Different Diagnostic Performance of Fibrinogen and D-Dimer in Periprosthetic Joint Infection: A Propensity Score Matched Study

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Abstract

Background: Fibrinogen(Fbg) and D-dimer were introduced as biomarkers for the diagnosis of PJI. However, previous researches have reported controversial outcome on the diagnostic value of D-dimer in comparison to Fbg, CRP and ESR.

Aim: This study aims to: 1.Determine the optimal threshold of plasma Fbg and D-dimer in the diagnosis of PJI and compare their diagnostic value to that of CRP and ESR. 2.Investigate if Fbg and D-dimer performs differently than CRP and ESR in different types of PJI.

Methods: 115 revision cases after total hip arthroplasty(THA) and total knee arthroplasty(TKA) were identified. 30 PJI cases were matched to 60 Aseptic cases based on demographic characteristics using propensity score matching. Sensitivity, Specificity, Receiver operating characteristics(ROC), Negative predictive value(NPV) and Positive predictive value(PPV) were calculated and compared.

Results: The optimal threshold is 1.69 mg/L for D-dimer and 3.655g/L for Fbg. Plasma Fbg, D-dimer, CRP and ESR were significantly higher in the PJI group than the Aseptic group. Fbg, D-dimer, CRP and ESR showed sensitivity of 0.83, 0.67, 0.83 and 0.8 respectively and showed specificity of 0.87, 0.77, 0.92 and 0.82 respectively. ROC curve showed that CRP has the highest AUC(0.90), followed by Fbg(0.89), ESR(0.88) and D-dimer(0.77).

Conclusion: Plasma Fbg exhibited similar diagnostic performance comparing to CRP and ESR. Plasma D-dimer is of limited diagnostic value. In our study, Fbg and D-dimer did not show better diagnostic performance in any subtypes of PJI. Further studies are required to investigate the difference between serum D-dimer and plasma D-dimer in arthroplasty population.

Article Summary

Article focus:

1. Determine the optimal threshold of plasma Fbg and D-dimer in the diagnosis of PJI
2. Compare the diagnostic value of Fbg and D-dimer to that of CRP and ESR and explore potential causes
3. Investigate if Fbg and D-dimer performs differently than CRP and ESR in different types of PJI

Key Messages:

1. Plasma Fbg exhibited similar diagnostic performance comparing to CRP and ESR
2. Plasma D-dimer is of limited diagnostic value
3. Further studies are required to investigate the difference between serum D-dimer and plasma D-dimer in arthroplasty population

Introduction

The diagnosis of periprosthetic joint infection(PJI) has been challenging for decades. Current diagnostic criteria include physical findings, culture, histological analysis and serological/synovial fluid biomarkers[1, 2]. However, physical signs are sometimes subtle in PJI patients. Histological analysis is unavailable until after the operation. Leukocyte count and other markers from synovial have good diagnostic value. But it can be difficult to acquire sufficient amount of joint fluid to perform culture and run other tests[3]. On the other hand, venous blood samples are more easily accessible. Erythrocyte sedimentation rate(ESR) and C-reactive protein(CRP) are essential serological markers in the diagnostic process. However, ESR and CRP can be normal in cases where PJI is caused by low-virulence organism[4, 5]. Therefore, novel biomarkers that are easily accessible would improve efficiency and accuracy in the diagnosis of PJI, especially if they exhibit good diagnostic performance in chronic and low-virulence infections.

Novel biomarkers including D-dimer, fibrinogen(Fbg), alpha-defensin and IL-6 were introduced to improve the diagnostic criteria of PJI[6]. D-dimer and Fbg are routinely tested in most medical facilities. Parvizi et al[1] introduced D-dimer in the 2018 MSIS criteria, in which it plays an equal role to that of CRP. However, research has reported controversial outcome on the diagnostic value of D-dimer in comparison to Fbg, CRP and ESR. Different optimal threshold for diagnosis were utilized[3, 7–9]. Shahi et al[3] reported high diagnostic value of D-dimer. Li et al[8] reported limited value of D-dimer while Fbg showed promising diagnostic value. Limited evidence was found on whether they are valuable in recognizing infections caused by low-virulence pathogens and chronic infections.

Therefore, this study aims to: 1.Determine the optimal threshold of plasma Fbg and D-dimer in the diagnosis of PJI. 2.Compare the diagnostic value of Fbg, D-dimer, CRP and ESR. 3.Investigate if Fbg and D-dimer performs differently than CRP and ESR in different types of PJI.

