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Diagnostics and treatment for bone and joint infections

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Diagnostics and treatment for bone and joint infections

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Editorial: Advancing the fight against bone and joint infections: a special issue in diagnostics and treatment

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KEYWORDS

osteomyelitis, periprosthetic joint infection, spondylodiscitis, implant associated infection, bone infection

Editorial on the Research Topic
Diagnostics and treatment for bone and joint infections

In the relentless pursuit of medical progress, researchers and healthcare professionals are continually striving to improve diagnostics and treatment strategies for bone and joint infections. We are delighted to present a special issue in Frontiers in Surgery, dedicated to the crucial theme of "Diagnostics and Treatment of Bone and Joint Infections." This collection of manuscripts brings together a wealth of knowledge and expertise, shedding light on various aspects of these challenging infections. We extend our heartfelt gratitude to the authors, reviewers, and the dedicated editorial team who have contributed to the realization of this remarkable compilation.

First and foremost, we express our sincere appreciation to the authors who have passionately devoted their time and expertise to share their valuable research findings. Their commitment to advancing our understanding of bone and joint infections has brought forth groundbreaking contributions to this special issue. Without their dedication, the wealth of knowledge presented within these manuscripts would not have been possible. We would also like to extend our deepest gratitude to the reviewers who diligently provided their time, expertise, and constructive feedback. Their meticulous evaluation and insightful suggestions have played an invaluable role in ensuring the high quality and scientific rigor of the manuscripts in this special issue. Furthermore, we extend our heartfelt thanks to the editorial team, whose unwavering support and guidance have been instrumental in the success of this special issue. Their commitment to maintaining the highest standards of scholarly publication, along with their astute management and organization, has facilitated the realization of this ambitious endeavor.

Within this special issue, several noteworthy manuscripts have made significant contributions to the field of bone and joint infection research. The manuscript titled "Symptom Duration is Associated with Failure of Periprosthetic Joint Infection Treated with Debridement, Antibiotics, and Implant Retention" provides crucial insights into prognostic factors in periprosthetic joint infections. Similarly, the manuscript titled "Treatment of Periprosthetic Joint Infection and Fracture-Related Infection with a Temporary Arthrodesis Made by PMMA-Coated Intramedullary Nails – Evaluation of

Technique and Quality of Life in Implant-Free Interval" explores an innovative treatment approach and its impact on patients' quality of life.

In addition, the manuscript titled "Development and Validation of a Diagnostic Model for Differentiating Tuberculous Spondylitis from Brucellar Spondylitis Using Machine Learning: A Retrospective Cohort Study" demonstrates the potential of machine learning in differentiating between two challenging forms of spondylitis. The manuscript titled "Risk Factors for Tuberculous or Nontuberculous Spondylitis After Percutaneous Vertebroplasty or Kyphoplasty in Patients with Osteoporotic Vertebral Compression Fracture: A Case-Control Study" highlights crucial risk factors associated with spondylitis following spinal procedures. Moreover, the manuscript titled "Therapy of Chronic Extensor Mechanism Deficiency After Total Knee Arthroplasty Using a Monofilament Polypropylene Mesh" offers innovative therapeutic approaches for addressing complications after knee arthroplasty. Additionally, the manuscripts discussing the use of D-lactate as a biomarker for periprosthetic joint infection, the C-reactive protein to lymphocyte ratio as a predictor of surgical site infection after posterior lumbar interbody fusion and instrumentation, and the impact of time to reimplantation on reinfection risk in two-stage revision for periprosthetic infection provide valuable insights into diagnosis and treatment strategies.

The culmination of these manuscripts serves as a testament to the relentless pursuit of researchers and healthcare professionals in combating bone and joint infections. Their tireless efforts, dedication, and enthusiasm to prevent and effectively treat these devastating types of infections are commendable. Their research not only enhances our understanding but also provides hope for improved outcomes, enhanced patient care, and a future where bone and joint infections are conquered.

In conclusion, we express our sincere gratitude to all the researchers, doctors, and healthcare professionals who have contributed to this special issue. Their collective efforts bring us closer to our shared goal of combating bone and joint infections, alleviating patient suffering, and improving overall healthcare outcomes. Together, let us continue the journey towards a future free from the devastating impact of these infections.

Author contributions

MR wrote the editorial. MC and IS revised the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Risk factors for tuberculous or nontuberculous spondylitis after percutaneous vertebroplasty or kyphoplasty in patients with osteoporotic vertebral compression fracture: A case-control study

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Objectives: The contributing factors for spondylitis after percutaneous vertebroplasty (PVP) or percutaneous kyphoplasty (PKP) remain unclear. Here, we sought to investigate the factors affecting spondylitis occurrence after PVP/PKP. We also compared the clinical characteristics between patients with tuberculous spondylitis (TS) and nontuberculous spondylitis (NTS) following vertebral augmentation.

Methods: Literature searches (from January 1, 1982 to October 16, 2020) using MEDLINE, EMBASE, Google Scholar and Web of science databases were conducted to identify eligible studies according to predefined criteria. The local database was also retrospectively reviewed to include additional TS and NTS patients at our center.

