The Risk Factors of Polymicrobial Periprosthetic Joint Infection: A Single-Center Retrospective Cohort Study.

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Title: The Risk Factors of Polymicrobial Periprosthetic Joint Infection: A Single-center Retrospective Cohort Study.

Running title: The Risk Factors of Polymicrobial Periprosthetic Joint Infection

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24 Project guarantor: Jiying Chen and LiBo Hao. The author(s) read and approved the
25 final manuscript.

26 **Conflict of Interest Statement:**

27 Each author certifies that he or she has no commercial associations

28 **Ethical review committee statement:**

29 This study was performed in accordance with the ethical standards in the 1964

30 Declaration of Helsinki. All methods were carried out in accordance with relevant
31 guidelines and regulations. And Institutional review board approval was obtained
32 prior to the commencement of this study

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35

36 **Abstract:**

37 **Background:** Periprosthetic joint infection is a serious complication after total joint
38 arthroplasty and polymicrobial PJI which compose a subtype of PJI often indicate
39 worse outcomes compared to monomicrobial periprosthetic joint infection. However, a
40 literature review suggested that there were limited number studies evaluating the risk
41 factors of polymicrobial PJI.

42 **Materials and methods:** Between 2015 January and 2019 December, a total of 64
43 polymicrobial PJI patients and 158 monomicrobial PJI patients in a tertiary center were
44 included in this study and corresponding medical records were scrutinized. The
45 diagnosis of PJI was based on 2014 MSIS criteria. Logistic regression was used to
46 identify the association between various variables and polymicrobial PJI and ROC
47 curve was used to identify their efficiency.

48 **Results:** The prevalence of polymicrobial PJI is about 28.28% in our cohorts. After
49 adjusting, the presence of previous revisions (OR, 1.93; $p < 0.01$), isolation of
50 enterococci (OR, 11.36; $p < 0.01$), isolation of *Escherichia coli* (OR, 6.55; $p < 0.01$),
51 infection with atypical organisms (OR, 9.85; $p < 0.01$), infection with gram-negative
52 organisms (OR, 6.33; $p < 0.01$), isolation of streptococcus spp (OR, 1.93; $p < 0.01$), and
53 infection with CNS (OR, 1.93; $p < 0.01$) were risk factors of polymicrobial PJI
54 compared to monomicrobial PJI. However, knee infection is a protection factor of
55 polymicrobial PJI with an adjusted OR=0.0479 ($p=0.023$).

Conclusion: This study demonstrated that the prevalence of polymicrobial PJI is about 28.28% in PJI patients. Moreover, the presence of sinus tract and previous joint revisions were risk factors for identifying different bacterial species in the intraoperative specimens. Therefore, in these PJI cases, it is necessary to examine multiple specimens of both intraoperative tissue and synovial fluid for increasing the detection rate and obtaining resistance information.

Backgrounds:

Total knee arthroplasty (TKA) and total hip arthroplasty (THA) are successful surgeries during the last century but some severe complications occur after total joint arthroplasty (TJA). Periprosthetic joint infection (PJI) is a serious complication after TJA and lays a huge burden on both orthopedic doctors and PJI patients.[1-3]

Polymicrobial PJI, accounting for 6% to 37% of PJI, is a subtype of PJI and some studies revealed that polymicrobial PJI was associated with reduced cure rate compared to monomicrobial PJI[1, 2, 4]. The management of polymicrobial PJI is tough and requires repeated revisions, higher treatment cost, administration of board-range antibiotics and multiple antibiotics to fight against PJI pathogens. Therefore, the treatment of polymicrobial PJI is associated with higher motility, higher costs, and more complications[5-8].

However, a literature review suggested that the studies about polymicrobial PJI were limited because of the relatively low occurrence rate of polymicrobial PJI. Despite a fact that some studies revealed that the presence of sinus and certain cultured

77 pathogens was associated with a higher risk of polymicrobial PJI, there are still some
78 uncertainties regarding the risk factors of polymicrobial PJI[1, 2, 5]. Moreover, few
79 studies revealed the distribution of polymicrobial PJI pathogens in Asian.

