Change in Serum Markers Failed to Predict Persistent Infection after Two-stage Exchange Arthroplasty

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Abstract

Background

Two-stage exchange arthroplasty is a viable choice for prosthetic joint infection (PJI). After removing the infected prosthesis and implanting an antibiotic-loaded spacer in first stage, the proper timing of reimplantation is crucial for successful treatment. So far, there is no gold reference to determine the eradication of PJI before reimplantation. The combination of serum indicators, synovial white cell count (WBC), culture results, intraoperative histology, and clinical symptoms is used extensively to guide the timing of reimplantation. However, the proper timing of reimplantation was ill defined.

Purpose

We wonder: (1) the utility of serum indicators, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), interleukin-6 (IL-6) and fibrinogen, when predicted failure of reimplantation; (2) correlation between primary culture results and serum markers' change.

Method

A retrospective review of 226 patients treated with a two-stage exchange arthroplasty from 2014 to 2017 was conducted. PJI was diagnosed by using the Musculoskeletal Infection Society (MSIS) criteria. Serum biomarkers and organisms results at the set of PJI diagnosis and reimplantation were reviewed. Treatment success was defined according to the Delphi consensus criteria with a minimum follow-up of 2 year; receiver operator characteristic (ROC) depicted the utility of change in four serum markers when predicted failure.

Results

The ROC area under the curves (AUC) was 0.543 in CRP, 0.572 in IL-6, 0.621 in ESR, 0.463 in fibrinogen and the combination of them was 0.709 when predicted persistent PJI using value change. The AUC of ROC was 0.521 in CRP, 0.472 in IL-6, 0.413 in ESR, 0.552 in fibrinogen and the combination was 0.630 when determine reimplantation by percent change. No significant association was found between culture results and change in serum markers.

Conclusion

Neither percent change nor value change in serum makers was proved to be poor markers when predicted persistent PJI, and initial causative organism didn't influence the normalize of serum markers. Persistent PJI after TJA was still tough to diagnose. The combination of clinical symptom, pathology results, synovial fluid analysis and serum markers may improve the utility.

Introduction

Management of prosthetic joint infection (PJI) is a tough problem for our clinicians, with high prevalence after total joint arthroplasty (TJA)[1, 2]. In North America and East Asia, two-stage exchange arthroplasty is widely applied to chronic PJIs after TJA[3, 4]. After removing the infected prosthesis and implanting an antibiotic-loaded spacer in first stage, the proper timing of reimplantation is crucial for successful treatment[5]. So far, there is no gold reference to determine the eradication of PJI before reimplantation. The combination of serum indicators, synovial white cell count (WBC), culture results, intraoperative histology, and clinical symptoms is used extensively to guide the timing of reimplantation.

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are two most acceptable serum indicators in predicting PJI[6–11]. But the relativity and utility of both indicators was suspected by several researches. In spite of their doubtful threshold cutoff levels, the normalization of both markers was reported failed to predict control of PJI[5–7, 11]. Several other serum biomarkers were studied by researchers. Interleukin-6 (IL-6) was proved to be useful in diagnose PJI[12–14], and Hoell et al reported the good utility of IL-6 in predicting failure of reimplantation[15]. Li et al reported fibrinogen had good performance in diagnosis of PJI[16]. However, more research is needed to determine the accuracy and reliability of these serum indicators in predicting the proper timing of reimplantation.

Instead of a numerical threshold, the 2018 International Consensus Meeting recommended that the down trend in serum markers was viable to determine the proper timing of reimplantation. But opposite result was found by Stambough et al[17]. Stambough et al[17] found the area under the receiver operator curves was 0.530 for percent or delta change in ESR and 0.482 in CRP when predicted persistent PJI, indicating both were poor markers. Considering the value of fibrinogen and IL-6 in diagnosing PJI, change in these serum markers may be viable to predict failure after reimplantation. Besides, instead of percent change, the utility of the value change in serum markers should be investigated.

As contradictory existed whether change in serum markers can guide the timing of reimplantation in two-stage exchange arthroplasty after total joint arthroplasty (TJA), we wonder: (1) the utility of serum indicators, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), interleukin-6 (IL-6) and fibrinogen, when predicted failure of reimplantation; (2) correlation between primary culture results and serum markers' change.