Results: Thirty studies from the literature and 11 patients from our local institute were identified, yielding a total of 23 TS patients and 50 NTS patients for analysis. Compared with NTS group, patients in the TS group were more likely to have a history of trauma before PVP/PKP treatment. Univariate analyses of risk factors revealed pulmonary tuberculosis and diabetes were significant factors for TS after PVP/PKP. Analyzing NTS, we found obesity, a history of preoperative trauma, urinary tract infection, diabetes and multiple surgical segments (≥2) were significantly associated with its occurrence following PVP/PKP treatment. Multivariate logistic analyses showed a history of pulmonary tuberculosis and diabetes were independent risk factors for TS after PVP/PKP, while diabetes and the number of surgically treated segments independently influenced NTS development.

Conclusions: A history of pulmonary tuberculosis and diabetes were independent risk factors for TS. For NTS, diabetes and the number of surgically treated segments significantly influenced the occurrence of postoperative spinal infection. These data may be helpful for guiding risk

stratification and preoperative prevention for patients, thereby reducing the incidence of vertebral osteomyelitis after PVP/PKP.

KEYWORDS

percutaneous vertebroplasty, percutaneous kyphoplasty, tuberculous spondylitis, nontuberculous spondylitis, pyogenic spondylitis, risk factors

Introduction

Percutaneous vertebroplasty (PVP) or percutaneous kyphoplasty (PKP) is currently widely used for the treatment of osteoporotic vertebral compression fractures (OVCFs) (1). Although it is relatively safe and effective, PVP/PKP can still cause complications in some situations. Among them, bone cement leakage is most frequently encountered and may lead to neurological dysfunction or even pulmonary embolism. Generally, infection of the vertebral body treated with subsequent PVP/PKP is rare, with an incidence of less than 1% (2). The most common type of spondylitis is purulent infection caused by bacteria (3). In addition, cases of tuberculous spondylitis (TS) after bone cement infusion have also been documented in the literature (2, 3). TS, the most common and severe form of bone tuberculosis, accounts for 50% of extrapulmonary tuberculosis cases and its incidence is very low in developed Western countries (4), while in developing countries, probably due to the lack of medical equipment (e.g., imaging systems and examination laboratories) and inadequate levels of diagnosis and treatment, the mortality rate from tuberculosis is much higher than in developed Western countries (4).

Currently, the cause of spondylitis after PVP/PKP remains unclear. Studies have demonstrated that the pathogen may already exist in patients before PVP/PKP treatment, the process of bone cement injection and vertebral augmentation initiates the occurrence of subsequent spinal infections (2). For example, infections involving the visceral organs (such as urinary tract infection, cholecystitis, meningitis) or pathogen adhesion in the skin may contribute to nontuberculous spondylitis (NTS) after PVP/PKP (2, 5, 6). Regarding TS following PVP/PKP surgery, some studies have proven that a history of pulmonary tuberculosis is closely related to the occurrence of spondylitis (2, 7, 8).This may be due to the presence of tuberculosis bacteria in recovered pulmonary tuberculosis patients, and PVP/PKP may allow these quiescent tuberculosis bacteria to spread around the bone cement, leading to infection (2).

Noticeably, patients undergoing PVP/PKP therapy generally have an advanced age, and infectious spondylitis in this patient group tends to progress rapidly once it develops (9), which may pose a challenge for subsequent treatment (usually requiring traumatic debridement surgery and long-term use of antibacterial drugs with side effects (2, 10, 11), and it can even lead to catastrophic consequences. Therefore, it is necessary to summarize the influencing factors of secondary vertebral infection after PVP/PKP to guide prevention approaches to reduce postoperative spinal infections, thus improving the clinical outcome of patients. In this study, we aimed to investigate the factors affecting spondylitis occurrence after PVP/PKP. We also compared the clinical characteristics between patients with TS and NTS.

Methods and materials

Literature review

A literature search through the MEDLINE, EMBASE, Google Scholar and Web of science databases was conducted to identify eligible studies from January 1, 1982 to October 16, 2020. The keywords or combinations used for the search were ("spondylitis" or "spondylodiscitis" or "osteomyelitis" or "bacterial" or "fungal" or "pyogenic" or "tuberculosis" or "bacterial spondylitis" or "pyogenic spondylitis" or "tuberculous spondylitis" or "tubercular spondylitis" or "mycobacteria tuberculosis" or "TB" or "Pott's" or "infection" or "infectious") and ("spine" or "spinal" or "vertebral" or "cervical spine" or "thoracic spine "or "lumbar spine") and ("VP" or "PVP" or "PKP" or "vertebroplasty" or "kyphoplasty" or "augmentation" or "percutaneous vertebroplasty" or "percutaneous kyphoplasty"). To obtain comprehensive results and to avoid omissions, no restrictions were applied for the above keywords. Moreover, we also manually reviewed the references of the included studies to find any potential documents that met the inclusion criteria. The detailed process for the literature search is shown in **Figure 1**. We included OVCF (It is directly described in the literature, and no specific inspection method is described) patients who developed a vertebral infection (including TS and NTS) after undergoing PVP/PKP surgery. The exclusion criteria of the study included: failing to offer any evidence of etiology or histopathology for diagnosis confirmation (for NTS, the diagnosis should be based on the pathogenic growth observed in the culture of infected tissues, while a diagnosis of TS requires detection of *Mycobacterium tuberculosis* in the tissue culture, or positive acid-fast staining or pathology findings showing caseous necrosis and/or granulomatous inflammation and/or