80 To address the problems mentioned above, we performed a single-center
81 retrospective study to determine 1) the distribution of pathogens in polymicrobial PJI
82 patients 2) the risk factors associated with risk factors of polymicrobial PJI

83

Material and methods:

Patients:

Institutional review board approval was obtained prior to the commencement of this study and informed consents were obtained before revisions. Between 2015 and 2019, a total of 843 revision patients were included consequentially in this study initially. And the inclusion criteria were as follows: 1) PJI patients based on the 2014 MSIS criteria 2) No spacer implantation. Exclusion criteria: Culture-negative PJI patients were excluded from this study. The corresponding medical records were extracted and then, these data were scrutinized manually. After selection, a total of 256 PJI patients were included in this study and the process of selection was shown in figure 1.

Moreover, following information was extracted: the age, sex, body mass index (BMI), involved joint, the type of identified pathogens, previous revisions, the nature of the surgical treatment, the presence of sinus tract, the levels of ESR, CRP. Previous revisions were defined as the patients received surgeries on the same joint after primary total joint arthroplasty.

The diagnosis of polymicrobial PJI

The PJI diagnosis was based on the 2014 Musculoskeletal Infection Society (MSIS) criteria [9]. The patients with PJI in which at least 2 different organisms were isolated from the culture of synovial fluid or intraoperative tissue were considered to have polymicrobial PJI. A total of 64 PJI patients were considered to have polymicrobial PJI according to this definition.

Culture and microbiological analysis:

According to the standard protocol at our institution, specimens obtained was sent for aerobic, anaerobic, and fungal cultures, with a mean number of 5 samples taken from each PJI patient. After culture, the pathogens isolated were identified and antibiotic sensitivity tests (AST) were performed. A matrix-assisted laser desorption-isolation time-of-flight mass spectrometer (VITEK-MS (BioMérieux)) was used to identify the pathogens isolated from culture.

Statistically analysis:

The variables were divided into continuous variables and dichotomous data based on the types of data. A normal distribution test was used to evaluate the distribution of continuous variables. The continuous variables were described as means if the normal distribution was achieved. Otherwise, corresponding medians were calculated. Random 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. Logistic regression was used to evaluate the relationship between the potential risk factors and polymicrobial PJI. OR and adjusted OR were used to evaluate the relative risk of these potential risk factors. The statistical analysis was performed on SPSS (IBM; version 26.0). $P < 0.05$ indicates statistical significance.

Results:

1. Demographic characteristic of PJI patients

The mean ages were 59 and 64.2 years in the polymicrobial PJI and monomicrobial groups, respectively. The percentages of knees were 37.5% and 59.5% in these two groups, respectively. The percentage of males in these two groups was 42.2% and 44.9%, respectively. Besides, the percentages of the presence of sinus tracts in these two groups were 48.4% and 10.8%. The details of these two groups were summarized in table 1.

2. The distribution of pathogens in PJI patients.

The percentage of *S. aureus* in polymicrobial PJI and monomicrobial PJI was 13% and 29%, respectively. The percentage of CNS in the two group was 32.1% and 35.4%, respectively. The percentage of fungus in the two group was 35% and 56%, respectively. The percentage of gram-positive bacillus in the two group was 6.4% and 5.1%, respectively. The details about the distribution of pathogens in PJI patients was shown in Table 2.

3. The risk factors of polymicrobial PJI

In the univariate the presence of a sinus tract (OR, 3.405), the presence of previous revisions (OR, 2.512), knee infection (OR, 0.402) isolation of enterococci (OR, 2.669;), infection with atypical organisms (OR, 4.371), infection with gram-negative organisms (OR, 2.593), isolation of streptococcus spp (OR, 5.499), and infection with CNS (OR, 1.773)

Moreover, in the multivariate logistic regression analysis, two patient characteristics were found to be the significant independent risk factors of