Methods

Approval from the Institutional Ethics Committee was obtained. We retrospectively reviewed admission records from December 2012 to March 2020. Patients admitted for revision total knee arthroplasty and revision total hip arthroplasty were recorded. Patients were excluded if they 1.underwent revision surgery for dislocation and acute periprosthetic fracture(< 3 weeks); 2.underwent 2nd stage revision(reimplantation) surgery following PJI; Patients were then divided into the PJI group and Aseptic group based on MSIS criteria[10]. Initial screen yielded 34 PJI cases and 68 Aseptic cases.

Propensity score matching were used to match each PJI cases to 2 Aseptic cases. Following covariates were matched: 1.age, 2.sex, 3.height, 4.weight, 5.BMI, 6.Comorbidities(if the patient has coagulation disorder, auto-immune disease, malignancy or takes anticoagulation medication or immunosuppressant). 4 PJI cases were excluded due to unsuccessful match. Eventually, 30 PJI cases were matched to 60 Aseptic cases. The process of patient selection and matching is shown in Fig. 1.

Blood samples were taken 1–3 days following admission and prior to the day of surgery. Plasma D-dimer, Fbg, CRP and ESR were tested among a series of preoperative examination. Pre-operative joint aspirations were taken when PJI is suspected. Results of physical examination, culture and time of onset were recorded.

Statistical analysis were conducted with SPSS 25. Propensity score matching were conducted using STATA 14. The ROC curve was generated by Graphpad 8.0. Continuous variables were analyzed by Unpaired T test and recorded as mean and standard deviation. Dichotomous variables were analyzed by Chi-square test and recorded as frequencies and ratio. A p value less than 0.05 is considered statistically significant. The sensitivity, specificity, positive predictive value(PPV) and negative predictive value(NPV) of each biomarker were calculated and recorded with 95% confidence intervals(95% CI). Positive predictive value is the probability that subject with a positive test result has the disease. Negative predictive value is the probability that subject with a negative test result does not have the disease. Youden index was used to determine the optimal threshold for D-dimer and Fbg. Receiver operating characteristics(ROC) curve was generated, area under curve(AUC) and its 95% CI exhibited the diagnostic value of each biomarkers.

Results

The demographic characteristics of included cases were listed in Table1, there is no statistical difference in terms of gender, age BMI and comorbidities between the two groups. There were significantly higher proportion of knee cases in the PJI group than Aseptic group. The level of plasma D-dimer, Fbg, CRP and ESR were significantly higher in the PJI group than Aseptic group(Table 1).

Table 1
Demographic characteristics and biomarkers between groups

	PJI(n = 30)	Aseptic(n = 60)	P Value
Age(yrs)	61.50 ± 13.55	65.70 ± 9.41	0.135
Sex			0.755
Male	10	22	
Female	20	38	
BMI	26.05 ± 3.80	24.89 ± 3.78	0.175
Hip/Knee			0.005
Hip	9	37	
Knee	21	23	
Comorbidity*	10	16	0.511
D-dimer(mg/L)	3.50 ± 3.20	1.13 ± 0.90	< 0.001
Fbg(g/L)	4.57 ± 1.30	3.02 ± 0.69	< 0.001
CRP(mg/L)	52.53 ± 61.55	4.76 ± 5.59	< 0.001
ESR(mm/h)	56.23 ± 30.42	18.69 ± 16.08	< 0.001
Comorbidity* Patients with coagulation disorder, auto-immune disease, other infections, malignancy, taking anti-coagulation medication, taking immunosuppressor			

The optimal threshold of D-dimer and Fbg was determined based on Youden Index. The optimal threshold is 1.69 mg/L for D-dimer and 3.655 g/L for Fbg. ROC curve showed that CRP has the highest AUC(0.90), followed by Fbg(0.89), ESR(0.88) and D-dimer(0.77)(Fig. 2). CRP and Fbg had the highest sensitivity of 0.83, which is followed by ESR(0.80). CRP had the highest specificity(0.92), which is followed by Fbg(0.87) and ESR(0.82). D-dimer showed the lowest sensitivity(0.67) and specificity(0.77). The positive predictive value for CRP, Fbg, ESR and D-dimer were 0.83, 0.76, 0.69 and 0.58 respectively. The negative predictive value for CRP, Fbg, ESR and D-dimer were 0.92, 0.91, 0.89 and 0.82 respectively. The diagnostic performance of Fbg, D-dimer, CRP and ESR is listed in Table 2.

