

References

1. Wainwright TW, Gill M, McDonald DA, Middleton RG, Reed M, Sahota O, et al. Consensus statement for perioperative care in total hip replacement and total knee replacement surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. Acta Orthop. 2020;91(1):3–19.
2. Kapadia BH, Berg RA, Daley JA, Fritz J, Bhave A, Mont MA. Periprosthetic joint infection. Lancet. 2016;387(10016):386–94.
3. Cancienne JM, Werner BC, Browne JA. Complications After TKA in Patients With Hemophilia or Von Willebrand's Disease. J Arthroplast. 2015;30(12):2285–9.
4. Pannu TS, Villa JM, Riesgo AM, Patel PD, Barsoum WK, Higuera-Rueda CA. Serum D-Dimer in the Diagnosis of Periprosthetic Knee Infection: Where Are We Today? J Knee Surg. 2020;33(2):106–10.
5. Wu H, Meng Z, Pan L, Liu H, Yang X, Yongping C. Plasma Fibrinogen Performs Better Than Plasma d-Dimer and Fibrin Degradation Product in the Diagnosis of Periprosthetic Joint Infection and Determination of Reimplantation Timing. J Arthroplast. 2020;35(8):2230–6.
6. Xu C, Qu PF, Chai W, Li R, Chen JY. Plasma fibrinogen may predict persistent infection before reimplantation in two-stage exchange arthroplasty for periprosthetic hip infection. J Orthop Surg Res. 2019;14(1):133.

7. Parvizi J, Tan TL, Goswami K, Higuera C, Della Valle C, Chen AF, et al. The 2018 Definition of Periprosthetic Hip and Knee Infection: An Evidence-Based and Validated Criteria. J Arthroplast. 2018;33(5):1309–4.e2.

8. Saxena A, Baratz M, Austin MS, Purtill JJ, Parvizi J. Periprosthetic joint infection can cause abnormal systemic coagulation. J Arthroplast. 2011;26(1):50–7. 7.e1.

9. Shahi A, Kheir MM, Tarabichi M, Hosseinazadeh HRS, Tan TL, Parvizi J. Serum D-Dimer Test Is Promising for the Diagnosis of Periprosthetic Joint Infection and Timing of Reimplantation. The Journal of bone joint surgery American volume. 2017;99(17):1419–27.

10. Li R, Shao HY, Hao LB, Yu BZ, Qu PF, Zhou YX, et al. Plasma Fibrinogen Exhibits Better Performance Than Plasma D-Dimer in the Diagnosis of Periprosthetic Joint Infection: A Multicenter Retrospective Study. The Journal of bone joint surgery American volume. 2019;101(7):613–9.

11. Xu H, Xie J, Yang J, Chen G, Huang Q, Pei F. Plasma Fibrinogen and Platelet Count Are Referable Tools for Diagnosing Periprosthetic Joint Infection: A Single-Center Retrospective Cohort Study. J Arthroplast. 2020;35(5):1361–7.

12. Zhang Q, Dong J, Zhou D, Liu F. Circulating D-Dimer versus Fibrinogen in the Diagnosis of Periprosthetic Joint Infection: A Meta-Analysis. Surgical infections. 2020.

13. Parvizi J, Gehrke T. Definition of periprosthetic joint infection. J Arthroplast. 2014;29(7):1331.

14. Camerer E, Kolstø AB, Prydz H. Cell biology of tissue factor, the principal initiator of blood coagulation. Thrombosis research. 1996;81(1):1–41.

15. Franco RF, de Jonge E, Dekkers PE, Timmerman JJ, Spek CA, van Deventer SJ, et al. The in vivo kinetics of tissue factor messenger RNA expression during human endotoxemia: relationship with activation of coagulation. Blood. 2000;96(2):554–9.

16. Tapper H, Herwald H. Modulation of hemostatic mechanisms in bacterial infectious diseases. Blood. 2000;96(7):2329–37.

17. Levi M, Keller TT, van Gorp E, ten Cate H. Infection and inflammation and the coagulation system. Cardiovascular research. 2003;60(1):26–39.

18. Iversen N, Strekerud FG, Abildgaard U. Tissue factor pathway inhibitor (TFPI) in disseminated intravascular coagulation: low levels of the activated factor X-TFPI complex. Blood coagulation fibrinolysis: an international journal in haemostasis thrombosis. 2000;11(7):591–8.

19. Levi M, ten Cate H, van der Poll T, van Deventer SJ. Pathogenesis of disseminated intravascular coagulation in sepsis. Jama. 1993;270(8):975–9.

20. Balato G, Ascione T, De Franco C, De Matteo V, Verrazzo R, Smeraglia F, et al. Blood loss and transfusion rate in patients undergoing two-stage exchange in infected total knee arthroplasty. J Biol Regul Homeost Agents. 2020;34(3 Suppl. 2):1–5.
21. Casbard AC, Williamson LM, Murphy MF, Rege K, Johnson T. The role of prophylactic fresh frozen plasma in decreasing blood loss and correcting coagulopathy in cardiac surgery. A systematic review. Anaesthesia. 2004;59(6):550–8.

22. Sequeira SB, Labaran LA, Bell JE, Amin RM, Rao SS, Werner BC. Compensated Cirrhosis Is Associated With Increased Risk of Complications Following Total Hip Arthroplasty in a Large Medicare Database. The Journal of arthroplasty. 2020.

Table

Table 4

The 2014 MSIS criteria for PJI diagnosis:

| (1) Elevated serum C-reactive protein (CRP) AND erythrocyte sedimentation rate (ESR) |
| (2) A single positive culture |
| (3) Elevated synovial fluid white blood cell (WBC) count or ++ change on leukocyte esterase test strip |
| (4) Elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%) |
| (5) Positive histology analysis of periprosthetic tissue. (>=5 neutrophil cells per HP) |

* PJI was defined if more than 3 of following 5 criteria exist.

Figures
Figure 1

the selection process of patients included in this study.
Figure 2

The ROC Curve of Different Coagulation Markers for PJI Diagnosis
This condition reveals that the change of coagulation cascade in PJI group is mainly ascribed to the change of intrinsic pathway and extrinsic pathway instead of the common pathway (Fig 3).

**Supplementary Files**

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- appendix1.docx