The Screening of Fixation-Related Infection in Patients Undergoing Conversion Total Hip Arthroplasty after Failed Internal Fixation of Hip Fractures: A Single-Central Retrospective Study

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Objective: To evaluate the diagnostic values of preoperative plasma fibrinogen and platelet count for screening fixation-related infection (FRI) in patients undergoing conversion total hip arthroplasty (cTHA) after failed internal fixation of hip fractures.

Method: This was a single-center retrospective study. Data were retrospectively analyzed for 435 patients who underwent cTHA in our hospital from January 2008 to September 2020. They were divided into infected (n = 30) and non-infected groups (n = 405) according to the 2013 International Consensus Meeting (ICM) criteria. The diagnostic sensitivity and specificity of plasma fibrinogen and platelet count were determined using receiver operating characteristic (ROC) curves. Optimal predictive cutoffs of these two markers were determined based on the Youden index. In addition, the diagnostic value of preoperative serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) for screening FRI were also evaluated based on the cutoffs recommended by the 2013 ICM Criteria. Finally, the diagnostic ability of various combinations of the plasma fibrinogen and platelet count as well as serum CRP and ESR was re-assessed.

Results: The numbers of patients with and without FRI were 30 (6.9%) and 405 (93.1%), respectively. Areas under the ROC curves were 0.770 for fibrinogen, 0.606 for platelet, 0.844 for CRP and 0.749 for ESR. The optimal predictive cutoff of fibrinogen was 3.73 g/L, which gave sensitivity of 60.0% and specificity of 90.5%. The optimal predictive cutoff for platelet was 241.5 x 10^9/L, which gave sensitivity of 46.7% and specificity of 83.7%. The CRP gave sensitivity of 66.7% and specificity of 92.5% with the predetermined cutoff of 10 mg/L, while the ESR gave sensitivity of 67.5% and specificity of 72.4% % with the predetermined cutoff of 30 mm/h. The combination of CRP and ESR showed high specificity of 93.2% but low sensitivity of 66.7%, while the corresponding values for CRP with fibrinogen were satisfied both for sensitivity of 80.0% and specificity of 78.7%. The combination of these four biomarkers gave sensitivity of 73.3% and specificity of 85.7%.

Conclusion: Preoperative serum CRP, ESR, plasma fibrinogen and platelet count have low sensitivity on their own for screening FRI in patients, but the combination of CRP with fibrinogen shows promise for that.

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**Introduction**

Hip fractures, which are quite common and place a heavy burden on medical services, are a significant cause of morbidity and mortality. Several surgeries, such as reduction and percutaneous pinning with three cancellous screws, hemiarthroplasty and total hip arthroplasty, are used to manage hip fracture. For the non-elderly population, the main causes of hip fractures are high-energy injuries. Depending on the fracture site, degree of displacement and overall state of health, some hip fractures in these non-elderly patients can be treated with open or closed reduction and internal fixation, which allow retention of the femoral head. Orthopedic surgeons can anatomically reconstruct the hip joint and restore its alignment, but these procedures are associated with severe postoperative complications such as post-traumatic osteoarthritis, nonunion and necrosis of the femoral head, which can lead to severe pain and disability. In the event that fixation of hip fractures fails, conversion total hip arthroplasty (cTHA) can be a satisfactory salvage procedure that relieves pain and restores the function of involved joint.

However, up to 18% of patients scheduled for cTHA due to failed internal fixation of hip fractures may have pre-existing fixation-related infection (FRI), which may associate with significantly higher risk of postoperative periprosthetic joint infection (PJI) after cTHA than primary total hip arthroplasty (6.9% vs 0.5%). PJI, a catastrophic complication after total hip or knee arthroplasty, is associated with longer hospital stay, greater hospitalization expenses, and higher rates of morbidity and mortality. Hence, screening for preexisting FRI before cTHA is particularly important for reducing risk of postoperative PJI.

