

# Thromboelastography Performs Well for the Diagnosis of Periprosthetic Joint Infection.

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## Research article

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# Abstract

**Background:** Coagulation-related biomarkers are drawing new attention in diagnosing periprosthetic joint infection (PJI). Thromboelastography (TEG) analysis provides a comprehensive assessment of coagulation and therefore could be a promising test for PJI. This study aims to assess the value of TEG in diagnosing PJI and to determine the clinical significance of TEG in analyzing reimplantation timing for the second-stage revision.

**Methods:** From October 2017 to September 2020, 62 patients who underwent revision arthroplasty were prospectively included, PJI was defined by 2011 Musculoskeletal Infection Society (MSIS) criteria. Twenty-three patients were diagnosed with PJI (Group A) and the other 39 patients were included as aseptic loosen (Group B). Seventeen patients in Group A finished two-stage revision in our center. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), D-dimer and TEG parameters (K (clotting time), Angle ( $\alpha$ -angle), MA (maximum amplitude), A30 (amplitude at 30 min), TPI (thrombodynamic potential index)) were measured preoperatively in all included patients. Receiver operating characteristic curves were applied to evaluate the diagnostic value of these biomarkers.

**Results:** ESR (AUC 0.953, sensitivity 81.82, specificity 94.87) performed best in PJI diagnosis, followed by MA (AUC 0.895, sensitivity 82.61, specificity 97.44) and CRP (AUC 0.893, sensitivity 82.61, specificity 94.74). When these biomarkers combined in pairs, the diagnosis value improved compared with any individual biomarker. The overall success rate of the two-stage revision was 100%. ESR and MA showed valuable in determining the time of reimplantation, with their values all decreased below cut-off values before reimplantation.

**Conclusion:** TEG could be a promising test in assisting PJI diagnosis, and a useful tool in judging the proper timing of reimplantation.

## Background

Periprosthetic joint infection (PJI) is one of the most troublesome complications of total hip or knee arthroplasty, it exacerbates the burdens of the individual and health care system [1–4]. As the number of surgeries has surged year by year, the totality of PJI patients increased subsequently [5]. However, the diagnosis and treatment of PJI were quite challenging, besetting clinician for a long period.

Current diagnostic methods of PJI mainly include serological testing, synovial fluid testing, and intraoperative histological pathology [2, 5]. Although the diagnostic criteria are well defined, no gold standard has yet been found [4, 6]. Similarly, the treatment of PJI troubles clinician a lot, as no widely accepted criteria has been proposed [7, 8]. Nowadays, two-stage revision is the standard procedure for periprosthetic joint infection, but the proper time to perform the second-stage revision is still under debate [9].

As literature has revealed the closed correlations between the coagulation cascade and infection course, coagulation-related biomarkers are in the spotlight. Some biomarkers, such as D-Dimer and fibrinogen (Fib) have been proved promising in PJI diagnosis [10–13] and determining the timing of reimplantation [10, 14].

Thromboelastography (TEG) is a routine test of coagulation that assesses the whole process of the clotting along time in the body [15], TEG provides a full-scale evaluation of clot formation, elasticity, and duration with measures describing various coagulation elements [16]. K-value (clotting time) reflects the rate of blood clot formation and is an indicator of fibrinogen function [17], Angle ( $\alpha$ -angle) represents the clot growth rate, MA (maximum amplitude) means the maximum clot amplitude [18], A30 (amplitude at 30 min) measures clot strength at 30 minutes after MA [19], and TPI (thrombodynamic potential index) was derived from MA and K value [20]. TEG yields information about all phases of coagulation and provides further information over standard coagulation tests [16, 21]. Plentiful literature has proved that TEG is useful in evaluating coagulation status, predicting bleeding in patients with severe sepsis, monitoring hemostasis during cardiac surgery and liver transplant procedures, etc. [15, 21, 22]. However, no study has reported its value in diagnosing PJI and guiding reimplantation timing for the second-stage revision before.

The purpose of this study was carried to investigate (1) the value of TEG in distinguishing PJI from aseptic loosening, and (2) the ability of TEG parameters in guiding the proper time for the second-stage revision. This was compared with ESR, CRP, and D-Dimer.