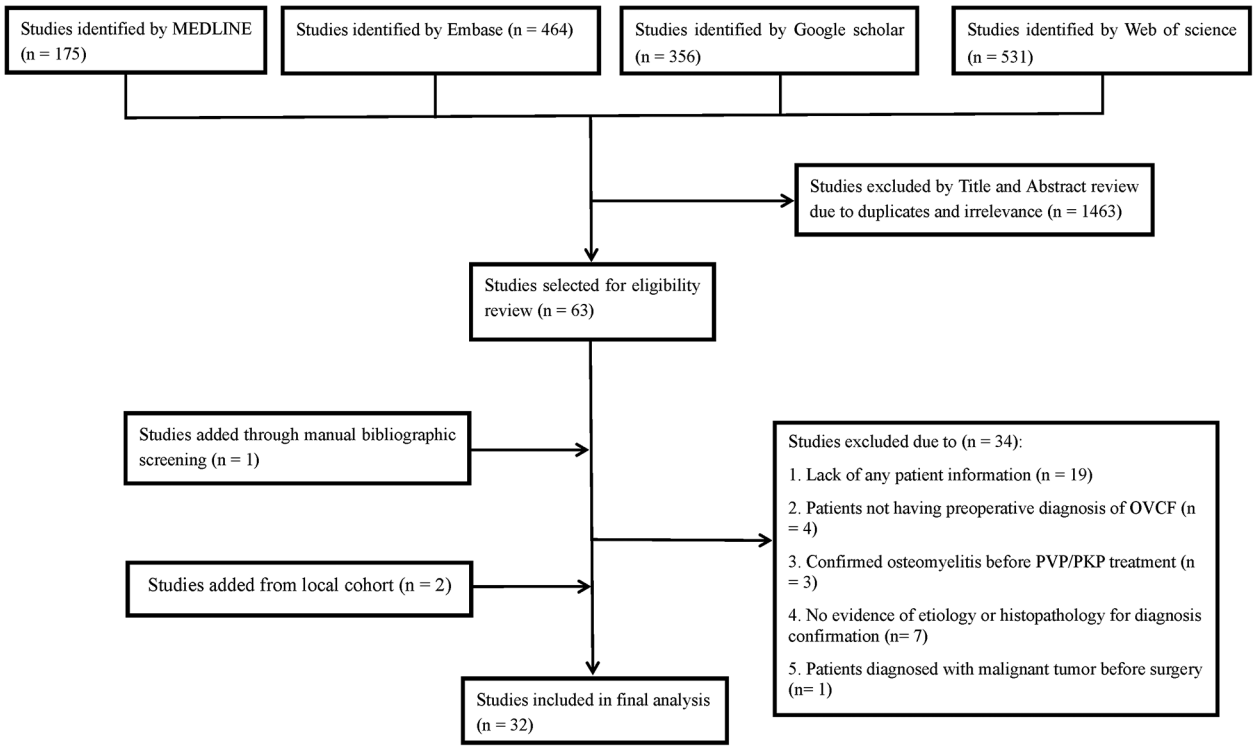

FIGURE 1
Flow diagram of literature search showing studies identified, included and excluded at each stage.

multinucleated giant cells); patients with confirmed vertebral osteomyelitis before PVP/PKP treatment; patients not having a preoperative diagnosis of OVCF (including those with pathological fractures or others); patients diagnosed with malignant or benign tumors before surgery; and patients without any information eligible for analysis.

Two investigators independently screened the publications based on the inclusion criteria and extracted clinical data for each patient. Any dispute was resolved through consensus. Patient information obtained from the studies included the following: demographics (age and sex), clinical characteristics (including OVCF location, number of segments treated by PVP/PKP and preoperative neurological function, a history of trauma (the specific injury mechanism is not explained in detail, and the description only reflects the "trauma history"), the presence or absence of pulmonary tuberculosis, obesity, smoking, and other comorbidities [such as diabetes, rheumatoid arthritis, pneumonia, chronic obstructive pulmonary disease, urinary tract infection, and high blood pressure], radiological findings (the occurrence of paravertebral abscesses at first diagnosis of infection), microbiological results and laboratory tests (including the pathogens as well as WBC, ESR, CRP levels at the time of diagnosis), treatment (including revision surgery or not and the specific type of surgery), the time interval between PVP/PKP and the first diagnosis of spinal infection, follow-up time and clinical outcomes of the patients (recovery, limited mobility/assisted walking and death).

Local cohort

A total of 1935 OVCF patients who were treated with PVP/PKP in our institute from March 2003 to March 2020 were identified. This duration of study was determined as the similar period in which the included cases were reported in the literature to allow for comparability. The medical records of the patients were reviewed retrospectively to include eligible cases with postoperative spondylitis. Patients in the local cohort were diagnosed with osteoporosis by bone density scans; all 8 patients included in this institution fell from low. The diagnosis of postoperative NTS was confirmed by microbiological evidence showing pathogenic growth in tissue culture. Postoperative TS was determined by acid-fast staining and the histopathological results of the lesion tissues. In total, 6 NTS cases and 5 TS cases after PVP/PKP were identified in our hospital. The overall incidence of spinal infection following PVP/PKP surgery was 0.57%. Among the 11 cases with postoperative spondylitis, two TS cases were previously described in our study (9). Using the PS matching plug-in of

SPSS, 114 patients who did not develop vertebral osteomyelitis after PVP/PKP treatment in our hospital during the same period were randomly selected as the control group, and there was no significant difference in age or sex between it and the infected groups (control vs. TS: $t = 0.828$, $P = 0.645$ for age and $\chi^2 = 0.550$, $P = 0.458$ for sex; control *vs* NTS: $t = 0.003$, $P = 0.994$ for age and $\chi^2 = 2.253$, $P = 0.133$ for sex). The included patients with PVP/PKP in our hospital had normal preoperative inflammatory blood parameters and would not have undergone surgery otherwise. In addition, all patients received prophylactic intravenous antibiotics, specifically cefuroxime 0.5 g, on the day before surgery, the day of surgery, and the day after surgery. None of the patients included in our institution had any other form of surgical site infection or prolonged wound healing time during their hospitalization. Postoperatively, all patients underwent regular clinical and imaging follow-up, and the final follow-up time was November 2020. Patient clinical data were directly obtained from medical records.