To screen for such FRI, blood biomarkers are superior to synovial markers because they are cost-effective and easily accessible. Moreover, a reliable biomarker needs a high diagnostic sensitivity to screen infections as much as possible because an early and accurate diagnosis of FRI is crucial for the formulation and implementation of treatment regimens, preservation of the involved joint function and management of patients’ expectations. These biomarkers recommended by the Musculoskeletal Infection Society, serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), were used for screening PJI after total hip or knee arthroplasty, but their abilities for screening FRI in patients scheduled for cTHA due to failed internal fixation of hip fractures are unclear. Furthermore, the level of CRP and ESR may not elevate in patients with PJI caused by low-virulent organisms such as *Propionibacterium acnes*. Therefore, it is particularly important to evaluate the diagnostic value of CRP and ESR and find other potential markers or combinations for screening FRI before cTHA.

Surgeons are familiar with plasma fibrinogen and platelet as basic parameters of coagulation function that is screened routinely for each patient scheduled for surgery, preoperatively. Besides, plasma fibrinogen level and platelet count are also strongly associated with body’s inflammatory state and infection, and they have shown potential for screening PJI before revision knee or hip arthroplasty. However, it is unclear whether they could be used to detect FRI in patients undergoing cTHA after failed fixation of hip fractures. Hence, the present retrospective study was conducted: (i) to evaluate the ability of fibrinogen level and platelet count for diagnosing FRI in patients undergoing cTHA for failed fixation of hip fractures; (ii) to compare the diagnostic value of these two markers with that of CRP and ESR; and (iii) to evaluate the diagnostic value of these two markers when combined with CRP and/or ESR.

**Materials and Methods**

**Study Design**

From January 2008 to September 2020, patients who underwent cTHA after failed fixation of hip fractures at our institute were retrospectively enrolled in our study, which was approved by the Ethics Committee of our hospital (approval no. 2020–1004). The Committee waived the requirement for written informed consent because the study was retrospective, it did not have any adverse effect on patients’ health, and it reported anonymized patient data. This study was registered in the Chinese Clinical Trial Registry (registration no. ChiCTR2000039989).

**Inclusion and Exclusion Criteria**

Patients were enrolled consecutively if they underwent cTHA after failed internal fixation for hip fractures, which included: (i) post-traumatic osteoarthritis; and (ii) nonunion and necrosis of the femoral head, which were identified according to procedure codes of the International Classification of Diseases (10th revision), Clinical Modification. A total of 454 patients were included initially, after which five patients were excluded due to: the admission registration numbers, unique information of each patient in our hospital, were absent caused by the update of the electronic medical record system; and 14 patients who had undergone reimplantation arthroplasty were also excluded due to their complex source of pathogens and uncertain duration of infection.

**Diagnostic Definition of Fixation-Related Infection and Data Extraction**

FRI in this study was defined according to the 2013 International Consensus Meeting (ICM) Criteria. All patients were classified as infected or non-infected based on the criteria.
The following data were extracted from our hospital’s electronic medical records: sex and age; comorbidities including hypertension, diabetes, chronic obstructive pulmonary disease, coronary heart disease, autoimmune diseases and malignant tumors; results of laboratory tests including serum CRP, ESR, plasma fibrinogen and platelet count; pathology results of soft tissue located around the implant; and results of pathogenic cultures of synovial fluid collected before and during surgery.

**Laboratory Evaluations of Tested Markers**
Fasting venous blood samples were collected and assayed in a timely manner as reported. The tested markers included plasma fibrinogen level, platelet count, ESR and serum CRP. Hip joints of patients with suspected infection (based on acute-phase reactants, values of CRP and ESR, and clinical signs) were aspirated by ultrasound surgeons preoperatively under ultrasound guidance. The obtained synovial fluid samples were sent for cultures. Additionally, four or more soft tissue samples for each patient were also collected during surgery and sent for cultures. Synovial fluid samples around the implant were biopsied during surgery and sent for histologic analysis and cultures. Cultures of synovial fluid were maintained for 5 days routinely, however, if preoperative cultures proved to be negative and there was a high clinical suspicion for FRI, the cultures were extended to 3 weeks. Mycobacterial cultures were performed only for higher-risk patients. In addition, the definition of positive histology was: five or more polymorphonuclears in at least five high powered-fields.

