

The Change of Coagulation Profile in Two-staged Arthroplasty for Periprosthetic Joint Infection Patients—A Retrospective Cohort Study

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Research article

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Abstract

Aims Periprosthetic joint infection (PJI) a serious complication of total joint arthroplasty. We performed a retrospective cohort study to evaluate 1) the change of coagulation profile in two-staged arthroplasty patients 2) the relationship between coagulation profile and the outcomes of reimplantation.

Method: Between 2011 January and 2018 December, a total of 202 PJI patients who were performed with two-staged arthroplasty were included in this study initially. They were followed up at least 2 years and corresponding medical records were scrutinized to establish the diagnosis of PJI based on the 2014 MSIS criteria. The coagulation profile was recorded at two designed points 1) preresection and 2) preimplantation. Then, the difference of coagulation profile between preresection and preimplantation was evaluated. Besides, receiver operating characteristic curves (ROC) were used to evaluate the diagnostic efficiency of coagulation profile and the change of coagulation profile for predicting persistent infection before reimplantation.

Results: The levels of APTT, INR, platelet count, PT, TT and plasma fibrinogen before spacer implantation were significantly higher than that before reimplantation. No significant difference was detected in the levels of D-dimer, ACT, AT3 between the two groups. The AUC of the combined coagulation profile and the change of combined coagulation profile for predicting persistent infection before reimplantation was 0.667 (95%CI:(0.511,0.823) and 0.667 (95%CI: (0.526,0.808)), respectively.

Conclusion: The coagulation profile before preresection is different from that before preimplantation in two-staged arthroplasty and the coagulation markers may play a role in predicting infection eradication before reimplantation when two-stage arthroplasty is performed.

Level of Evidence: level III, diagnostic study

Introduction

Total joint arthroplasty (TJA) is one of the most successful surgeries during the last century and patients with advanced joint diseases can achieve pain relief and functional recovery after this surgery. However, periprosthetic joint infection (PJI) is a disastrous complication after total joint arthroplasty and often indicates unfavorable outcomes[1, 2]. Although two-staged arthroplasty is a preferred treatment for chronic PJI, it is still difficult to predict persistent infection before reimplantation[3]. And inappropriate implantations can lead to treatment failure. Besides, a failure of second stage reimplantation can result in more disastrous complications and the needs for further arthroplasty, arthrodesis and amputation[4].

The pathogens of PJI are known to impair their hosts by endotoxin and exotoxin which can stimulate immune cells to produce various cytokines such as IL-6, TNF and IL-6[5–7]. These secreted cytokines may disrupt normal coagulation cascade and cause abnormal coagulation profile in PJI patients. Some studies revealed that the coagulation profile of PJI patients was different from that of non-PJI patients. It suggests that PJI patients suffer from abnormal coagulation. The subclinical abnormal coagulation can

increase the risk of epidural hematoma formation and impair incision healing after surgery theoretically[6–8]. However, a review of literatures suggests that the studies about the relationship between coagulation system and the clinical outcomes of PJI are limited[9–12]. And we hold the opinion that the effects of pathogens on coagulation system may disappear and the corresponding abnormal coagulation profile may return to normal when the pathogens are eradicated because the endotoxin and exotoxin produced by pathogens are removed.

Based on the opinion mentioned above, we propose a hypothesis that the coagulation profile of PJI patients before reimplantation is different from that before spacer implantation when infection is controlled and the changed coagulation profile can play a role in predicting persistent infection before reimplantation. Some studies revealed that plasma fibrinogen can play a role in predicting persistent infection before reimplantation in two-stage exchange arthroplasty for PJI. It is consistent with our hypothesis. However, there is still a lack of comprehensive studies evaluating the change of coagulation profiles in two-staged exchange arthroplasty and the association between the coagulation profile before reimplantation and the outcomes of two-stage exchange arthroplasty[13, 14].

In a bid to address the problems mentioned above, we perform a retrospective cohort study with at least two years follow-up to evaluate 1) the change of the coagulation profile in two-staged arthroplasty PJI patients 2) the use of coagulation profile in predicting persistent infection before reimplantation.