Methods

Patients

After the Institutional Review Board approval, we retrospectively reviewed all patients underwent two-stage reimplantation between 2014 and 2017 (n=226). All patients were confirmed to be chronic PJI, as acute hematogenous and perioperative infection were excluded[18]. We excluded 7 fungal PJI, 26 patients with potential inflammatory rheumatism disease (rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, etc), and 30 PJI with hardware fixation, because of uncertain changes in serum indicators in these patients[11, 19, 20]. 15 patients were excluded for less than the minimum 2-year follow-up. Furthermore, 14 patients who referred to our hospital with antibiotic-loaded cement were excluded for

lack of detailed data in serum indicators at the time of resection. 12 participants were excluded because they were satisfied with spacer and refused reimplantation. There are 122 patients left. In this research, MSIS criteria[21] was considered as gold reference to diagnose PJI before resection, and 13 PJIs were excluded without matching MSIS criteria. There are final 109 patients in analysis with the minimum 2-year follow-up and complete record of serum biomarkers, and all patients matched the MSIS criteria when diagnosed PJI.

We reviewed all medical record of patients in detail, including patients' characteristics, American Society of Anesthesiologists (ASA) score, risk factors, surgical history of the same site, pathology results, and organism culture results. Values of four main serum biomarkers including serum ESR, CRP, fibrinogen and IL-6 were identified before resection and reimplantation. The threshold values was over 30mm/hr for ESR and 10mg/L for CRP referred to MSIS criteria[21], and the upper limit was 12 pg/mL for and 1.25mg/mL for fibrinogen[16, 22] when diagnose PJI. The change of serum indicators was evaluated by percent change (using values of serum markers in time of reimplantation divide values in time of resection) and value change (using values of serum markers in time of resection minus values in time of reimplantation).

Treatment protocol

All patients underwent an institutional standard two-stage exchange arthroplasty, including removal of prosthesis, placement of antibiotic-loaded articulating cement spacer and thoroughly debridement at the time of first stage procedure. Vancomycin (2-4 g per 40 g) and meropenem (1-2 g per 40 g) were mixed in polymethylmethacrylate (PMMA) spacers. Histology analysis and organism culture was conducted regularly. After insertion of cement, all patients accepted 6-8 weeks inter venous antibiotic depends on culture sensitivity reports. For negative result, a broad-spectrum antibiotic therapy was applied. At least 2-week antibiotic holiday was stipulated before reimplantation. During two-stage revision, the antibiotic-loaded cement was removed. 4-6 L sterilized saline water was used to irrigate the joint after thoroughly debridement. Three to five samples were sent to frozen sections, aerobic and anaerobic cultures according to surgeon' suspicion.

Definition of persistent PJI and treatment success

Persistent PJI for this study was defined as :1. Re-infection after reimplantation, based on MSIS criteria, 2. Long-term antibiotic suppression after reimplantation, 3. Death relating to PJI, 4. Matched MSIS criteria at the time of reimplantation, 5. A pathogen is isolated by culture from at least two separate tissue or fluid samples obtained from the affected prosthetic joint.

We determined treatment success using the Delphi consensus criteria[23, 24], which matches the following: 1. a healed wound without fistula, drainage, pain, or infection recurrence caused by the same organism strain; 2. no subsequent surgical intervention for infection after reimplantation surgery; 3. no occurrence of PJI-related mortality.

Statistical analysis

All of the statistical analyses were performed with the statistical software packages R (<http://www.R-project.org>, The R Foundation). Categorical data were summarized as absolute values and percentage. Continuous data were presented as median and interquartile range (IQR). The demographic and clinical characteristics between groups were compared with the use of the Student's *t*-test if they were normally distributed or the Mann-Whitney test if not normally distributed for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Receiver operating characteristic (ROC) curves were generated to determine the diagnostic value of each test for the assessment of persistent PJI. The area under the curve (AUC) was calculated. A p-value less than 0.05 was considered significant.