**Sample Size Estimation**
The minimal sample size was estimated using MedCalc 12.7 (MedCalc Software bvba, Ostend, Belgium). Areas under the receiver operating characteristic curve (AUC) of tested markers for screening for PJI were previously reported to be 0.887 for CRP, 0.842 for ESR, 0.834 for platelet count and results of pathogenic cultures of synovial fluid collected before and during surgery.

Receiver operating characteristic curves were generated to describe the relationships between the true-positive rate (sensitivity) and false-positive rate (1-specificity), as well as to calculate AUCs together with their 95% confidence intervals (CIs). Positive predictive value (PPV) and negative predictive value (NPV) were also calculated. Optimal predictive cutoffs were determined for plasma fibrinogen and platelet count using the Youden index, while the optimal cutoffs for CRP and ESR were referenced from the Musculoskeletal Infection Society criteria as 10 mg/L and 30 mm/h, respectively. All statistical analyses were carried out using SPSS 24 (IBM, Armonk, NY, USA) and MedCalc 12.7 (MedCalc Software bvba, Ostend, Belgium).

**Results**

**Baseline Characteristics**
A total of 435 patients were included in our analysis, which consisted of 30 patients with FRI (6.9%) and 405 without it (93.1%), as shown in Fig. 1. The clinicodemographic characteristics of the two groups were summarized in Table 1.

**Values of Tested Markers**
All tested markers were significantly higher in the infected group than the non-infected group (Table 2): CRP, 13.70 (6.29–27.93) vs 2.72 (1.86–4.52) mg/L (P < 0.001); ESR, 34.50 (24.00–69.25) versus 18.00 (9.00–32.25) mm/h (P < 0.001); plasma fibrinogen, 3.85 ± 1.03 versus 2.89 ± 0.68 mg/L (P < 0.001); and platelet count, 215.93 ± 95.27 versus 177.87 ± 65.48 × 10^9/L (P = 0.039).

**Diagnostic Value of Tested Markers Individually**
We assessed the ability of the four tested markers for screening FRI individually. The AUCs with 95% CIs were 0.844 (0.753–0.936) for serum CRP, 0.749 (0.667–0.830) for ESR, 0.770 (0.665–0.876) for plasma fibrinogen and 0.606 (0.489–0.722) for platelet count. The sensitivity and specificity of CRP were 66.7% and 92.5% with a predictive cutoff of 10.00 mg/L. The sensitivity and specificity of ESR were 67.5% and 93.1%.
72.4% with a predictive cutoff of 30.00 mm/h. Based on the Youden index, the optimal predictive cutoff of fibrinogen was 3.73 g/L with a sensitivity of 60.0% and a specificity of 90.5%. The sensitivity and specificity of platelet count were 46.7% and 83.7% with an optimal predictive cutoff of 241.50 \times 10^9/L according to its Youden index (Table 3 and Figure 2A).

**Diagnostic Value of Tested Markers Combined Each Other**

We systematically assessed different combinations of the tested markers for screening FRI due to the sensitivity of all tested markers were unsatisfied by their own. Among them, the combination of CRP with plasma fibrinogen gave an AUC of 0.817 (0.714–0.919), with the highest sensitivity of 80.0% and satisfied specificity of 78.7%. The combination of CRP and ESR gave the highest specificity of 93.2% but low sensitivity of 66.7% (Table 4 and Figure 2B–D). Although the AUC combination of CRP and ESR was higher than that of CRP and fibrinogen, the latter has higher sensitivity.

**Culture Results of the Infected Patients**

Finally, we summarized the microorganisms in our infected group, which showed most of them were relatively low-virulent bacteria such as *Staphylococcus epidermidis* or fungi, the high-virulent microorganism such as *Staphylococcus aureus* \(^{21}\) was absent (Table 5).