Materials And Methods

A total of 202 PJI patients treated with two-staged arthroplasty were included in this study initially. All patients were performed with two-staged arthroplasty for PJI treatment in our center. The exclusion criteria were as follows: 1) patients who were exposed to anticoagulation agents within 2 weeks before reimplantation and pre-resection. 2) periprosthetic fracture 3) periprosthetic dislocation 4) patients who received coronary stents, filter implantation and internal fixation implantation. 5) the patients who didn't receive new prosthesis reimplantation after spacer implantation. 6) the patients who receive spacer implantation in other joint centers. Finally, a total of 130 patients were included in this study and the details were shown in Fig. 1. The medical records of PJI patients were scrutinized and the diagnosis of PJI was based on the 2014 MSIS criteria. All patients were followed for at least 2 years. After spacer implantation, 6 weeks of IV antibiotics was administered based on antibiotics susceptibility tests, following by po. antibiotics until the infection was controlled. Reimplantation were performed when antibiotics administration was withdrawn. The outcomes of follow-up were used to evaluate the prognosis of 2-staged reimplantation. Treatment failure was defined when the same joint underwent reoperation because of infection during follow-up period. Besides, following data were collected to reflect the coagulation profile of PJI patients: APTT, TT, INR, prothrombin time(PT), plasma D-dimer, plasma fibrinogen, plasma Ca⁺, platelet count, antithrombin 3 and prothrombin activity(PTA).

Statistical analysis:

The variables were divided into continuous variables and dichotomous data based on the types of data. Normal distribution test was used to evaluate the distribution of continuous variables. The continuous variables were described as means if normal distribution was achieved. Otherwise, corresponding medians were calculated. Rank sum test and student t test were used to detect the difference if the corresponding applicable conditions were met. Dichotomous data were described as frequencies and compared by chi-squared test subsequently. $P < 0.05$ indicates statistical significance. Paired tests were used to compare the difference of coagulation profile between pre-resection and pre-implantation. Receiver operating characteristic curves (ROC) were used to evaluate the efficiency of coagulation profile in predicting persistent infection before reimplantation. Logistic regression was used to build diagnostic models based on the coagulation profile. Youden's index was used to identify optimal cut-off. SPSS (IBM; version 26.0) was used to perform statistical analysis.

Results

1. Demographic characteristics:

The median ages in treatment success group and treatment failure were 63 and 60 years, respectively. The median BMI in success group and failure group was 23.95 kg/m² and 28.72 kg/m², respectively. The percentage of female in success group and failure group was 58.62% and 35.71%, respectively. The percentage of knee in success group and failure group was 42.24% and 57.14%, respectively. The percentage of patients with inflammatory joint diseases in success group and failure group was 5.17% and 7.14%, respectively. The details of the demographic characteristics were summarized in table 1.

2. The change of coagulation profile in PJI two-staged arthroplasty

The levels of APTT, INR, platelet count, PT and plasma fibrinogen before spacer implantation (group A) were significantly higher than that before reimplantation (group B). No significant difference was detected in the levels of plasma D-dimer and AT3 between the two groups. The median APTT in group A was 38.3s and 35.9s in group B. The median PT in group A was 13.5s and 13.3s in group B. The median TT in group A was 15.9s and 15.85s in group B. The median INR in group A was 1.04 and 1.02 in group B. The median plasma fibrinogen in group A was 4.86g/L and 3.36g/L in group B. The median platelet count in group A was 277109/dl and 195 109/dl in group B. The median plasma Ca in group A was 2.23 mmol/L and 2.26 mmol/L in group B. The details about the change of coagulation profiles were shown in Table 2. Besides, no significant difference was revealed between the coagulation profile in treatment success group and that in treatment failure group. The details of the coagulation profile before reimplantation (treatment failure versus treatment success) were shown in table 3.

3. The association between the coagulation profile and treatment outcomes of two-staged arthroplasty.

The diagnostic value of coagulation profile was evaluated in ROC curves (Fig 2). The AUCs of plasma D-dimer, platelet count, APTT, TT, INR before reimplantation for predicting persistent infection were 0.542(0.359,0.725), 0.560(0.417,0.702), 0.526(0.377,0.674), 0.482(0.29,0.674) and 0.632(0.479,0.786), respectively. Moreover, the coagulation profile was combined by logistic regression (appendix 1.) based on significantly up-regulated markers. The AUC of the combined coagulation profile was 0.667 (95%CI: (0.511,0.823)). And the diagnostic efficiency of coagulation profile before reimplantation was depicted in table 4. Besides, the diagnostic values of the change in coagulation profile from preresection to preimplantation were shown in ROC curves (Fig 3). The AUCs of Δ D-dimer, Δ plasma fibrinogen, Δ platelet count, Δ APTT, Δ PT, Δ INR and Δ TT for infection eradication were 0.611(0.403,0.819), 0.549(0.363,0.736), 0.528(0.374,0.682), 0.546(0.378,0.714), 0.545(0.392,0.699), 0.626(0.488,0.765) and 0.493(0.327,0.659), respectively. The AUC of the combined coagulation profile was 0.667(0.526,0.808). The diagnostic efficiency of the change in coagulation profile from preresection to preimplantation was shown in Table 4. Besides, the change of coagulation profile was combined by logistic regression (appendix2).