Statistical analyses

All statistical analyses were performed by using SPSS 26.0 (SPSS, Chicago, Illinois, USA). Continuous data are expressed as the mean ± standard deviation and were analyzed by Student's *t*-test, while categorical data are presented as the frequency or composition ratio and were analyzed by the chi-square test or Fisher's exact test. The multivariate logistic regression model was used to assess the independent risk factors for vertebral infection after PVP/PKP surgery, in which the factors that were found to be statistically significant ($P < 0.1$) in our univariate analysis, as well as important predictors reported in the literature, were included (2, 7, 8). All tests were two-sided, and $P < 0.05$ was considered to be statistically significant.

Results

Patient characteristics in the TS and NTS groups

A total of 30 studies met the inclusion criteria (2, 3, 5, 7–10, 12–34). Among them, 10 discussed TS after PVP/PKP, 19 analyzed the occurrence of postoperative NTS, and 1 evaluated both TS and NTS. After review, 20 TS patients and 44 NTS patients were identified from these studies. With an additional 5 TS patients and 6 NTS patients from our local center, a total of 23 TS patients and 50 NTS patients were finally included in this study. The clinical data of the included patients are shown in **Tables 1**, **2**.

In the TS group, the average time interval from index surgery to the diagnosis of spondylitis was 8.45 ± 11.68 months. All patients received anti-tuberculosis drug treatment after surgery. Among them, one was treated with triple drugs (isoniazid, rifampicin and ethambutol), 13 were treated with quadruple drugs (isoniazid, rifampicin, pyrazinamide and ethambutol), and the remaining 9 were treated with anti-tuberculosis regimens that were not described. Twenty patients underwent revision surgery, among which 2 patients underwent anterior debridement and bone graft fusion; 12 patients underwent combined anterior and posterior debridement, instrumentation, and bone graft fusion; and 6 patients underwent one-stage posterior debridement, fixation

TABLE 1 Summary of the clinical characteristics in TS patients.

Variables	Categories	*n* (%)
Age (years)	Continuous	23 (71.5 ± 8.7)
Sex	Female	19 (82.6)
	Male	4 (17.4)
Preoperative neurological dysfunction	No	10 (90.9)
	Yes	1 (9.1)
Trauma	No	6 (42.9)
	Yes	8 (57.1)
Location	Thoracic	7 (30.4)
	Lumber	15 (65.2)
	Thoracic and Lumber	1 (4.4)
Number of surgically treated segments	One	17 (73.9)
	Two or more	6 (26.1)
Type of surgery	PVP	15 (65.2)
	PKP	8 (34.8)
Diabetes	No	15 (68.2)
	Yes	7 (31.8)
Rheumatoid arthritis	No	21 (95.5)
	Yes	1 (4.5)
Pulmonary tuberculosis	No	9 (45)
	Yes	11 (55)
COPD	No	20 (90.9)
	Yes	2 (9.1)
Hypertension	No	15 (68.2)
	Yes	7 (31.8)
WBC	Continuous	17 (7.4 ± 2.3)
ESR	Continuous	17 (52.4 ± 19.7)
CRP	Continuous	17 (42.7 ± 34.4)
Time interval to infection	Continuous	23 (8.5 ± 11.7)
Paravertebral abscess	No	1 (10)
	Yes	9 (90)
Outcomes	Recovery	11 (50)
	Death	3 (13.6)
	Walking assistance	8 (36.4)

TS, tuberculous spondylitis; PVP, percutaneous vertebroplasty; PKP, percutaneous kyphoplasty; COPD, chronic obstructive pulmonary diseases; WBC, white blood cell; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

TABLE 2 Summary of the clinical characteristics in NTS patients.