polymicrobial PJI: the presence of sinus (OR, 2.565; $p < 0.001$) and previous revisions (OR, 1.954; $p = 0.039$). Besides, the knee infection is a protection factor of polymicrobial PJI compared to the hip infection (OR, 0.479; $p = 0.023$). No other patient characteristics (including joint, sex and BMI) were identified as risk factors. Besides, in the multivariate logistic regression analysis, the adjusted OR of different pathogens was calculated after adjusting the presence of sinus and previous revisions. After adjusting, the presence of previous revisions (OR, 1.93; $p < 0.01$), isolation of enterococci (OR, 11.36; $p < 0.01$), isolation of *Escherichia coli* (OR, 6.55; $p < 0.01$), infection with atypical organisms (OR, 9.85; $p < 0.01$), infection with gram-negative organisms (OR, 6.33; $p < 0.01$), isolation of *Streptococcus* spp (OR, 1.93; $p < 0.01$), and infection with CNS (OR, 1.93; $p < 0.01$) were risk factors of polymicrobial PJI compared to monomicrobial PJI. However, knee infection is a protection factor of polymicrobial PJI with a adjusted OR=0.0479 ($p = 0.023$). The details about the risk factors of polymicrobial PJI were shown in Table 3.

Discussion:

Polymicrobial PJI is a serious complication after total joint arthroplasty and often indicates unfavorable prognosis compared to monomicrobial PJI. However, the studies about the risk factors of polymicrobial PJI are limited. This study evaluated the risk factors of polymicrobial PJI and revealed some findings.

Culture-negative PJI weren't included from this study because previous antibiotics administration is a major cause of culture-negative PJI and the exclusion of this

group can lower this confusion from antibiotics. Polymicrobial PJIs accounted for 10.5% to 19% of THA PJIs and 9% to 12.3% of TKA PJIs in previous studies[1]. We have observed that the percentage of polymicrobial PJI in culture-positive PJI is about 28.82% and it is consistent with previous reports[10].

The distribution of pathogens in polymicrobial PJI is like that in monomicrobial PJI patients. *Staphylococcus* spp, including *staphylococcus aureus* and CNS, is still the most comm isolated pathogen in polymicrobial PJI. However, the percentage of *streptococcus* spp in polymicrobial PJI is relatively higher than that in monomicrobial PJI. Our results were consistent with previous studies.

The presence of sinus tract is associated with higher risk of polymicrobial PJI and this result is consistent with previous studies[1, 2]. The sinus tract can become a shelter of pathogens and a pathway for causative agents to enter the joint cavity so that polymicrobial infection is more common in PJI patients with sinus tracts. Therefore, surgeons can obtain more specimens for cultures during revisions in PJI patients with sinus tracts with a bid to improve the detection rate of PJI pathogens by which antibiotic can be administrated more precisely.

Some studies suggested that repeated revision was a risk factor of PJI but the association between previous revisions wasn't revealed by other studies [2, 3]. Here, our studies revealed that the presence of previous revisions was also a risk factor of polymicrobial periprosthetic joint infection. Previous repeated procedures in the same joint can impair the surrounding blood supplies around the joints

189 potentially and then, the joints became vulnerable to various pathogens because of
190 the poor status of the soft tissues in these patients. It can be the reason of higher
191 risk of polymicrobial PJI in PJI patients with repeated revisions. Hence,
192 polymicrobial PJI should be specially noted in these PJI patients and board-range
193 antibiotics and more specimens for cultures can be optional.

194 Interestingly, Robert Cantey et. reported that age 65 years or older was associated
195 with polymicrobial PJIs. However, our result suggested that the mean and median ages
196 of polymicrobial PJI was lower than those of monomicrobial PJI. And the OR of age
197 65 years or older is 0.491 in the bivariate logistic regression (P value=0.018). To further
198 clarify this association, the confounding variate(the presence of sinus) was adjusted,
199 and the adjusted OR: 0.532 (p=0.044, 95%CI: (0.288, 0.983)). After adjusting
200 confounding variate (the presence of sinus and previous revisions), the adjusted
201 OR=0.561(p value=0.068). This result suggested that there are potential association
202 between previous revisions and the younger ages. Considering that younger patients
203 require a higher quality of life and they are more aggressive in the choice of surgery
204 than the elder ones, the negative contribution of age to polymicrobial PJIs may be
205 attributed to previous revisions.