Discussion

There is still a lack of comprehensive studies that evaluate the change of coagulation profile from reresection to reimplantation in two-staged arthroplasty up to now[3, 15, 16]. To address this problem, this study evaluated the change in coagulation profile during this period and the use of coagulation profile for predicting infection eradication in two-staged arthroplasty.

PJI pathogens can secret endotoxins and exotoxins by which stimulate immune cells to produce cytokines such IL-6, TNF- α and IL-6[5, 6]. These cytokines can impair normal coagulation system subsequently. Parvizi et. revealed that the INR in PJI patients is higher than that in aseptic loosening patients[6]. These studies indicated that PJI patients suffered from abnormal hypocoagulation. Our previous studies also showed similar results. The changed coagulation cascade may be ascribed to PJI pathogens and return to relatively normal when the pathogens were eradicated. This research revealed that the levels of APTT, PT, INR, plasma fibrinogen and platelet count before reimplantation were significantly lower than that before reresection. Unfortunately, no significant difference was detected when these variables were compared between the infection controlled and persistent infection groups. It may be the result of a small number of persistent infection patients.

The goal of two-staged arthroplasty for PJI treatment is to eradicate infection. However, defining the time for reimplantation is still challenging and previous studies failed to identify serologic markers to guide the time for reimplantation[3, 16]. Therefore, we evaluate the efficiency of the coagulation profile for predicting persistent infection. We found that the levels of INR and APTT before reimplantation may predict infection eradication despite relatively poor efficiency. Moreover, we built a logistic model based

on the change of INR, APTT and platelet count. This model performed better than anyone alone and some commonly used serologic markers such as ESR and CRP in predicting persistent infection.

The levels of APTT, INR and platelet count before reimplantation were significantly lower than that before spacer implantation. Therefore, we evaluated whether the change of these coagulation markers (Δ APTT, Δ INR and Δ platelet count) from preresection to preimplantation could indicate infection eradication. The change of coagulation profile may help doctors guide the timing of reimplantation. In 14 recurrent PJI cases, 7 cases underwent elevated APTT, INR and platelet count (Δ APTT > 0, Δ INR > 0 and Δ platelet count > 0). However, no statistical significance was detected between the recurrent rate in the elevated group (Δ APTT > 0, Δ INR > 0 and Δ platelet count > 0) and that in the non-elevated group (Δ APTT < 0, Δ INR < 0 and Δ platelet count < 0) because the sample size of recurrent infection is relatively small.

Other studies used modified MSIS criteria or repeat cultures as the indicator of persistent infection [17, 18]. However, these methods weren't used in this study because repeat cultures were fraught with high false negative rates and modified MSIS criteria were of limited efficiency. Besides, no good criteria are accepted commonly as the standard of persistent infection before reimplantation. Therefore, we hold the opinion that the follow-up outcomes of PJI patients can be a relatively accurate indicator for infection eradication because many PJI criteria were built based on the follow-up results [18]. And the relatively long follow-up period is one of our advantages over other studies.

A literature review suggested that many researchers failed to find accurate serological markers that indicated persistent infection such as ESR and CRP and our results revealed similar results. Some synovial fluid indicators can predict persistent infection such as synovial WBC count and the percentage of PMN [3, 19]. These findings indicated that the local response to persistent infection was more accurate than systemic response to that in the diagnosis of persistent infection. However, this study revealed that the combination of coagulation profile was of comparable efficiency compared to that of reported synovial fluid indicators.

D-dimer is a product of fibrin degradation and fibrinogen is the precursor of fibrin. But the fluctuation in Plasma fibrinogen and D-dimer wasn't detected in the same direction. Then we reviewed the original medical data and found that many data about the levels of plasma D-dimer were not accessible because this test weren't performed commonly in our center. Therefore, the statistical power is not strong enough to detect the difference of the levels of plasma D-dimer between preresection and preimplantation because of relatively small sample size compared to that of plasma fibrinogen.

The levels of APTT and INR before preresection is higher than that before reimplantation. It suggests that intrinsic and extrinsic coagulation pathways changed before reimplantation compared to that before preresection. And relatively robust TT revealed that the common pathway in coagulation cascade didn't change significantly between preresection and preimplantation. However, as shown in Fig. 4 [6], which part of intrinsic and extrinsic coagulation pathways changes significantly wasn't explored in this study. For example, which changed coagulation factor in intrinsic and extrinsic pathway cause the change of APTT and INR remained unknown. Moreover, this field need exploring further.