Results

General information and patients' follow-up

Patient characteristics and follow-up results were showed in Table 1. There were 54 (49.5%) males and 55 females (50.5%). The mean age was 60.4 ± 12.7 in success group and 60.3 ± 14.4 in re-infected patients. The mean BMI was 25.4 ± 3.7 kg/m² in success group compared 25.6 ± 3.9 kg/m² in failed group. 56 hips and 53 knees were included in the analysis. More prevalence of sinus was observed in re-infected group at the time of diagnosing PJI ($p=0.07$).

No significant difference was found in comorbidities, including diabetes, hepatitis, cardiovascular, carcinoma, previous surgical history, nephropathy, smoking, alcohol abuser and ASA>2.

The mean follow-up year was 3.1 ± 1.1 year in no re-infected group and 1.4 ± 1.3 year in re-infected patients. The interval of spacer insertion was 168.0 ± 136.5 days in success group and 162.7 ± 113.3 days in failure. There were 15 patients re-infected after reimplantation in two-stage exchange arthroplasty, and the total success rate was 86.2%.

Organism analysis

Details of causative organism at the set of spacer and culture result at the time of reimplantation in re-infected patients were recorded in Table2. Drug resistant organism was the most common causative bacteria for initial PJI (32,29.4%). The rest of causative organism included 21 (19.3%) coagulase negative staphylococcus (CNS), 18 (16.5%) staphylococcus, 5 (4.6%) enterococcus faecalis, 4 (3.7%) streptococcus, 5 (4.6%) gram-negative bacillus, 3 (2.8%) other organism and 10 (9.2%) polymicrobial organism. 11 (10.1%) patients were negative culture results but diagnosed PJI according to MSIS criteria. At the time of reimplantation, the culture result of re-infected patients consisted of 1 (0.9%) CNS, 2 (1.8%) gram-negative bacillus, 2 (1.8%) resistant PJI, 1 (0.9%) fungal PJI, 1 (0.9%) another organism and 8 (7.2%) unidentified organism.

Is there any difference in value of serum markers between success and failed group?

The value of ESR, IL-6, CRP and fibrinogen were compared between no re-infected patients and failed patients. The detail of each serum markers was recorded in Table 3. At the time of diagnosing PJI, the re-infected group exhibited significant higher value in all four serum markers. As for reimplantation, higher value of CRP and fibrinogen was observed, while IL-6 and ESR were comparable, indicating that the higher value of CRP and fibrinogen may relate to re-infection. The accurate value of CRP and fibrinogen needed further research.

Does percent change or value change in serum markers guide the timing of reimplantation?

Table 5 showed the percent change and value change from resection to reimplantation. No significant difference was found in neither value change of serum markers nor percent change of these. Furthermore, we depicted receiver operator curve (ROC) for value change (figure.1) and percent change (figure.2) of serum markers. Receiver operator curve area under the curve (AUC) was 0.543 in CRP, 0.572 in IL-6, 0.621 in ESR and 0.463 in fibrinogen when predicted failure by value change, demonstrated that all these serum markers were poor indicators. However, receiver operator curve AUC exhibited passable utility of the combination (AUC=0.709) of ESR, CRP, IL-6 and fibrinogen. With regard to percent change in determining the timing of reimplantation, receiver operator curve AUC indicated that CRP (AUC=0.521), IL-6 (AUC=0.472), ESR (AUC=0.413), fibrinogen (AUC=0.552) and the combination of them (AUC=0.630) were all meaningless markers.

Does the microbial culture result influence the value or percent change of serum markers?

Comparison of difference in value change and percent change of serum markers between resistant PJI (including MRSA, MRSE, VRE) and sensitive organism was showed in Table 5. The re-infected patient showed lower value change and higher percent change of ESR. And subgroup analysis between culture negative PJI and identified organism was exhibited in Table 6. No significant difference was found in neither value change nor percent change of all four serum markers.