| TABLE 1 The baseline characteristics of the two groups |
|-----------------------------------------------|
| **Variables** | **Infected group (n = 30)** | **Non-infected group (n = 405)** | **t or \( \chi^2 \) value** | **P value** |
|----------------|-----------------|----------------|-----------------|-----------|
| Demographic characteristics | | | | |
| Age (X ± S) | 52.52 ± 14.03 | 53.37 ± 13.67 | 0.329 | 0.742 |
| Female, N (%) | 10 (33.33%) | 189 (46.67%) | 2.001 | 0.157 |
| Comorbidities, N (%) | | | | |
| Hypertension | 4 (13.33%) | 79 (19.51%) | 0.689 | 0.405 |
| Diabetes | 3 (10.00%) | 28 (6.91%) | 0.363 | 0.547 |
| COPD | 2 (6.67%) | 4 (0.99%) | 3.723 | 0.054 |
| CHD | 0 | 6 (1.48%) | 0.864 | 0.353 |
| Autoimmune diseases | 1 (3.33%) | 8 (1.97%) | 0.218 | 0.641 |
| Malignant tumors | 0 | 7 (1.73%) | 1.009 | 0.315 |

CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease.

| TABLE 2 The values of tested markers in the two groups |
|-----------------------------------------------|
| **Variable** | **Infected group (n = 30)** | **Non-infected group (n = 405)** | **t value** | **P value** |
|----------------|-----------------|----------------|-----------|-----------|
| CRP (mg/L) | 13.70 (6.29–27.93) \(^{a}\) | 2.72 (1.86–4.52) \(^{a}\) | –4.013 | < 0.001 \(^*\) |
| ESR (mm/h) | 34.50 (24.00–69.25) \(^{a}\) | 18.00 (9.00–32.25) \(^{a}\) | –4.002 | < 0.001 \(^*\) |
| FIB (g/L) | 3.85 ± 1.03 | 2.89 ± 0.68 | –4.997 | < 0.001 \(^*\) |
| PLT (\( \times \) 10^9/L) | 215.93 ± 95.27 | 177.87 ± 65.48 | –2.15 | 0.039 \(^*\) |

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FIB, Fibrinogen; PLT, Platelet. \(^{a}\) data were presented as median (interquartile range). \(^*\) P < 0.05.

| TABLE 3 The diagnostic value of tested markers |
|-----------------------------------------------|
| **Variables** | **AUC (95%CI)** | **Youden index** | **Predictive cutoff** | **Sensitivity** | **Specificity** | **PPV** | **NPV** |
|----------------|-----------------|-----------------|-----------------|-----------|-----------|-----------|-----------|
| CRP (mg/L) | 0.844 (0.753–0.936) | 0.592 | 10.00 | 66.7% | 92.5% | 39.7% | 97.4% |
| ESR (mm/h) | 0.749 (0.667–0.830) | 0.291 | 30.00 | 67.5% | 72.4% | 15.3% | 96.8% |
| FIB (g/L) | 0.770 (0.665–0.876) | 0.505 | 3.73 | 60.0% | 90.5% | 31.9% | 96.8% |
| PLT (\( \times \) 10^9/L) | 0.606 (0.489–0.722) | 0.304 | 241.50 | 46.7% | 83.7% | 17.5% | 95.5% |

95%CI, 95% confidence interval (CI); AUC, areas under the curve; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; FIB, Fibrinogen; NPV, negative predictive value; PLT, Platelet; PPV, positive predictive value.
**Fig. 2** Receiver operating characteristic (ROC) curves of included markers. (A) Single markers of erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP), plasma fibrinogen (FIB) and platelet (PLT); (B) combinations of two markers; (C) combinations of three markers; (D) combinations of four markers.