We have shown that the coagulation profile may play a role in guiding the timing of implantation. The increase in the levels of APTT and INR may indicate infection eradication and surgeons can take these markers into account before reimplantation. We believe that surgeons should continue to combine various diagnostic tools rather than certain single marker to guide the timing of reimplantation, including the change of coagulation profile, serologic markers, clinical characteristics and so on. For example, reduced APTT, INR and platelet count before reimplantation compared to that before presection may predict higher success rate of reimplantation. And how to identify the timing of reimplantation still need to be explored further.

This study still has some limitations. First, two-staged arthroplasty is a relatively successful surgery and the the rate of treatment failure is low in our centre. Therefore, a large sample size is needed to reach statistical significance when comparing the difference of coagulation profile between successful group and persistent infection group. However, the sample size in this study is limited after strict inclusion and exclusion. Second, this study was performed in a tertiary centre. The patients admitted to our joint centre often suffered from severe infection and received previous treatments in other joint centres so that spacer exchange was not rare in this tertiary centre. This fact can trigger a selection bias. Third, there is no gold standard for the diagnosis of infection eradication and we use follow-up results to evaluate infection eradication. However, some subclinical infection may be missed by patients or doctors during follow-up. This fact can trigger some biases. Finally, some patients underwent repeat debridement and spacer exchange before reimplantation. Decision of this nature was based on a combination of clinical appearance and laboratory tests. Besides, the patients refused to receive reimplantation after spacer implantation and the patients receive spacer implantation in other joint centres were excluded from this study. These conditions can also add additional bias to this study.

Conclusion

The coagulation profile is different between presection and preimplantation in two-staged arthroplasty and the coagulation markers may play a role in predicting infection eradication before reimplantation when two-stage arthroplasty is performed.

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

TT

Thrombin time

Declarations

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

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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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Tables

Table 1 Demographic characteristics:

	<i>Treatment success</i> N=116	<i>treatment failure</i> n=14	<i>P values</i>
Age	63(27,84)	60(24,76)	0.942
Female (n,%)	68, 58.62%	5, 35.71%	0.103
Knee (n,%)	49, 42.24%	8, 57.14%	0.288
BMI*	23.95[16.6-36.49]	28.72(221,28.7)	0.108
ASA			
2	63, 54.31%	10, 71.42%	0.223
3	6, 5.17 %	0	1
4	0	0	1
Liver disease(n,%)	3, 2.59%	0	1
Kidney disease(n,%)	1, 0.86%	0	1
Heart disease(n,%)	9, 7.76%	1, 7.14%	1
DM(n,%)	19, 16.38%	0	1
Inflammatory joint diseases (n,%)	6, 5.17%	1, 7.14 %	1
Spacer interval(day)*	120.5(32,535)	144(52,308)	0.47
Causative pathogens			
CNS	50, 43.10%	2, 14.29%	0.038
S. aureus	7, 6.03%	4, 28.57%	0.019
Enterococcus spp	5, 4.31%	0	1
Streptococcus spp	8, 6.90%	1, 7.14%	1
Gram-negative bacteria	10, 8.62%	4, 28.57%	0.045
Fungi	5, 4.31%	0	1
Other pathogens	6, 5.26%	1, 7.14%	0.559
Culture negatie	40, 34.48%	3, 21.43%	0.385

Values were given as medians (minimum, maximum)

Table 2 The change of coagulation profile in PJI two-staged arthroplasty

<i>Coagulation profile</i>	<i>preresection</i>	<i>preimplantation</i>	<i>P values</i>
<i>APTT[s]</i>	38.3(18.1,62.9)	35.9(23.7,51.6)	3.7304E-8
<i>PT[s]</i>	13.5(11.7,39)	13.3(11.9,16.8)	0.016132
<i>TT[s]</i>	15.9(14,21.1)	15.85(4,19.1)	0.183
<i>INR</i>	1.04(0.86,1.97)	1.02(0.87,1.38)	0.002989
<i>Plasma fibrinogen(g/L)*</i>	4.86(2.30,8.08)	3.36(1.21,8.9)	1.4157E-14
<i>Plasma Ca(mmol/L)</i>	2.23(1.2,2.27)	2.26(1.9,2.58)	0.157994
<i>AT3(%)</i>	86(2.28,125)	89(2.88,129)	0.306830
<i>D-dimer(ug/ml)</i>	1.57(0.2,6.39)	1.49(0.17,12.27)	0.577211
<i>Platelet count$\times 10^9/dl$</i>	277(262,292)	207(196,218)	3.1664E-15

*P<0.05

Values were given as medians (minimum, maximum)

*values were given as means(95%CI)

Table 3 The difference of coagulation profile between controlled infection group and persistent infection group before reimplantation.