Discussion

PJI is still a tough problem after total joint arthroplasty, and two-stage exchange arthroplasty was proved to be the viable treatment for prosthetic joint infection after total joint arthroplasty, with the success rate range from 65% to 100%[25]. The proper timing of reimplantation was crucial to the survivorship of implant. Considering the unreliability of clinical symptom, lagging of pathology and scarcity of synovial fluid, serum biomarkers still played an important role in predicting the persistent infection after reimplantation. Though several authors failed to determine the threshold of ESR and CRP[6, 7, 10], the utility of fibrinogen and IL-6 in predicting failure after reimplantation was reported by some articles[13, 26].

Our research investigated the value change and the percent change of four common serum markers (ESR, CRP, IL-6 and fibrinogen) between resection and reimplantation. The AUC of ROC was no more than 0.70 in all serum markers, and the combination of serum markers didn't improve the diagnose utility, indicated

that neither value change nor percent change of these four serum markers were poor utility in determining reimplantation. Higher value of CRP was observed in both resection and reimplantation, and elevated fibrinogen in reimplantation seemed to be related to increased failure rate. Besides, resistant PJI or culture negative result was not associated with change in serum markers.

We found that preresection CRP and IL-6 was significant higher in failed group. Besides, the value of fibrinogen and ESR had the tendency to be significance. This is no surprisingly given that the utility and threshold of the four serum markers had been thoroughly studied[16, 22, 27, 28]. However, at the time of reimplantation, values of CRP and fibrinogen were significant higher in re-infection. Kusuma et al[6] reported 76 PJI after total knee arthroplasty, and the AUC of ROC was 0.62 in ESR and 0.39 in CRP. Xu et al[26] also investigated 109 hips who underwent two stage exchange arthroplasty. They found that the value of fibrinogen may be the promising marker in predicting persistent PJI, and the threshold of fibrinogen was 3.61 g/L. Qu et al[29] reported high specificity but low sensitivity when the threshold of IL-6 set at 8.12 pg/ml, and the AUC of ROC was 0.59. The value of serum markers may be useful in predicting re-infection after two-stage exchange arthroplasty, but further study was needed to determine the accurate threshold of them. Besides, other serum markers, like procalcitonin, TNF- α and d-dimer, was reported to be viable by several articles[22, 30, 31].

Instead of numerical threshold value, the International Consensus Meeting recommended the downtrend of serological tests and results of synovial analysis to determinate the optimal timing of reimplantation. However, two traditional serum markers (ESR and CRP) were researched by Stambough et al[26], the AUC of receiver operator curve depicting percent change in Stambough et al was 0.530 for ESR and 0.482 for CRP. Ghanem et al[7] studied a consecutive series of 109 patients who underwent two-stage resection arthroplasty for infected TKA. The total success rate was 79% in their cohort. The value change of ESR and CRP was depicted by ROC, and the AUC of ROC was 0.503 in ESR and 0.545 in CRP. Both Stambough et al and Ghanem et al draw the opposite conclusion with ICM approval. We did, however, bring the change of IL-6 and fibrinogen into analysis. We found that neither value change nor percent change of these four lab markers was suitable indicators in predicating re-infection after two-stage exchange reimplantation. Down trend in serum markers were not significant associated with the eradication of infection, and this result may change we surgeon traditional thought.

Besides, no obvious correlation was observed in culture result and change of serum markers. Though significant lower value change in ESR was observed in resistant PJI, it could be ascribed to high virulence of MRSA, MRSE and VRE. As to culture negative organism, all serum markers in our research showed no difference with identified PJI. Berbari et al[32] reported 897 PJI, of whom 60 patients were culture negative. The 5-year estimate of survival free of treatment failure was 94% for patients treated with two-stage exchange. It seemed no higher recurrence rate in culture negative PJI if full dose antibiotic was used.

Until now, accurate diagnosis of eradication of infection is still difficult for our clinician. As our research proved the poor utility of change in four common serum markers when predicting persistent PJI, other

sensible ways like new biomarkers, biochemistry, histology should be put forward to detect infection. The combination of clinical symptom, value of serum markers, frozen section, synovial fluid WBC is still the most reliable method for our surgeon to judge the timing of reimplantation.