**TABLE 4 The combinational diagnostic value of the included markers**

| Variables                  | AUC (95%CI)   | Youden index | Sensitivity | Specificity | PPV  | NPV  |
|---------------------------|---------------|--------------|-------------|-------------|------|------|
| Combinations of two markers |               |              |             |             |      |      |
| CRP + FIB                 | 0.817 (0.714–0.919) | 0.587        | 80.0%       | 78.7%       | 21.8% | 98.2% |
| CRP + PLT                 | 0.853 (0.768–0.938) | 0.627        | 76.7%       | 86.0%       | 28.9% | 98.0% |
| CRP + ESR                 | 0.859 (0.785–0.932) | 0.599        | 66.7%       | 93.2%       | 42.1% | 97.4% |
| ESR + FIB                 | 0.775 (0.672–0.825) | 0.495        | 63.3%       | 86.2%       | 16.8% | 96.6% |
| FIB + PLT                 | 0.769 (0.664–0.875) | 0.520        | 60.0%       | 92.0%       | 35.7% | 96.9% |
| ESR + PLT                 | 0.738 (0.647–0.825) | 0.348        | 43.3%       | 91.5%       | 27.4% | 95.6% |
| Combinations of three markers |           |              |             |             |      |      |
| FIB + PLT + CRP           | 0.821 (0.723–0.920) | 0.610        | 73.3%       | 87.7%       | 30.6% | 97.8% |
| PLT + CRP + ESR           | 0.863 (0.790–0.936) | 0.610        | 73.3%       | 87.7%       | 30.6% | 97.8% |
| CRP + ESR + FIB           | 0.821 (0.724–0.917) | 0.579        | 66.7%       | 91.2%       | 36.0% | 97.4% |
| ESR + FIB + PLT           | 0.774 (0.671–0.876) | 0.489        | 56.7%       | 92.2%       | 35.0% | 96.6% |
| Combinations of four markers |         |              |             |             |      |      |
| CRP + ESR + FIB + PLT     | 0.828 (0.736–0.921) | 0.59         | 73.3%       | 85.7%       | 27.5% | 97.7% |

95% CI, 95% confidence interval (CI); AUC, areas under the curve; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; FIB, Fibrinogen; NPV, negative predictive value; PLT, Platelet; PPV, positive predictive value.
The incidence of PJI seems to be much higher after revision hip or knee arthroplasty. To our knowledge, the present study is the first to assess the plasma fibrinogen and platelet count for their potential value for screening for FRI in patients undergoing cTHA after failed internal fixation for hip fractures. Our study showed that all tested biomarkers including serum CRP, ESR, plasma fibrinogen and platelet count have an unsatisfactory sensitivity on their own, while the combination of plasma fibrinogen with serum CRP shows promise for effectively screening for FRI in these patient population.

The Incidence of Preexisting Fixation-Related Infection (FRI)
The incidence of preexisting FRI in our cohort was 6.9%, which is lower than the incidence of 18% reported in another study.7 The incidence of PJI seems to be much higher after cTHA than after primary total hip arthroplasty (6.9% vs 0.5%).9 This highlights the need for efforts such as the present study to improve our ability to screen FRI in patients before cTHA in order to minimize the risk of postoperative PJI.22 Blood markers are first-line tools for screening infection as they are easy-accessible and cost-effective, and a high diagnostic sensitivity is important for a reliable biomarker as it can reduce the missed diagnosis of infection in clinical practice.

The Value of C-Reactive Protein (CRP) and Fibrinogen for Screening Fixation-Related Infection (FRI)
Although CRP and ESR are often used to screen infections preoperatively, our results suggest that they lack adequate sensitivity in patients undergoing cTHA. By contrast, Gittings et al.2 reported that preoperative CRP and ESR are effective for screening FRI before cTHA, but their sample size involved only six infected patients may be insufficient, which may bring about significant bias for the diagnostic ability of CRP and ESR. In addition, the optimal cutoff of CRP was 7 mg/L, which was significantly lower than that introduced by the 2013 ICM criteria.20 In addition, the lower diagnostic ability of CRP and ESR in our study may associate with the low-virulent microorganisms,21 which are quite common in patients scheduled for cTHA due to failed internal fixation of hip fractures in our cohort. In addition, both plasma fibrinogen and platelet count are also unsatisfactory due to low sensitivity in our cohort. Fortunately, the combination of CRP and fibrinogen gave a high sensitivity and an adequate specificity, while the combination of CRP and ESR showed a high specificity but low sensitivity.