<i>Coagulation profile</i>	<i>Treatment success</i>	<i>Treatment failure</i>	<i>P value</i>
<i>APTT*</i>	35.3(23.7,46.1)	37.05(33.8,45.5)	0.755
<i>PT</i>	13.4(11.9,16.8)	13.2(12.3,15.1)	0.188
<i>TT</i>	15.8(4,18.6)	15.1(13.5,16.8)	0.827
<i>INR</i>	1.02(0.89,1.38)	1.01(0.93,1.19)	0.106
<i>Plasma fibrinogen</i>	3.19(1.21,6.1)	3.88(3.12,6.44)	0.822
<i>Plasma Ca*</i>	2.22(1.9,2.51)	2.22(2.01,2.39)	0.583
<i>AT3</i>	91(2.88,129)	90(77,116)	0.552
<i>D-dimer</i>	1.49(0.17,11.68)	1.1(0.69,4.72)	0.668
<i>Platelet count</i>	196.23(175.95,216.51)	195(152.48,237.52)	0.468
<i>ESR</i>	12(2,36)	11(4,30)	0.706
<i>CRP</i>	0.298(0.05,4.46)	0.71(0.1,2.57)	0.220

Values were given as medians (minimum, maximum)

*values were given as means (95%CI)

Table 4 The association between the coagulation profile and treatment outcomes of two-staged arthroplasty. Corresponding cut-off and predictive values:

	<i>AUC (95%CI)</i>	<i>Yonden index</i>	<i>Optimal cut-off</i>	<i>Sensitivity</i>	<i>specificity</i>
<i>The coagulation profile before reimplantation</i>					
APTT	0.526(0.377,0.674)	0.170	33.45	92.9	24.1
PT	0.608(0.454,0.762)	0.3	13.15	58.6	28.6
TT	0.482(0.29,0.674)	0.158	16.05	57.1	41.4
D-dimer	0.542(0.359,0.725)	0.262	1.19	66.2	60
Platelet count	0.560(0.417,0.702)	0.188	231.5	33	85.7
INR	0.632(0.479,0.786)	0.335	1.005	62.1	71.4
ESR	0.465(0.282,0.647)	0.083	31	8.3	100
CRP	0.615(0.427,0.803)	0.318	0.33	81.8	50
Combined coagulation profile	0.667(0.511,0.823)	NA	NA	NA	NA
<i>The change of coagulation profile from preresection to preimplantation</i>					
APTT	0.546(0.378,0.714)	0.145	-3.8	78.6	21.4
PT	0.545(0.392,0.699)	0.175	0.95	18.3	81.7
TT	0.493(0.327,0.659)	0.096	2.5	10	100
D-dimer	0.611(0.403,0.819)	0.278	-0.395	70.7	57.1
Platelet count	0.528(0.374,0.682)	0.248	56.5	63.3	61.5
INR	0.626(0.488,0.765)	0.235	0.05	57.1	66.4
Plasma fibrinogen	0.549(0.363,0.736)	0.227	0.365	79.8	57.1
Combined coagulation profile	0.667(0.526,0.808)	NA	NA	NA	NA