Table 2
Diagnostic performance of each biomarkers

	Threshold	Sensitivity(95% CI)	Specificity	AUC (95%CI)	PPV*	NPV*
Fbg(g/L)	3.655	0.833 (0.645–0.937)	0.867 (0.645–0.937)	0.892 (0.815–0.968)	0.758	0.912
D-dimer(mg/L)	1.69	0.667 (0.471–0.821)	0.767 (0.637–0.862)	0.786 (0.686–0.885)	0.588	0.821
CRP(mg/L)	10	0.833 (0.645–0.937)	0.917 (0.809–0.969)	0.903 (0.828–0.979)	0.833	0.917
ESR(mm/h)	30	0.8 (0.609–0.916)	0.817 (0.691–0.901)	0.881 (0.805–0.956)	0.686	0.891
PPV* Positive Predictive Value, NPV* Negative Predictive Value						

In the PJI group, 9 cases were defined as acute PJI (diagnosis within 3 months after primary implantation), they all had positive culture. 21 cases were defined as chronic PJI. Among them, 5 cases had negative culture, 16 cases had positive culture. For acute PJI, the positive rate of Fbg, D-dimer, CRP and ESR were 88.9%, 77.8%, 100% and 77.8%, respectively. For chronic PJI, the positive rate of Fbg, D-dimer, CRP and ESR were 57.1%, 61.9%, 52.4% and 61.9%, respectively. For culture negative PJI, the positive rate of Fbg, D-dimer and CRP were 40%, the positive rate of ESR was 80%. *Coagulas-negative Staphylococcus* were identified in 9 cases, *Coagulas-positive Staphylococcus* were identified in 4 cases. Types of infection and responsible pathogens were listed in Table 3.

Table 3
, Types of PJI and identified pathogens

	Acute (n = 9)	Chronic (n = 21)	Total (n = 30)
Culture negative	0	5	5
Culture positive	9	16	25
<i>Coagulas-negative staphylococcus</i>			
<i>Staphylococcus epidermidis</i>	0	8	8
<i>Staphylococcus captis</i>	1	0	1
<i>Coagulas-positive Staphylococcus</i>			
<i>Staphylococcus aureus</i>	2	2	4
<i>Streptococcus</i>			
<i>Streptococcus mitis</i>	0	1	1
<i>Streptococcus pneumoniae</i>	1	0	1
<i>Streptococcus agalactiae</i>	1	0	1
<i>Streptococcus anginosus</i>	0	1	1
<i>Escherichia coli</i>	1	2	3
<i>Brucella</i>	1	0	1
<i>Salmonella</i>	1	0	1
<i>Klebsiella pneumoniae</i>	0	1	1
<i>B.fragilis</i>	0	1	1
<i>Corynebacterium rhizogenes</i>	1	0	1

Discussion

Fibrinogen and D-dimer are by product following the process of fibrin clot breakdown. Both fibrinogen and D-dimer represent the activation of coagulation process[11]. Studies have looked into the relationship between the coagulation process and inflammation process. Coagulation biomarkers have pro-inflammation effect: Fibrin mediates inflammation process and D-dimer promotes neutrophil & monocyte activation. Persistent inflammation process also contributes to hyper coagulable state[12, 13].

Based on the AUC of each biomarkers, Fbg(0.89), CRP(0.90) and ESR(0.88) exhibited similar diagnostic value, while D-dimer(0.79) exhibited poor diagnostic value comparing to other biomarkers. The sensitivity and specificity of D-dimer were much lower than that of Fbg, CRP and ESR. Previous researches have

reported conflicting results towards D-dimer and its role in the diagnosis of PJI. One assumption is that serum and plasma D-dimer exhibit different diagnostic performance. In serum sample, D-dimer is measured after standardized coagulation. Cross-linked fibrin degradation products are in the blood before standardized coagulation and are mostly included in the sample after coagulation. The fibrin degradation product remained in the serum sample would add to part of serum D-dimer measured, which may result in higher level of serum D-dimer comparing to plasma D-dimer. However, The effect of remained fibrin degradation product in serum sample could not be quantified[14–16]. Paniccia et al[14] found serum D-dimer was significantly higher than plasma D-dimer in the majority of pregnant women. They found no correlation between serum D-dimer and plasma D-dimer. To our knowledge, there is no study reporting the difference between serum and plasma D-dimer in arthroplasty populations. Current studies reported limited diagnostic value of plasma D-dimer and controversial results regarding to serum D-dimer. 2 studies[8, 17] reported limited diagnostic value of plasma D-dimer comparing to CRP and ESR. Shahi et al[3] reported promising results of serum D-dimer, while Pannu et al[18] and Huang et al[7] reported limited diagnostic value of serum D-dimer.