### Table 5 Culture results of the infected patients

| Variables                      | N (composition ratio (%)) |
|--------------------------------|---------------------------|
| Culture negative               | 11 (36.7)                 |
| Culture positive               | 19 (63.3)                 |
| Staphylococcus epidermidis     | 8 (42.1)                  |
| Staphylococcus hominis         | 2 (10.4)                  |
| Escherichia coli               | 2 (10.4)                  |
| Group B streptococcus agalactiae | 1 (5.3)                    |
| Staphylococcus Kong           | 1 (5.3)                   |
| Staphylococcus haemolyticus   | 1 (5.3)                   |
| Sphingomonas paucimobilis      | 1 (5.3)                   |
| Staphylococcus tetragenus     | 1 (5.3)                   |
| Staphylococcus warneri        | 1 (5.3)                   |
| Candida albicans              | 1 (5.3)                   |

The Roles of Fibrinogen in Inflammation and Infection
Appropriate levels of fibrinogen, a glycol protein secreted from the liver, are required for hemostasis and homeostasis, and levels can reflect injury, inflammation and infection. In pediatric sepsis, fibrinogen levels lower than 2 g/L are strongly associated with higher risk of death, while in COVID-19 patients, elevated fibrinogen level is associated with higher risk of a poor outcome. Previous studies have suggested that fibrinogen has potential for diagnosing PJI before revision hip and knee arthroplasty. The present study extends that literature to suggest diagnostic potential for undergoing cTHA after failed fixation for hip fractures.

Further work should clarify how fibrinogen can reflect PJI or FRI. As an acute-phase reactant, fibrinogen level in plasma can elevate rapidly in the early stages of infection. Fibrinogen also works as an inflammatory mediator to defend against infection; it facilitates cell-to-cell adhesion between leukocytes and the endothelium, it regulates leukocyte migration and function according to the inflammatory stimulus, and it helps clear bacteria. Future studies should examine in detail how fibrinogen may be involved in infection around the implant. Nevertheless, fibrinogen has already gained recognition for its significant function during infectious process and screening of PJI or FRI.

The Value of Platelets for Screening FRI and Its Roles in Inflammation and Infection
Platelets, a type of blood cell derived from bone marrow megakaryocytes, help mediate hemostasis and thrombosis as well as inflammatory processes and infectious diseases. Platelet plays an important role in infection, including pathogen recognition through receptors on the platelet surface and pathogen clearance. After activation, platelets can secrete various antimicrobial proteins and chemokines that inhibit pathogen growth and replication and that activate the body’s innate and adaptive immune responses. Activation of platelets can reflect inflammatory diseases such as systemic lupus erythematosus and infections with viruses such as dengue, human immunodeficiency virus and Ebola. Maternal platelet parameters are strongly related to adverse neonatal outcomes during sepsis and respiratory distress. Platelet count may help differentiate COVID-19 from influenza infection, especially in seasonal outbreaks of the latter.
Our study suggests that platelet count may also help screen for FRI among patients undergoing cTHA when combined with CRP, which is in line with previous studies.17,41 However, the diagnostic sensitivity of the combination of platelet count and CRP is lower than that of fibrinogen combined with CRP.

The Limitations of Our Study
Some limitations in our study should be mentioned. First, our sample was relatively small and came from one institute. Our findings should be verified and extended at other centers. Second, for lack of sufficient patients with liver diseases, blood system diseases or inflammatory diseases, we did not correct for the potential influence of these comorbidities, which can significantly impact the level of plasma fibrinogen and platelet count.3,5,25,42 Third, since this was a retrospective study, we could not collect certain data, such as the results of synovial fluid tests conducted at other hospitals. Although the diagnostic cutoffs determined here for fibrinogen and platelet count may not be generalizable to all patient populations, our results establish the potential of these two biomarkers for screening FRI among patients undergoing cTHA after failed internal fixation for hip fractures, especially when combined with the traditional inflammatory marker CRP. This may provide an accessible, cost-efficient way to detect such FRI and thereby reduce risk of postoperative PJI.

Conclusion
Preoperative CRP, ESR, fibrinogen and platelet count have low sensitivity on their own for screening FRI in patients undergoing cTHA after failed internal fixation of hip fractures, but the combination of CRP with fibrinogen shows promise for that. Larger studies from other institutions should confirm our findings.

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Ethics Statement
This study was approved by the Ethics Committee of our hospital (approval no. 2020–1004). The Committee waived the requirement for written informed consent because the study was retrospective, it did not have any adverse effect on patients’ health, and it reported anonymized patient data.

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