## Methods

We conducted this retrospectively study of all revision total hip and total knee arthroplasties done at our hospital from October 2017 to September 2020, under the ethical approval from the institutional review board of our hospital. Totally 145 patients' records were acquired. Among them, 61 patients were diagnosed with PJI according to the MSIS criteria [23], and 84 patients were defined as aseptic loosening. Patients were excluded if one or more of the following situations exist: (1) lack of data; (2) recent use of anticoagulants; (3) with inflammatory arthritis such as rheumatoid arthritis, ankylosing spondylitis; (4) blood diseases such as thrombocytopenic purpura; (5) formation of deep vein thrombosis of lower limbs; (6) liver diseases; (7) malignancy; (8) infection of other tissue or organ.

Ultimately, 62 patients were included in this study: 23 in group A (patients undergoing revision arthroplasty for the treatment of PJI) and 39 in group B (patients receiving revision arthroplasty due to aseptic loosening). Eighty-three patients were excluded due to lacking needed data of the study ( $n = 55$ ), deep vein thrombosis formation of lower limbs ( $n = 24$ ), taking oral warfarin recently due to coronary stent implantation ( $n = 2$ ), urinary tract infection ( $n = 1$ ) and rheumatoid arthritis ( $n = 1$ ).

Patients' fasting venous blood samples were collected routinely on the second day of admission, then were sent to the clinical laboratory of our hospital for blood examination, including blood routine examination, conventional coagulation tests, and TEG. It takes about 30 minutes to acquire test results.

Group B was treated with a one-stage revision. While the two-stage revision for group A consisted of the following procedure: 1) The first stage revision was taking out the former prosthesis supervised with implantation of antibiotic-loaded cement spacers (4 g vancomycin/ 160 g gentamicin-containing bone cement). 2) At least 3 months after the first stage of treatment, surgeons made decisions whether to implant a new prosthesis or continue antibiotics protocols based on clinical symptoms combined with laboratory parameters.

All included patients were regularly followed up at 1 month, 3 months, 6 months, 1 year, and then each year after discharge. Functional outcomes, as well as complications, and the reason for any reoperation were recorded. According to Delphi based consensus, success or failure of reimplantation was defined by (1) control of infection, as characterized by a healed wound without fistula, drainage, or pain; (2) no subsequent surgical intervention for infection after reimplantation surgery; and (3) no occurrence of PJI-related mortality [24, 25].

## Statistical Analysis

The statistical analysis was calculated by IBM SPSS Statistics 26.0, and  $P < 0.05$  was considered statistically significant. Independent-sample t-tests were used for data conforming to normal distributions, the Mann-Whitney U tests were used for data not conforming to normal distributions, and categorical variables were summarized using chi-squared tests. Receiver operating characteristic (ROC) curves were drawn by MedCalc 19.0.7, and the areas under the curves (AUCs), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+ LR), and negative likelihood ratio (-LR) of each test were calculated. The Youden index was applied to determine these biomarkers' optimal cutoff value for the diagnosis of PJI. The scatterplot was drawn by GraphPad Prism software (version 8).

## Results

The demographic characteristics of each group are shown in Table 1. We can notice that there were no statistically significant differences between baselines of the two study groups, except for involved joints. Hip joint accounted for 87.18% in Group B and 30.43% in Group A, which was found to be statistically significant.

We noticed statistically significant differences in our tested markers between Group A and Group B ( $P < .001$ ) as shown in Table 1. The median values of CRP, ESR, D-Dimer, and TEG parameters (Angle, MA, A30, TPI) of Group A were significantly higher than Group B ( $P < .001$ ), while K median value was lower ( $P < .001$ ), on the contrary. Of note, this result demonstrated hypercoagulability existing in PJI patients.

To evaluate and compare the diagnostic value of tested markers, we drawn ROC curves (receiver operator characteristic curve) of each inflammatory and fibrinolytic marker, as shown in Fig. 1, and then calculated the AUC (area under the curve) of each ROC curve (Table 2). We determined these biomarkers' optimal cutoff value for the diagnosis of PJI according to the Youden index, and further figured up the sensitivity,

specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio of these inflammatory markers in the diagnosis of PJI, all these statistics were shown in Table 2. The AUCs for CRP, ESR, D-Dimer were 0.893 (95% confidence interval (CI), 0.787–0.958), 0.953 (95% CI, 0.866–0.991) and 0.717 (95% CI, 0.588–0.824) respectively. And AUCs of TEG parameters were ranging from 0.800 (K, 95%CI, 0.680–0.891) to 0.895 (MA, 95%CI, 0.790–0.958). Among all tested biomarkers, ESR had the highest AUC, and D-Dimer had the lowest AUC. Among TEG parameters, AUC of MA ranked first, followed by A30, TPI, Angle, and K. Although the AUC was lower than that of ESR, MA achieved a better sensitivity and specificity.