206 To further analyze the relationship between previous revisions and polymicrobial
207 PJI, the reasons of previous revisions were collected and analyzed. Previous PJI is the
208 major cause of previous revisions (56 cases), followed by aseptic loosening (6 cases).
209 Then, bivariate logistic regression was performed to analysis the relationship between
210 the two factors and polymicrobial PJI. Our result revealed that they were risk factors of

polymicrobial PJI. However, it is hard to discern whether the revision is the cause or the reason of polymicrobial PJI because several PJI patients received revisions in other joint center where the protocols of pathogens culture is heterogeneous and previous revisions can also be the consequence of polymicrobial PI where polymicrobial PJI are associated with increased number of revisions operations and lower cure rate compared to monomicrobial PJI[7]. However, polymicrobial PJI should be noted when a PJI patient with previous revisions was admitted and then, optimal pathogen detection protocols can be chosen such as repeated joint aspiration and more periprosthetic tissues for culture when revisions are performed[11-13].

In line with prior studies, certain types of pathogens are more likely to be isolated from polymicrobial periprosthetic joint infection compared to monomicrobial PJI such enterococcus, streptococcus, CNS and atypical pathogens[1, 2, 4, 5, 14, 15]. Doctors should take this fact into account to guide antibiotics administration when these pathogens were isolated from PJI patients. Besides, the interesting association between certain pathogens and polymicrobial PJI patients indicated that polymicrobial periprosthetic joint infection can be noted when these pathogens were cultured from PJI patients and board-range antibiotics can be optional in PJI patients with these pathogens. Moreover, we also performed a correlation analysis to explore the positive association between different pathogens in polymicrobial PJI group. Unfortunately, no positive association was detected (not shown in this study). It can be attributed to the relatively small sample size in the PJI group. Therefore, further multi-center studies focusing on the association between the pathogens in polymicrobial PJI is necessary

because the clarification on this association can guide empirical antibiotic use more precisely. And molecule diagnostics with high sensitivity such as the metagenomic next-generation sequencing (mNGS) can be used to detect polymicrobial PJI when these pathogens were detected by cultures[16].

There were several limitations in this study. Firstly, this study was performed in a tertiary joint center retrospectively and thus has some inherent limitations and selection bias. For example, previous antibiotics can affect microbiological results but the history of antibiotics administration can't be evaluated comprehensively in this study because of the limited medical records. Therefore, we exclude culture-negative PJI patients from this study in a bid to lower this effect. However, bias was also added after exclusion. Secondly, the prognosis of these PJI patients was not included in this study and this field needs to be explored further. Thirdly, only knees and hips were included in this study and no other joints were evaluated in this study. This nature of the study design can also add some bias to this study and further studies including other joints are necessary. Finally, no co-infective bacterial and fungal PJIs were included in this study but Stevenson et. reported that these patients suffered from unfortunate outcomes. Therefore, the risk factors of co-infective bacterial and fungal PJIs need to be explored further[17].

Conclusions:

Polymicrobial PJI, which occurred at a relative low rate, is a serious complication after total joint arthroplasty but the studies about polymicrobial PJI was limited. Here, our study reveals some risk factors of polymicrobial periprosthetic joint infection. In

line with previous, polymicrobial PJI was associated with the presence of sinus tract. Besides, we found that hip PJI and the presence of previous revisions were also risk factors of polymicrobial PJI. Moreover, certain types of pathogens such as CNS, enterococcus, streptococcus spp and atypical pathogens were more common in the polymicrobial PJI than those in the monomicrobial PJI patients. These risk factors should be considered when antibiotics administration was performed.

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Availability of data and materials:

All data and materials were in full compliance with the journal's policy. And the data were obtained in Department of Orthopedic Surgery, The First Medical Center, Chinese PLA General Hospital. The datasets used and during the current study are available from the corresponding author on reasonable request.

Abbreviations:

TJA: Total joint arthroplasty

PJI: periprosthetic joint infection

MSIS: Musculoskeletal Infection Society criteria

CNS: coagulase negative staphylococci

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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). Institutional review
board approval was obtained prior to the commencement of this study and
informed consents were obtained before revisions.

Consent for publication

We have obtained consent to publish from the participants.

Competing interests

All authors declare that they have no competing interests.

Authors' Contributions:

Study design: Hao Li. Data collection/validation: Hao Li and Erlong Niu.
Data analysis: Hao Li. Result interpretation: Hao Li. Reporting and editing:

Jun Fu and Libo Hao. Final approval of the version to be submitted: Jiying
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368

Figures

Figure 1

The process of PJI cases included in this study.

Supplementary Files

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- [table1.pdf](#)

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