Racial difference is considered one of the reason for different diagnostic value of D-dimer in different studies. However, based on the data from previous researches, studies published in USA reported controversial outcome on the diagnostic value of D-dimer[3, 18], so did studies published in China[7, 8, 17, 19].

Plasma Fbg showed comparable diagnostic performance comparing to CRP and ESR. Our result is in consistent with the results from Li et al[8]. Fibrinogen has been found to play several key roles in antimicrobial host defense. Fibrinogen can limit growth and dissemination of bacteria within infected tissue and can support activation of host immune cells.[20]. In peritoneal infection, fibrinogen can contain *Staphylococcus aureus* and other pathogens[21].

Fbg and D-dimer did not exhibit better diagnostic performance than CRP and ESR in chronic PJI. There were 21 cases with chronic PJI in our series. Among them, Fbg was positive in 12 cases. D-dimer was positive in 13 cases, CRP was positive in 11 cases, ESR was positive in 13 cases. There were 5 PJI cases with negative culture results. Fbg, D-dimer and CRP were positive in 2 cases, ESR was positive in 4 cases. *Coagulas-negative Staphyloccus* were identified in 9 cases, Fbg and CRP were positive in all cases, D-dimer was positive in 7 cases, ESR was positive in 8 cases. Unlike our series, Shahi et al[3] reported that D-dimer was positive in 17 of 19 PJI cases with negative culture result, performing better than CRP and ESR.

Patients' comorbidities and demographic characteristics could influence the results of each biomarkers. In our study, patients with comorbidities were not excluded. Each PJI case were matched to 2 Aseptic cases based on comorbidities and demographic characteristics using propensity score matching. No significant difference was found in sex, age, height, BMI and comorbidities between the two groups. Propensity score matching was utilized to eliminate bias caused by confounding factors. Another benefit of matching is to gain more efficiency in studies with a small sample size.

Our study has several limitations: 1. due to the rare incidence of PJI, we did not acquire enough cases to further analyze the diagnostic performance of biomarkers in different subtypes of PJI. 2. 4 cases were excluded because no suitable matches were found, which further limited the sample size of our study 3. there were significantly more knee cases in the PJI group than in the Aseptic group, which may lead to potential bias.

Strength/limitation

1. Propensity score matching was utilized to eliminate bias caused by confounding factors(age, sex, BMI, comorbidity). Another benefit of matching is to gain more efficiency in studies with small sample size.
2. Sample size was limited in our study.
3. There were significantly more knee cases in the PJI group than in the Aseptic group, which may lead to potential bias.

Conclusion

The level of plasma Fbg and D-dimer is significantly higher in the PJI group. Plasma Fbg exhibited similar diagnostic performance comparing to CRP and ESR. Plasma D-dimer is of limited diagnostic value. In our study, Fbg and D-dimer did not show better diagnostic performance in any subtypes of PJI. Further studies are required to investigate the difference between serum D-dimer and plasma D-dimer in arthroplasty population.

Declarations

Acknowledgement

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The analysis was mainly conducted in Peking Union Medical College Hospital.

Statement

All authors declare no conflict of interest.

Approval from the Institutional Ethics Committee of Peking Union Medical College Hospital was obtained.

Informed consents were obtained from all subjects.

All methods were carried out in accordance with guidelines of diagnostic study.

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Figures

Figure 1

Propensity score matching were used to match each PJI cases to 2 Aseptic cases. Following covariates were matched: 1.age, 2.sex, 3.height, 4.weight, 5.BMI, 6.Comorbidities(if the patient has coagulation disorder, auto-immune disease, malignancy or takes anticoagulation medication or immunosuppressant). 4 PJI cases were excluded due to unsuccessful match. Eventually, 30 PJI cases were matched to 60 Aseptic cases. The process of patient selection and matching

Figure 2

The optimal threshold of D-dimer and Fbg was determined based on Youden Index. The optimal threshold is 1.69 mg/L for D-dimer and 3.655g/L for Fbg. ROC curve showed that CRP has the highest AUC(0.90), followed by Fbg(0.89), ESR(0.88) and D-dimer(0.77)