We further studied the diagnosis value of combination of tested parameter in pairs, and calculated AUC, sensitivity, specificity, PPV, NPV, +LR, and -LR of different combinations, all these statistics were exhibited in Table 3. The combinations of TEG parameters and CRP/ESR led to the improvement both in AUC, sensitivity, and specificity, except for ESR + MA and ESR + A30. And CRP + A30 achieved an obvious boost in diagnosis value.

After searching the history database management system, data of 17 patients who underwent two-stage revision surgery were available. The other 6 patients were unable to re-admit for the second staged surgery due to short intervals from the first staged surgery (less than 3 months). No patients showed the failure of reimplantation during the follow-up period ( $17.29 \pm 8.29$  (range 3–28) months) according to Delphi based consensus, but 2 of 17 patients had poor knee function with limited range of motion. By comparing tested biomarkers between stage 1 (the stage before spacers insertion) and stage 2 (the stage after re-admission for the second stage) of PJI patients, and then found all our tested markers except for D-Dimer ( $P = 0.059$ ) were statistically significant differences. Then we analyzed D-Dimer, ESR, CRP, and TEG parameters (K, Angle, MA, A30, TPI) of stage 1 and stage 2, then compared each patient's parameters with corresponding cutoff value and found that numerical value of ESR and MA had all decreased below the cutoff value during stage 2 (Fig. 2).

## Discussions

Plenty of studies have revealed the close association between coagulation and infection. Many researchers believed, endotoxins or components of the bacterial cell wall can trigger changes in coagulation through tissue factor (TF) released by a variety of cells, such as vascular endothelial cells and monocytes, and maintain TF in high expression by stimulating the release of cytokines, such as interleukins (ILs) and tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) [21, 26, 27]. Correspondingly, coagulation-related biomarkers, have recently been proved as valuable markers in the diagnosis of PJI. Geng Bin et al. [10] reported fibrinogen as a promising marker to aid in diagnosing PJI. Wu Hao et al. [12] demonstrated fibrinogen exhibits pretty value in PJI diagnosis. D-Dimer has been adopted as a minor criterion in the 2018 International Consensus Meeting (ICM) criteria for PJI, but it raised a hot debate after that. Qian Hu et al. [5] and Leilei Qin et al. [6] found D-Dimer is a valuable test for PJI diagnosing. Jiren Yan et al. [28] led a meta-analysis and found that D-Dimer is an effective serum biomarker for PJI diagnosis in patients without a history of hypercoagulation disease or inflammatory arthritis. While Tejbir et al. [2] and Rui Li et

al. [29] reported D-Dimer has a poor diagnostic value for PJI. Lauren et al. [30] found D-Dimer results vary significantly in different laboratories, even for the same sample, so they disagreed D-Dimer as a PJI diagnosis criterion. In our study, D-Dimer exhibited a low value in PJI diagnosing, and its numerical values were still high after ESR and CRP were decreased in the normal range.

However, these conventional coagulation biomarkers can only reflect the quantitative changes of platelet and fibrinogen. TEG is measuring all coagulation proteins and cellular elements on clot formation; it can trace the whole coagulation process from the beginning of coagulation to the lysis of blood clots and show the whole process in a form of a graph [17]. TEG has been widely applied in monitoring hemostasis during cardiac surgery and liver transplant procedures [21], guiding transfusion requirements in trauma patients, and during surgery and assessing septic coagulopathy in severely ill patients [15]. TEG can provide comprehensive coagulation status of our body, and provides additional data compared with standard coagulation tests [21]. Many studies have compared TEG and conventional coagulation tests in many clinical fields. Hani et al. [16] demonstrated TEG provides more information about the hemostatic state of patients with cirrhosis more than that of conventional coagulation tests. Cuizhu Luo et al. [31] reported TEG may be a reliable alternative to conventional coagulation methods for diagnosing sepsis-induced coagulopathy.

There is no study evaluating TEG's value in diagnosing PJI yet. Thus, we conducted the study to compare the value of TEG with the three most used biomarkers (CRP, ESR, and D-Dimer) in diagnosing PJI. In the present study, we highlight the value of ESR in diagnosing PJI, with AUC, the optimal cutoff, sensitivity, and specificity for ESR were 0.953, 34.0mm/h, 81.82%, and 94.87%. D-Dimer has the smallest AUC, and it is still high in PJI patients before the second stage surgery. The results are similar to several other studies [11, 12, 29], though small differences in the numerical value of AUC, cutoff value, sensitivity, and specificity. To the best of our knowledge, no study before has reported the value of TEG in the diagnosis of PJI. Our study found MA achieved a pretty good diagnosis value, with a specificity was 97.44%. And the combination of CRP/ESR with TEG parameters (K, Angle, MA, A30, TPI) achieved higher sensitivity and specificity than any individual, except for the two combinations (ESR + MA, ESR + A30). Although AUCs of these parameters were smaller than ESR, TEG is still a promising diagnosis testing for PJI.