Figures

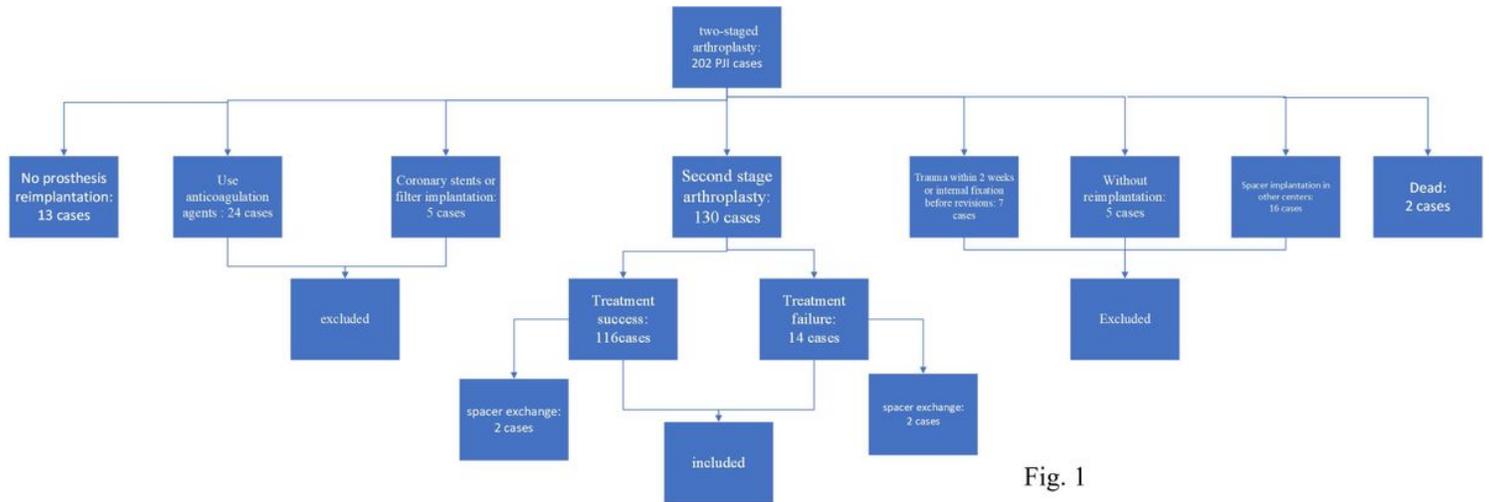


Fig. 1

Figure 1

The medical records of PJI patients were scrutinized and the diagnosis of PJI was based on the 2014 MSIS criteria. All patients were followed for at least 2 years. After spacer implantation, 6 weeks of IV antibiotics was administrated based on antibiotics susceptibility tests, following by po. antibiotics until the infection was controlled.