Variable	Categories	*n* (%)
Age (years)	Continuous	50 (70.5 ± 10.4)
Sex	Female	32 (64)
	Male	18 (36)
Preoperative neurological dysfunction	No	11 (100)
	Yes	0 (0)
Trauma	No	21 (80.8)
	Yes	5 (19.2)
Location	Thoracic	15 (30.6)
	Lumber	31 (63.3)
	Thoracic and Lumber	3 (6.1)
Number of surgically treated segments	One	34 (68)
	Two or more	16 (32)
Type of surgery	PVP	32 (78.0)
	PKP	9 (22)
Diabetes	No	34 (73.9)
	Yes	12 (26.1)
Rheumatoid arthritis	No	42 (91.3)
	Yes	4 (8.7)
Pneumonia	No	44 (93.6)
	Yes	3 (6.4)
COPD	No	44 (95.7)
	Yes	2 (4.3)
UTI	No	35(76.1)
	Yes	11 (23.9)
Hypertension	No	31 (67.4)
	Yes	15 (32.6)
Obesity	No	42 (91.3)
	Yes	4 (8.7)
Smoking	No	42 (91.3)
	Yes	4 (8.7)
WBC	Continuous	38 (11.7 ± 13.0)
ESR	Continuous	37 (66.7 ± 33.3)
CRP	Continuous	38 (65.3 ± 74.9)
Time interval to infection	Continuous	41 (6.4 ± 14.1)
Paravertebral abscess	No	1 (9.1)
	Yes	10 (90.9)
Pathogens	*Staphylococcus aureus*	16 (34.0)
	Enterobacter	4 (8.5)
	Staphylococcus epidermidis	3 (6.4)
	Roseomonas mucosa	1 (2.1)
	Aeromonas hydrophila	1 (2.1)
	Acinetobacter	1 (2.1)
	Hemolytic streptococcus	2 (4.3)
	Enterococcus faecalis	4 (8.5)
	Methicillin-resistant staphylococcus aureus	1 (2.1)
	Methicillin sensitive staphylococcus aureus	1 (2.1)
	Achromobacter xylosoxidans	1 (2.1)
	Salmonella	1 (2.1)
	Peptpstreptococcus	1 (2.1)
	Propionibacterium	1 (2.1)
	Salmonela choleraesuiss	1 (2.1)
	Coagulase-negative staphylococcal	2 (4.3)
	Streptococcus agalactiae	1 (2.1)
	Staphylococcus saccharolyticus	1 (2.1)
	Parvimonas micra	1 (2.1)
	Granulicatella adiacens	1 (2.1)
	Serratia marcescens, Stenotrophomonas maltophilia and *Burkholderia cepacia*	1 (2.1)
	Corynebacterium and *Propionibacterium*	1 (2.1)
Outcomes	Recovery	30 (62.5)
	Death	10 (20.8)
	Walking assistance	8 (16.7)

NTS, nontuberculous spondylitis; PVP, percutaneous vertebroplasty; PKP, percutaneous kyphoplasty; COPD, chronic obstructive pulmonary diseases; WBC, white blood cell; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; UTI, urinary tract infection.

and bone graft fusion. The remaining 3 patients were treated by unreported types of surgery. *Mycobacterium tuberculosis* was detected by polymerase chain reaction of the infected tissues in 2 patients, while TS was confirmed by findings from both polymerase chain reaction and acid-fast staining of the infected lesions in 14 patients. In 6 patients, TS diagnosis was made based on histopathological examination of the infected tissues showing granulomatous inflammation and/or caseous necrosis and/or multinucleated giant cells. The remaining 1 case had an unknown method of diagnosis. The average follow-up time was 26.2 ± 25.5 months. At the last follow-up, 11 patients experienced a good recovery ("good" was defined as walking normally without the aid of a walking aid), 8 patients required walking assistance, and 3 patients died (one due to paraplegia, the other due to bacteremia and multiple organ failure, and the third patient did not specify the cause of death).

In the NTS group, the average time interval from the index surgery to the diagnosis of spinal infection was 6.36 ± 14.14 months. All patients received anti-infective treatment after surgery, and there were differences in the use of drugs across the studies. Forty-three patients underwent revision surgery, of whom 8 received anterior debridement and bone graft fusion, 25 received combined anterior and posterior debridement, fixation, and bone graft fusion, and 10 received one-stage posterior debridement, instrumentation and bone graft fusion. The remaining 2 cases were treated with an unknown type of surgery. The growth of pathogenic bacteria was detected in the tissue culture of the lesions for all patients. The average follow-up time was 16.7 ± 12.1 months. At the end of the follow-up, 30 patients had a good recovery, 8 patients required walking assistance, and 10 patients died.

Comparison of clinical features between the TS and NTS groups

The comparison results of the clinical characteristics of patients in the TS group and the NTS group are shown in Table 3. The analysis results showed that patients in the TS group were more likely to have a history of trauma before PVP/PKP treatment. However, due to the small number of TS groups providing trauma history data, this result may be biased. Analyzing the characteristics of infection after its occurrence, we found that the infection time of the TS group patients was longer than that of the NTS patients, while the ESR index of the NTS group patients was higher than that of the TS group patients, but these differences were not statistically significant. There were no significant differences between the TS group and the NTS group in other clinical data.

TABLE 3 Comparison of clinical features between TS and NTS group.

Variable	Categories	TS (*n*)	NTS (*n*)	Statistics	*P*-value
Age (years)	Continuous	23 (71.5 ± 8.7)	50 (70.5 ± 10.4)	0.442	0.695
Sex	Female Male	19 4	32 18	2.591	0.107
Preoperative neurological dysfunction	No Yes	10 1	10 0	–	1.000
Trauma	No Yes	6 8	21 5	4.359	**0.037**
Location	Thoracic Lumber Thoracic and Lumber	7 15 1	15 21 3	0.836	0.658
Number of surgically treated segments	One Two or more	17 6	34 16	0.262	0.609
Type of surgery	PVP PKP	15 8	32 9	1.244	0.265
Diabetes	No Yes	15 7	34 12	0.243	0.622
Rheumatoid arthritis	No Yes	21 1	42 4	-	1.000
COPD	No Yes	20 2	44 2	-	0.319
Hypertension	No Yes	15 7	31 15	0.004	0.948
WBC	Continuous	17 (7.4 ± 2.3)	38 (11.7 ± 13.0)	2.130	0.186
ESR	Continuous	17 (52.4 ± 19.7)	37 (66.7 ± 33.3)	7.612	0.052
CRP	Continuous	17 (42.7 ± 34.4)	38 (65.3 ± 74.9)	5.677	0.130
Time interval to infection	Continuous	23 (8.5 ± 11.7)	41 (6.4 ± 14.1)	0.423	0.549
Paravertebral abscess	No Yes	1 9	1 10	-	1.000

Bold values indicate $P < 0.05$; TS, tuberculous spondylitis; NTS, nontuberculous spondylitis; PVP, percutaneous vertebroplasty; PKP, percutaneous kyphoplasty; COPD, chronic obstructive pulmonary disease; WBC, white blood cell; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

Univariate analyses of risk factors for TS or NTS after PVP/PKP

A comparison of the clinical data between the TS group and the control group is shown in Table 4. Our analysis revealed that TS patients were more likely to have pulmonary

TABLE 4 Comparison of clinical features between TS and Control group.