Performing the second-stage revision in proper timing is the key to boost the success rate of PJI treatment. To find the best timing for re-implantation, researchers worldwide have never stopped exploring. In recent years, various indicators have been reported. Hoell et al. [32] reported CRP was not a reliable parameter to exclude persistent infection. Tao Bian et al. [33] also concluded that ESR and CRP were of limited value in determining reimplantation timing by pooled analysis. And some researchers found coagulation-related biomarkers performed well in guiding reimplantation. Alisina Shahi et al. [14] highlighted D-Dimer in determining the optimal timing of reimplantation. And Geng Bin [10] reported fibrinogen is a useful tool in assessing infection outcomes after first-stage surgery. But a small sample of both studies limited their credibility. In our study, we found that ESR and MA were good indicators in determining reimplantation timing. Our study showed a 100% success rate of two-stage revision, which is higher than most published studies. Several reasons are contributing to this result: 1) follow-up time of 4

patients were shorter than 1 year, which may be not enough to judge the control of infection. 2) Although widely adopted by many researchers, Delphi-based consensus was not the golden standard for evaluating the success of the two-stage revision. It overlooks the functional outcome of the surgery. When taken the function outcome, our success rate would be lower.

According to the results of the study, TEG appears to have the following advantages. First, as a regular and routine serological testing for coagulation, the TEG test does not bring additional costs or suffering to patients. Second, TEG parameters may be applied to differentiate PJI from aseptic loosening, especially the combination of CRP with MA/A30. Finally, MA/A30 appears to be a useful tool in assessing infection control after spacers insertion.

Our study has several limitations. Firstly, the samples in this study were too small, a larger sample size might have produced different results. Secondly, lower extremity Doppler ultrasound was routinely performed to exclude venous thromboembolism of the lower limb, which didn't rule out clots in a different portion of the patient's body. If clots undetected have existed in Group A, the diagnostic value of studied parameters would be overestimated. While if in Group B, the influence would be reversed. Moreover, we did not consider the use of antibiotics of PJI patients before admission to our hospital. Furthermore, the study has some inherent biases of a retrospective study. Last but not least, we only checked the TEG of PJI patients before spacers insertion and before reimplantation, rather than checked them regularly. Hence, the changing trend of these biomarkers' levels in patients with PJI is not clear.

## Conclusion

This study reports that five TEG parameters (Angle, MA, A30, TPI) levels are statistically different from PJI patients to patients with aseptic loosen and those who are readmitted for reimplantation in two-stage arthroplasty. With high specificity, MA is a useful biomarker in diagnosing PJI and assessing infection control after first-stage surgery.

## Abbreviations

PJI: periprosthetic joint infection; TEG: thromboelastography; MSIS: Musculoskeletal Infection Society; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; K: clotting time; Angle:  $\alpha$ -angle; MA: maximum amplitude; A30: amplitude at 30 min; TPI: thrombodynamic potential index; Fib: fibrinogen; ROC: receiver operating characteristic curves; AUCs the areas under the curves; PPV: positive predictive value; NPV: negative predictive value; +LR: positive likelihood ratio; -LR: negative likelihood ratio; CI: confidence interval; TF: tissue factor; ILs: interleukins; TNF $\alpha$ : tumor necrosis factor  $\alpha$ ; ICM: International Consensus Meeting.

## Declarations

Ethics approval and consent to participate: The study has acquired the ethics approval and the waivers of informed consent (NO. SWYX2020-185) from the Biomedical Research Ethics Committee of Shandong Provincial Hospital.

Availability of data and material: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare they have no financial interests.

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Authors' contributions: TY, the first author, participated in the design of the study, searched the data, performed the analysis, and drafted the manuscript. YW, the second author, participated in the design of the study, searched the data. SS, the corresponding author, participated in the design of the study and helped to draft the manuscript. All authors have read and approved the final manuscript.

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## Tables

Table 1

Demographics of the Study Groups.