There were several limitations in our research. Firstly, it was a retrospective study and certain biases of retrospective study can't be avoidable. Though we reviewed most cases in document, some mistakes may have existed. Secondly, for lack of gold standard in diagnosing persistent PJI after reimplantation, we combined clinical symptom, serum markers, culture result and follow-up result to identify re-infection, which may reduce long-term failure rate. Thirdly, several surgeons in our hospital conducted the surgery. Though institutional guideline of therapy had been approved, difference still existed in the management of patients. Fourthly, limited by quantity of patients, we couldn't subanalysis the change trend between different organisms.

Declarations

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Availability of data and materials

We do not wish to share our data, because some of the patient's data regarding individual privacy, and according to the policy of our hospital, the data could not be shared with others without permission.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the General Hospital of People's Liberation Army and in accordance with the standards of the National Research Council.

Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

Authors' contributions

Contributors	Roles
Qiao Jiang	Manuscript writing; Data collection; Data analysis; Study conceive; Participated in the design of the study; Data interpretation; Project coordination
Xue Yang	Data collection; Data analysis; Study conceive; Participated in the design of the study; Data interpretation; Project coordination
Chi Xu	Data curation; Investigation; Methodology; Visualization; Writing - review & editing
Wei Chai	Data curation; Investigation; Methodology; Validation; Writing - review & editing
Yong-Gang Zhou	Data curation; Validation; Methodology; Validation; Writing - review & editing
Ji-Ying Chen	Project administration; Supervision; Writing - review & editing

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Tables

Table.1 Patient characteristics and comorbidities associated with failure after two-stage exchange arthroplasty

	Success (n=94)	Failure (n=15)	P-value
Patient characteristics			
Follow-up (year)	3.1 ± 1.1	1.4 ± 1.3	<0.001
Age (year)	60.4 ± 12.7	60.3 ± 14.4	0.826
BMI (kg/m ²)	25.4 ± 3.7	25.6 ± 3.9	0.937
Interval of spacer (day)	168.0 ± 136.5	162.7 ± 113.3	0.996
Male	43 (45.7%)	11 (73.3%)	0.056
Hip	49 (52.1%)	7 (46.7%)	0.784
Sinus	26 (27.7%)	8 (53.3%)	0.070
Comorbidities			
Diabetes	19 (20.2%)	3 (20.0%)	1.000
Hepatitis	3 (3.2%)	1 (6.7%)	0.452
Cardiovascular	10 (10.6%)	2 (13.3%)	0.670
Carcinoma	5 (5.3%)	1 (6.7%)	1.000
Previous surgical history	23 (24.5%)	6 (40.0%)	0.220
Nephropathy	2 (2.1%)	0 (0.0%)	1.000
Smoking	14 (14.9%)	1 (6.7%)	0.689
Alcohol abuser	5 (5.3%)	1 (6.7%)	1.000
ASA>2	11 (11.7%)	3 (20.0%)	0.405

BMI Body mass index, ASA American Society of Anesthesiologists

Table.2 Initial causative of prosthetic joint infection and culture result of re-infected patients at the time of reimplantation

Culture organism	Result
At the time of diagnosing PJI	
Staphylococcus aureus	18 (16.5%)
Coagulase negative Staphylococcus	21 (19.3%)
Enterococcus faecalis	5 (4.6%)
Streptococcus	4 (3.7%)
Gram-negative bacillus	5 (4.6%)
Resistant organism	32 (29.4%)
Polymicrobial PJI	10 (9.2%)
Other organism	3 (2.8%)
Culture negative	11 (10.1%)
At the time of reimplantation	
Coagulase negative Staphylococcus	1 (0.9%)
Gram-negative bacillus	2 (1.8%)
Resistant organism	2 (1.8%)
Fungal PJI	1 (0.9%)
Other organism	1 (0.9%)
Unidentified	8 (7.2%)

Table.3 Values of serum markers in the time of resection and reimplantation in prosthetic joint infection