Variable	Categories	TS (*n*)	Control (*n*)	Statistics	*P*-value
Age (years)	Continuous	23 (71.5 ± 8.7)	114 (70.5 ± 9.6)	0.828	0.645
Sex	Female Male	19 4	86 28	0.550	0.458
Preoperative neurological dysfunction	No Yes	10 1	103 11	< 0.001	1.000
Trauma	No Yes	6 8	70 44	0.503	0.478
Location	Thoracic Lumber Thoracic and Lumber	7 15 1	49 59 6	1.411	0.494
Number of surgically treated segments	One Two or more	17 6	98 18	0.782	0.376
Type of surgery	PVP PKP	15 8	80 34	0.221	0.638
Diabetes	No Yes	15 7	104 12	5.297	**0.021**
Rheumatoid arthritis	No Yes	21 1	103 11	0.131	0.717
Pulmonary tuberculosis	No Yes	9 11	99 15	16.467	< **0.001**
COPD	No Yes	20 2	101 13	< 0.001	1.000
Hypertension	No Yes	15 7	65 49	0.949	0.330

Bold values indicate $P < 0.05$; TS, tuberculous spondylitis; PVP, percutaneous vertebroplasty; PKP, percutaneous kyphoplasty; COPD, chronic obstructive pulmonary disease; WBC, white blood cell; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

tuberculosis and diabetes before receiving PVP/PKP. No significant differences were observed for other clinical characteristics between the two groups.

Similarly, the results of a comparison of the clinical features between the NTS and control subgroups are shown in Table 5. These outcomes showed that diabetes and multiple surgical segments (≥2) were significant factors for NTS after PVP/PKP. In addition, obese patients seemed to be more likely to develop NTS after surgery. Moreover, our study also indicated that a history of preoperative trauma and urinary tract infection were closely related to the occurrence of NTS, although the results were not statistically significant. No significant differences were seen between the two groups in terms of other clinical characteristics.

TABLE 5 Comparison of clinical features between NTS and Control group.

Variable	Categories	NTS (*n*)	Control (*n*)	Statistics	*P*-value
Age (years)	Continuous	50 (70.5 ± 10.4)	114 (70.5 ± 9.6)	0.003	0.994
Sex	Female Male	32 18	86 28	2.253	0.133
Preoperative neurological dysfunction	No Yes	11 0	103 11	0.272	0.602
Trauma	No Yes	21 5	70 44	3.490	0.062
Location	Thoracic Lumber Thoracic and Lumber	15 31 3	49 59 6	0.458	0.795
Number of surgically treated segments	One Two or more	34 16	98 18	5.558	**0.018**
Type of surgery	PVP PKP	32 9	80 34	0.933	0.334
Diabetes	No Yes	34 12	104 12	6.224	**0.013**
Rheumatoid arthritis	No Yes	42 4	103 11	< 0.001	1.000
Pneumonia	No Yes	44 3	100 14	0.619	0.432
COPD	No Yes	44 2	101 13	1.180	0.277
UTI	No Yes	35 11	100 14	3.346	0.067
Hypertension	No Yes	31 15	65 49	1.470	0.225
Obesity	No Yes	42 4	112 12	-	0.057
Smoking	No Yes	42 4	111 3	-	0.106

Bold values indicate $P < 0.05$; NTS, nontuberculous spondylitis; PVP, percutaneous vertebroplasty; PKP, percutaneous kyphoplasty; COPD, chronic obstructive pulmonary disease; WBC, white blood cell; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; UTI, urinary tract infection.

Multivariate logistic analyses of risk factors for TS or NTS after PVP/PKP

A multivariate logistic regression model showed that a history of pulmonary tuberculosis and diabetes were independent risk factors for TS after PVP/PKP (Table 6).

Similarly, multivariate analysis found that diabetes and the number of surgical segments were independently associated with the occurrence of postoperative NTS, while urinary tract infection, obesity and a history of trauma did not affect NTS development (Table 7).

Discussion

In this study, we summarized the influencing factors of spinal infection after PVP/PKP and analyzed the differences in clinical characteristics between TS and NTS patients. We found that a history of pulmonary tuberculosis and diabetes

TABLE 6 Multivariate logistic analyses of risk factors for TS after PVP/PKP.

Factors	Categories	Multivariate analysis	
		P-value	HR (95% CI)
Diabetes	No Yes	**0.005**	0.165 (0.047–0.580)
Pulmonary tuberculosis	No Yes	< **0.001**	0.103 (0.034–0.318)

Bold values indicate $P < 0.05$; TS, tuberculous spondylitis; PVP, percutaneous vertebroplasty; PKP, percutaneous kyphoplasty.

TABLE 7 Multivariate logistic analyses of risk factors for NTS after PVP/PKP.