Demographics	Group A (n = 23)	Group B (n = 39)	P Value
Age (y) <sup>a</sup>	64.13 ± 9.10	64.56 ± 10.88	.873
Gender <sup>b</sup>			.424
Male	10(43.48%)	13 (33.33%)	
Female	13 (56.52%)	26 (66.67%)	
BMI (kg/m <sup>2</sup> ) <sup>a</sup>	26.16 ± 2.83	25.55 ± 3.61	.493
Involved joint <sup>b</sup>			<0.01
Hip	7 (30.43%)	34 (87.18%)	
Knee	16 (69.57%)	5 (12.82%)	
Serum inflammatory and fibrinolytic markers			
CRP(mg/L)	45.71 ± 54.50	3.57 ± 4.62	< .05
ESR(mm/h)	57.59 ± 27.97	14.59 ± 10.33	< .001
D-Dimer(mg/L)	1.72 ± 1.22	1.06 ± 1.23	< .001
K(min)	1.26 ± 0.77	1.56 ± 0.41	< .001
Angle(°)	72.56 ± 7.38	67.80 ± 6.13	< .001
MA(mm)	71.23 ± 5.62	62.83 ± 4.03	< .001
A30(mm)	70.85 ± 5.79	62.36 ± 4.16	< .001
TPI(/sec)	126.28 ± 54.46	60.30 ± 26.24	< .001
BMI, body mass index; SD, standard deviation. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; K, clotting time; Angle, α-angle; MA, maximum amplitude; A30, amplitude at 30 min; TPI, thrombodynamic potential index.			
<sup>a</sup> The values are expressed as the mean ± SD.			
<sup>b</sup> The values are expressed as the numbers of patients, with the percentage in parentheses.			

**Table 2**

The Diagnostic Value of Inflammatory and Fibrinolytic Markers.

Markers	AUC	Optimal cutoff	Youden index	SEN (%)	SPE (%)	PPV (%)	NPV (%)	+LR	-LR
CRP(mg/L)	0.893	>8.8	0.7735	82.61	94.74	90.5	90.0	15.70	0.18
ESR(mm/h)	0.953	>34.0	0.7669	81.82	94.87	90.0	90.2	15.95	0.19
D-Dimer(mg/L)	0.717	>1.7	0.4013	47.83	92.31	78.6	75.0	6.22	0.57
K(min)	0.800	<1.3	0.5362	86.96	66.67	60.6	89.7	2.61	0.20
Angle(°)	0.803	>70.7	0.5619	86.96	69.23	62.5	90.0	2.83	0.19
MA(mm)	0.895	>68.1	0.8004	82.61	97.44	95.0	90.5	32.22	0.18
A30(mm)	0.893	>66.5	0.7492	82.61	92.31	86.4	90.0	10.74	0.19
TPI(/sec)	0.867	>84.4	0.7057	78.26	92.31	85.7	87.8	10.17	0.24
AUC, area under the curve; SEN, sensitivity; SPE, specificity; PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; -LR, negative likelihood ratio; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; K, clotting time; Angle, $\alpha$ -angle; MA, maximum amplitude; A30, amplitude at 30 min; TPI, thrombodynamic potential index.									

**Table 3**

The Diagnostic Value of Combined Inflammatory and Fibrinolytic Markers.

Markers	AUC	SEN (%)	SPE (%)	PPV (%)	NPV (%)	+LR	-LR
CRP + ESR	0.980	100.00	89.47	84.6	100.0	9.50	0.000
CRP + K	0.943	91.30	94.74	91.3	94.7	17.35	0.092
CRP + Angle	0.946	91.30	94.74	91.3	94.7	17.35	0.092
CRP + MA	0.995	100.00	94.74	92.0	100.0	19.00	0.000
CRP + A30	0.999	100.00	97.37	95.8	100.0	38.00	0.000
CRP + TPI	0.968	91.30	97.37	95.5	94.9	34.70	0.089
ESR + K	0.958	86.36	94.87	90.5	92.5	16.84	0.140
ESR + Angle	0.953	86.36	94.87	90.5	92.5	16.84	0.140
ESR + MA	0.948	90.91	89.74	83.3	94.6	8.86	0.100
ESR + A30	0.948	81.82	97.44	94.7	90.5	31.91	0.190
ESR + TPI	0.955	81.82	97.44	94.7	90.5	31.91	0.190
<p>AUC, area under the curve; SEN, sensitivity; SPE, specificity; PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; -LR, negative likelihood ratio; CRP, C-reactive protein; K, clotting time; Angle, <math>\alpha</math>-angle; MA, maximum amplitude; A30, amplitude at 30 min; TPI, thrombodynamic potential index; ESR, erythrocyte sedimentation rate.</p>							