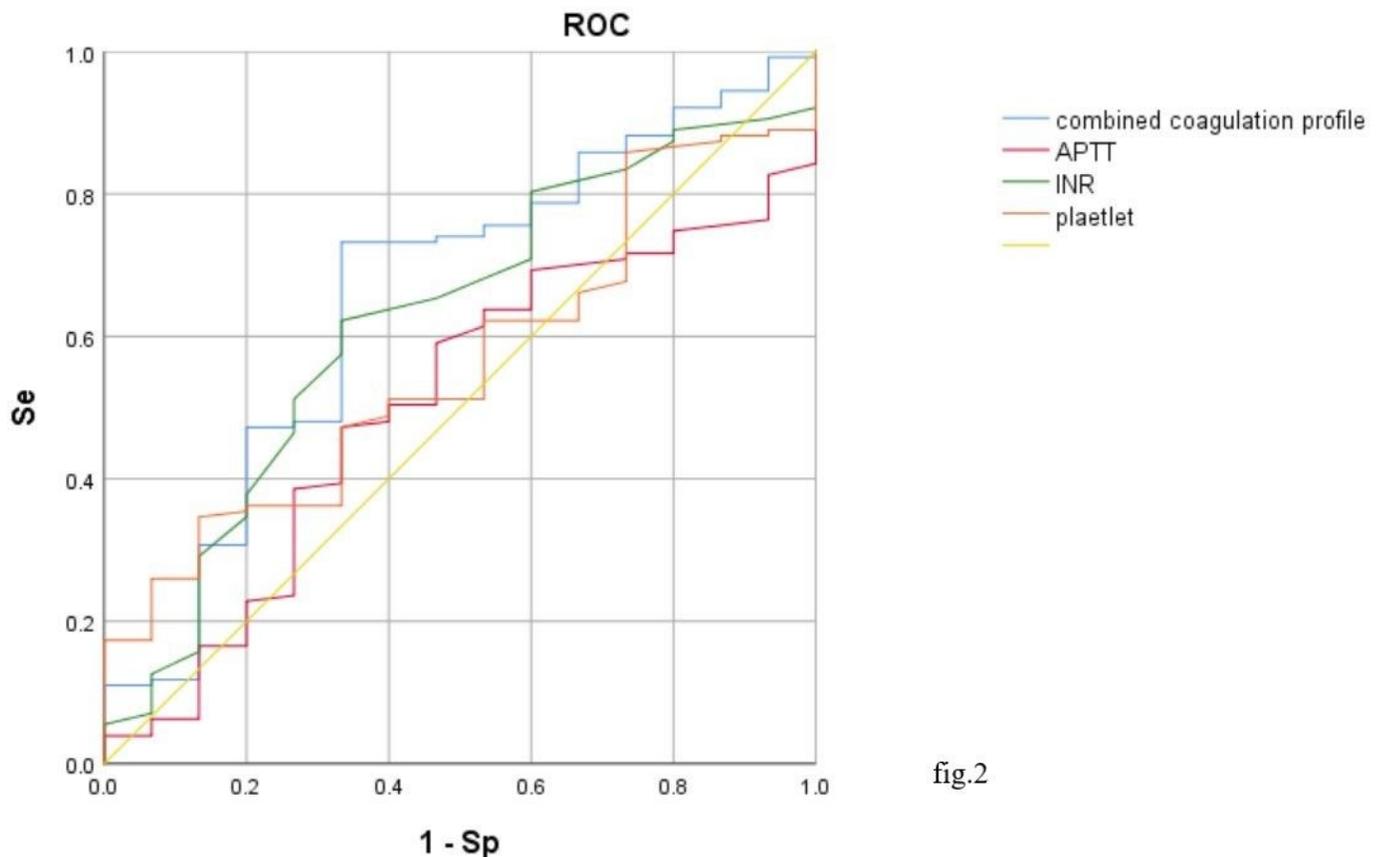


fig.2

Figure 2

The AUCs of plasma D-dimer, platelet count, APTT, TT, INR before reimplantation for predicting persistent infection were 0.542(0.359,0.725), 0.560(0.417,0.702), 0.526(0.377,0.674), 0.482(0.29,0.674) and 0.632(0.479,0.786), respectively. Moreover, the coagulation profile was combined by logistic regression (appendix 1.) based on significantly up-regulated markers. The AUC of the combined coagulation profile was 0.667 (95%CI:(0.511,0.823)).

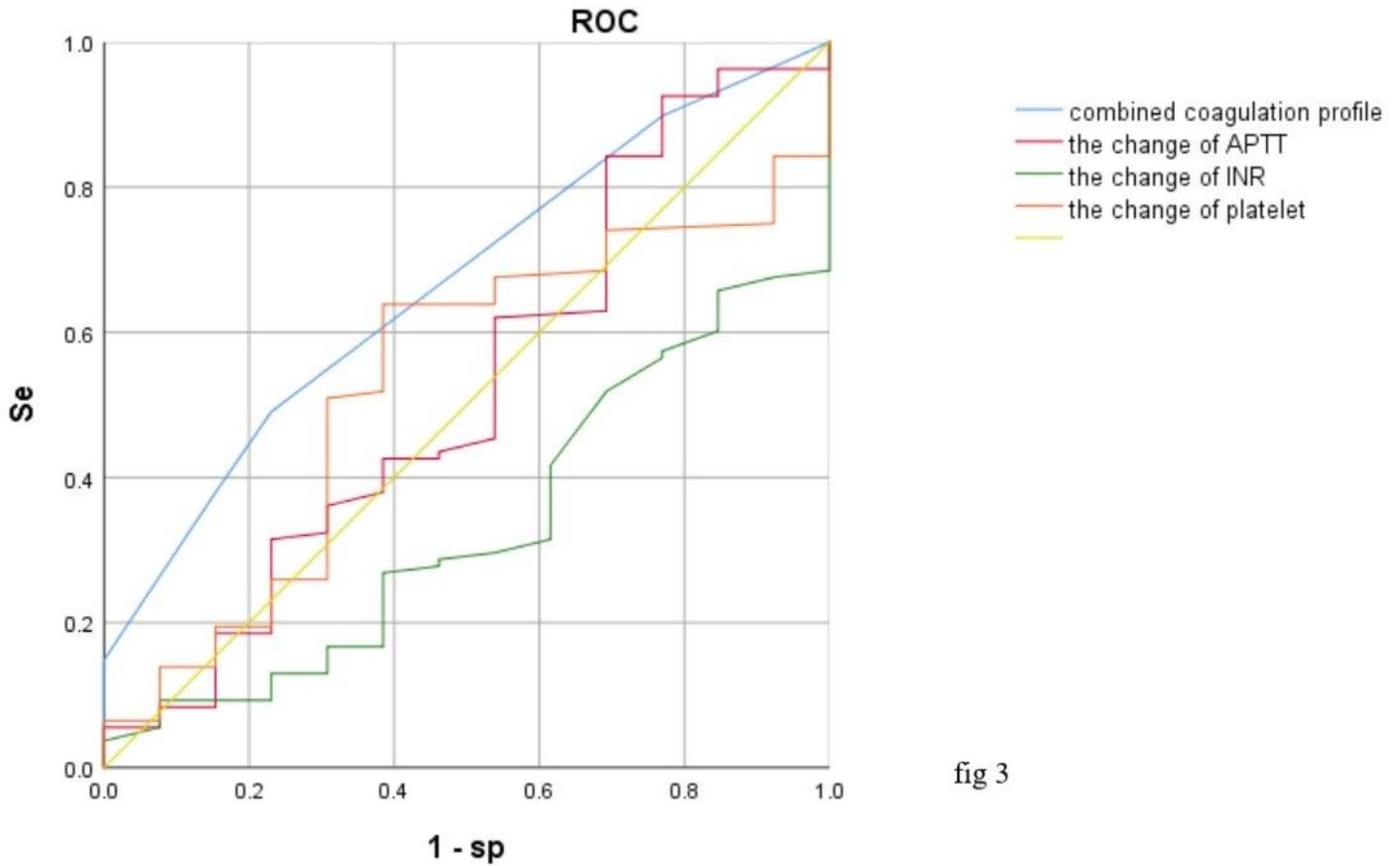


fig 3

Figure 3

The AUCs of Δ D-dimer, Δ plasma fibrinogen, Δ platelet count, Δ APTT, Δ PT, Δ INR and Δ TT for infection eradication were 0.611(0.403,0.819), 0.549(0.363,0.736), 0.528(0.374,0.682), 0.546(0.378,0.714), 0.545(0.392,0.699), 0.626(0.488,0.765) and 0.493(0.327,0.659), respectively.