Factors	Categories	Multivariate analysis	
		P-value	HR (95% CI)
Diabetes	No Yes	**0.041**	0.301 (0.095–0.954)
Obesity	No Yes	0.783	0.671 (0.039–11.429)
Number of surgically treated segments	One Two or more	**0.040**	0.345 (0.125–0.951)
Trauma	No Yes	0.094	2.771 (0.842–8.722)
UTI	No Yes	0.635	1.420 (0.334–6.046)

Bold values indicate $P < 0.05$; NTS, nontuberculous spondylitis; PVP, percutaneous vertebroplasty; PKP, percutaneous kyphoplasty; UTI, urinary tract infection.

were closely related to the development of postoperative TS, while diabetes and the number of segments treated with surgery independently affected the occurrence of NTS after vertebral augmentation. Moreover, it appeared that patients with trauma were more likely to develop TS after surgery. These data provide a comprehensive understanding of the factors associated with spondylitis after PVP/PKP and may be helpful for guiding preoperative risk stratification and prevention to reduce or even avoid the occurrence of postoperative spondylitis following PVP/PKP treatment.

Currently, there is still a lack of reports on factors affecting spinal infection after PVP/PKP. Our study found that diabetes was an independent risk factor for TS and NTS after PVP/PKP, similar to previous reports showing that diabetes is an important factor for postoperative spinal infection (35–37), which can significantly increase the risk of a spinal infection caused by several specific bacteria (such as *Staphylococcus aureus* and *Mycobacterium tuberculosis*) (38, 39). The mechanism by which diabetes could increase the incidence of postoperative spinal infection remains unclear. Previous studies have revealed that elevated resistin levels in diabetic patients can impair the chemotaxis and phagocytosis of neutrophils by interfering with phosphatidylinositol-3-kinase-dependent downstream pathways (40, 41). In addition, studies have pointed out that high blood sugar levels can weaken the function of antigen-presenting cells, thereby damaging the adaptive immune response mediated by T cells (7, 42, 43). Furthermore, OVCF patients receiving PVP/PKP treatment are generally of an advanced age and have a relatively low immunity (44, 45). These findings may provide a theoretical explanation for how diabetes can promote the incidence of spinal infection after vertebral augmentation. These data also highlight the importance of insulin use during the perioperative period for diabetes patients. However, it should be noted that whether the use of insulin alone can effectively reduce the presence of postoperative spondylitis in diabetic patients after PVP/PKP deserves further investigation, considering that diabetes is linked to various metabolic disorders (such as dyslipidemia, high uric acid, and hypertension).

Published data suggest that pulmonary tuberculosis is closely associated with the occurrence of TS after PVP/PKP. Although the precise mechanism is unknown, researchers consider that TS can occur in the case of active pulmonary tuberculosis by direct hematogenous dissemination of *Mycobacterium tuberculosis* or indirect spread of this pathogen through proximal para-aortic lymph nodes to the surgical site (8, 9). In contrast, some studies have shown that vertebral augmentation may cause tuberculosis infection by reactivating static *Mycobacterium tuberculosis* or inducing the release of this mycobacterium from infected macrophages to the surgically treated area under the condition of inactive pulmonary tuberculosis (7–9). In addition, for patients with diabetes or any other immunosuppressive disorders, the impaired adaptive immune response may also reactivate *Mycobacterium tuberculosis* or aggravate any existing tuberculosis (7, 42, 43). In this study, we found that pulmonary tuberculosis was a significant predictor for TS after PVP/PKP. This result provides the first statistical evidence to support the above speculations (7–9). Additionally, this finding also emphasizes the importance of monitoring patients with preoperative pulmonary tuberculosis after PVP/PKP, given that the risk of postoperative TS is high in these patients and that TS may progress rapidly in this situation (9).

In addition, this study also showed that the number of segments treated by PVP/PKP was a significant factor associated with NTS after surgery. This is not difficult to understand because more surgical levels are usually correlated with a longer operation time, which is generally considered to increase the risk of infection after spinal surgery (36). Another possible explanation may be the fact that more surgical segments commonly reflect severe preoperative trauma, which can likely reduce the specific adaptive immunity of T cells (46–48), thus leading to postoperative spondylitis. Another finding of this study was that obesity might increase the incidence of postoperative spondylitis after PVP/PKP, consistent with the findings of previous observations (49). A possible reason is that the abnormal regulation of hormones and adipokines in obese patients likely compromises T-cell function, thereby weakening the adaptive immune response to infection in this population (50).

Interestingly, our analysis found that preexisting infection in other regions of the body did not contribute to NTS occurrence after PVP/PKP, which contradicts previous reports in the literature (2, 5, 6). Prior data have indicated that vertebral augmentation as an invasive operation may lead to the relative susceptibility of the surgical area (the principle of *locus minoris resistentia*) (2), which then creates a microenvironment suitable for pathogens to invade the surgical site, thereby resulting in subsequent infection. Moreover, during the process of bone cement infusion, repeated C-arm fluoroscopy and frequent personnel movements during the surgery may also increase the risk of postoperative spinal infection. These factors offer a possible route for the development of spondylitis caused by external pathogens after PVP/PKP therapy, although this idea requires further confirmation.

In addition, frailty is one of the most serious global public health challenges we face right now. Rapidly aging populations have brought about an increase in the number of frailty older adults, which in turn has put increasing pressure on healthcare systems worldwide (51, 52). When a stressful event (e.g., acute illness, trauma) occurs, the functional capacity of frailty individuals deteriorates rapidly, but the patients we included did not have a complete frailty evaluation, so “frailty” was not included in this study, but its It is still a very meaningful variable that deserves further exploration in the future (53).