	Success (n=94)	Failure (n=15)	P-value
Pre-resection			
CRP (mg/l)	26.0 ± 29.1	39.5 ± 24.2	0.008
IL-6 (pg/ml)	18.8 ± 18.1	25.2 ± 10.4	0.008
ESR (mm/hr)	42.0 ± 25.4	53.1 ± 22.5	0.091
Fibrinogen (g/l)	4.9 ± 1.2	5.5 ± 1.0	0.105
Pre-reimplantation			
CRP (mg/l)	5.3 ± 6.8	17.1 ± 24.2	0.025
IL-6 (pg/ml)	4.9 ± 4.6	8.9 ± 8.3	0.102
ESR (mm/hr)	13.7 ± 10.8	15.1 ± 11.3	0.597
Fibrinogen (g/l)	3.4 ± 0.7	3.9 ± 1.0	0.033

Table.4 Value change and percent change of serum markers between resection and reimplantation in prosthetic joint infection

	Success (n=94)	Failure (n=15)	P-value
Value change of serum markers			
CRP (mg/l)	21.2 ± 29.4	21.6 ± 32.9	0.595
IL-6 (pg/ml)	30.9 ± 12.6	16.3 ± 15.9	0.374
ESR (mm/hr)	28.3 ± 22.3	38.1 ± 22.4	0.135
Fibrinogen (g/l)	1.5 ± 1.2	1.5 ± 1.6	0.647
Percent change of serum markers			
CRP (%)	43.2 ± 55.8	51.6 ± 55.7	0.795
IL-6 (%)	51.9 ± 81.7	51.6 ± 63.0	0.725
ESR (%)	40.9 ± 32.7	30.3 ± 22.8	0.283
Fibrinogen (%)	74.9 ± 45.6	75.0 ± 24.9	0.515

Table.5 Value change and percent change in sensitive organism versus resistant organism in initial prosthetic joint infection

	Sensitive organism (n=77)	Resistant organism [n=32]	P- value
Value change of serum markers			
CRP (mg/l)	22.3 ± 31.4	19.1 ± 23.0	0.920
IL-6 (pg/ml)	35.1 ± 13.3	14.1 ± 14.0	0.572
ESR (mm/hr)	33.3 ± 22.7	20.8 ± 19.5	0.006
Fibrinogen (g/l)	1.6 ± 1.4	1.4 ± 1.1	0.585
Percent change of serum markers			
CRP (%)	46.6 ± 55.0	38.8 ± 57.6	0.389
IL-6 (%)	53.6 ± 78.8	47.6 ± 80.8	0.269
ESR (%)	34.7 ± 27.0	50.8 ± 38.8	0.038
Fibrinogen (%)	76.2 ± 49.7	72.0 ± 21.3	0.894

Table.6 Value change and percent change in negative culture versus identified organism in initial prosthetic joint infection

	Negative culture (n=98)	Identified organism (n=11)	P- value
Value change of serum markers			
CRP (mg/l)	22.8 ± 30.1	15.9 ± 12.1	0.984
IL-6 (pg/ml)	30.8 ± 11.8	12.2 ± 15.0	0.556
ESR (mm/hr)	29.6 ± 22.5	29.9 ± 23.7	0.960
Fibrinogen (g/l)	1.5 ± 1.3	1.6 ± 1.3	0.798
Percent change of serum markers			
CRP (%)	45.0 ± 57.8	38.8 ± 30.4	0.644
IL-6 (%)	52.1 ± 82.5	49.3 ± 39.8	0.421
ESR (%)	40.0 ± 32.4	34.7 ± 24.6	0.759
Fibrinogen (%)	75.3 ± 45.2	71.7 ± 19.4	0.944

Figures

Figure 1

A-B Receiver operator curves for value change of serum markers in predicting failure after two-stage exchange arthroplasty: A. erythrocyte sedimentation rate (yellow slope), interleukin-6 (green slope), C-reactive protein (blue slope) and fibrinogen (purple slope). The black slope depicts 50% sensitivity and specificity; B. combination of these four serum markers (blue slope).

Figure 2

A-B Receiver operator curves for percent change of serum markers in predicting failure after two-stage exchange arthroplasty: A. erythrocyte sedimentation rate (yellow slope), interleukin-6 (green slope), C-

reactive protein (blue slope) and fibrinogen (purple slope). The black slope depicts 50% sensitivity and specificity; B. combination of these four serum markers (blue slope).

Figure 3

Flowchart of patients' characteristics