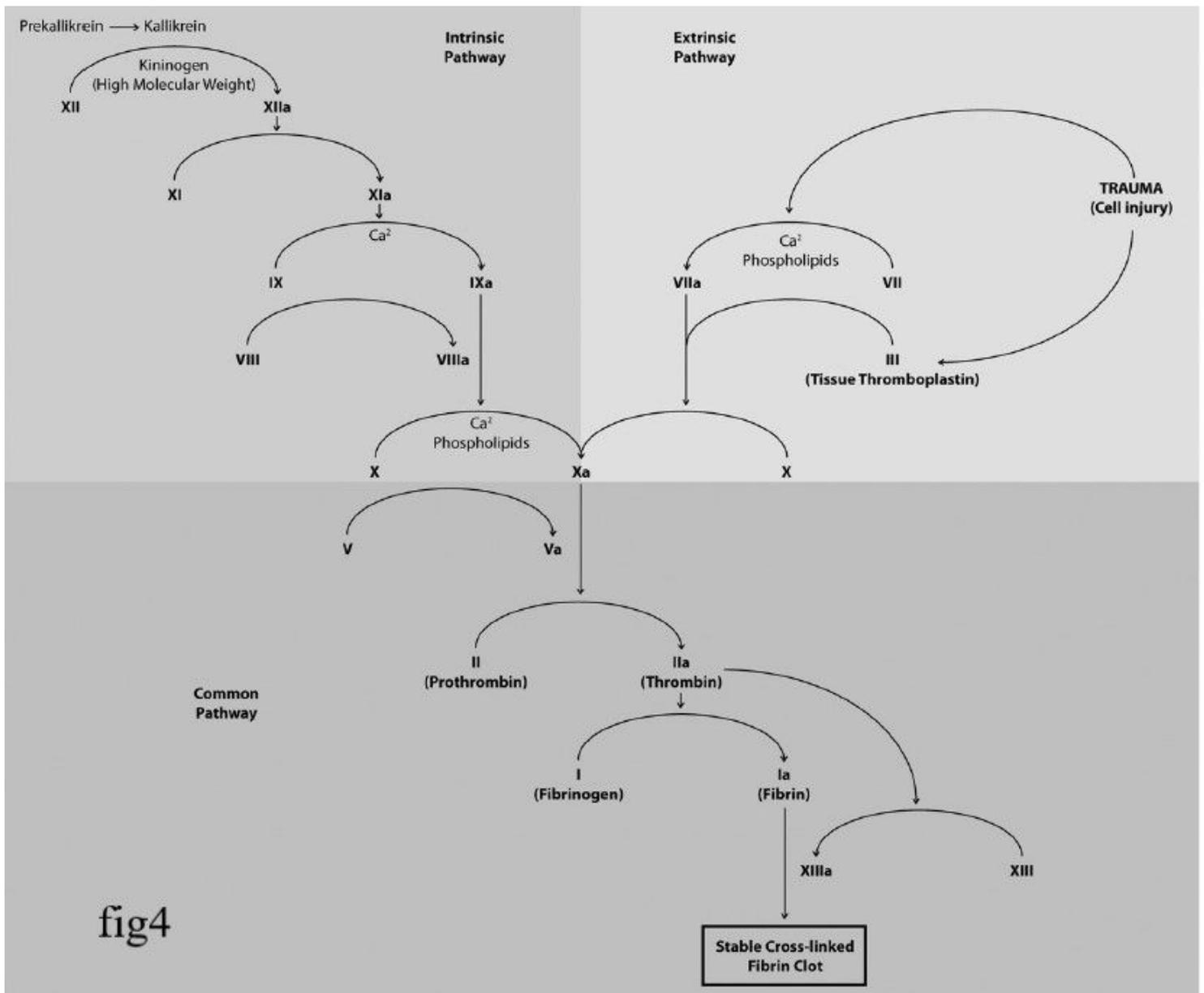


Figure 4

which part of intrinsic and extrinsic coagulation pathways changes significantly wasn't explored in this study. For example, which changed coagulation factor in intrinsic and extrinsic pathway cause the change of APTT and INR remained unknown. Moreover, this field need exploring further.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [appendix1.docx](#)
- [appendix2.docx](#)