Limitations

Most of the included studies failed to provide complete clinical data of the patients, which may introduce bias into the results. However, to minimize the heterogeneity among studies and to make the analysis results more reliable and the statistical analysis feasible, we simplified the grouping criteria for most variables in the data processing.

Conclusion

The present study performed a comprehensive summary of the risk factors for vertebral infection after PVP/PKP. We found that a history of pulmonary tuberculosis and diabetes were independent risk factors for TS. For NTS, our analysis revealed that diabetes and the number of surgically treated segments significantly influenced the occurrence of postoperative spinal infection. These data may be helpful for guiding risk stratification and preoperative prevention for patients, thereby reducing the incidence of vertebral osteomyelitis after PVP/PKP.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board at The First Affiliated Hospital, University of South China, Hunan, P.R. China. The patients/participants provided their written informed consent to participate in this study.

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

All authors participated in data acquisition. BWZ, JL, HQN and MXZ contributed to the conception and design of the study. BWZ, GHL and MXZ did the data analysis and interpretation. ZX, FSL, BYZ and MXZ contributed to drafting and revision of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Symptom duration is associated with failure of periprosthetic joint infection treated with debridement, antibiotics and implant retention

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Background: Debridement, antibiotics, and implant retention (DAIR) is an alternative treatment strategy for periprosthetic joint infection (PJI). However, no consensus exists regarding which patient population(s) may be most suitable for DAIR. This study aims to investigate the overall infection control rate and explore the prognostic factors associated with acute, hematogenous, and chronic PJIs treated with DAIR.

Methods: We retrospectively reviewed the included patients who were diagnosed with PJI and underwent DAIR at two institutions from 2009 to 2018 ($n = 104$). We collected the clinical data, including demographics, preoperative laboratory tests, Charlson Comorbidity Index, surgical information, and culture organism results. Treatment success was defined according to the criteria reported by Diaz-Ledezma. All patients were followed for at least one year unless failure preceded that time point. A multivariable analysis was utilized to identify prognostic factors associated with treatment, and a Kaplan-Meier survival analysis was used to depict the infection control rate.

Results: The overall treatment success rate in the current cohort of patients was 67.3% at a median 38.6 (interquartile range: 23.5, 90.7) months follow-up. Patients with a duration of infectious symptoms of more than ten days were more likely to fail ($P = 0.035$, hazard ratio 8.492, 95% confidence interval 1.159–62.212). There was no difference among acute, hematogenous, and chronic infections in terms of failure rate ($P = 0.161$).

Conclusions: DAIR is a reasonable treatment option for PJI, and its use in the setting of chronic infection does not appear to be a contraindication. Performing DAIR within ten days of the presentation of symptoms had a higher rate of treatment success.

KEYWORDS

knee, hip, total joint arthroplasty, periprosthetic joint infection, debridement antibiotics implant retention, symptom duration

Introduction

Total joint arthroplasty (TJA) is a successful surgery for relieving pain and improving function in patients when extensive joint destruction occurs (1). The number of TJA procedures has increased in the past 20 years, and periprosthetic joint infection (PJI) is a devastating complication that can occur (2). PJI can result in higher morbidity and mortality and represents a substantial financial burden to both patients and society (3).

Most surgeons utilize a two-stage revision protocol to treat PJI (4). Despite this, some concerns exist, including high rates of morbidity and mortality (5, 6), a long interval time of disability (7), and increased cost (8). For these reasons, surgeons have pursued prosthesis retention as a possible treatment option for PJI. PJI can be divided into acute, hematogenous, and chronic infection based on the time from index surgery and duration of symptoms. Initially, the failure rate associated with debridement, antibiotics use (including systemic or topical use), and implant retention (DAIR) procedures was high, even when applied to settings of acute or acute hematogenous infections (9, 10). With improvement in surgical technique in conjunction with more effective antibiotic protocols, the success rates of DAIR procedures have been significantly improved in more recent reports (11, 12).

Patient selection is of paramount importance when considering a DAIR procedure. Previous studies have investigated prognostic factors for success, including soft tissue status, patient comorbidities, type of bacteria, and other factors (13–15). However, the success rate of DAIR in the treatment of PJI varied greatly, ranging from 31%–66%. Among these studies, most groups only performed a DAIR procedure in the setting of an acute or acute hematogenous infection; the cutoff time for surgical intervention remains controversial (16). Koyonos et al. (17) extended the indications for a DAIR procedure to chronic infection, but reported the failure rate up to 72%. Currently, there does not appear to be an absolute contraindication to performing DAIR in PJI patients with a stable prosthesis (18). Despite this, no guidance regarding patient selection heretofore exists for utilizing DAIR in acute, hematogenous, and chronic PJIs.

In order to evaluate the success rate of DAIR in the setting of acute, hematogenous, and chronic cases of PJI, and explore associated prognostic factors, the following questions were devised: (i) what was the infection control rate associated with the DAIR procedure in our cohort patients? (ii) was there any difference(s) among the varying types of infections? And (iii) what are the prognostic factors associated with treatment failure after DAIR?

Methods

Study population

After the institutional review boards of Beijing Jishuitan Hospital and Chinese PLA general hospital approved this study (S2020-056-01), we retrospectively reviewed the electronic medical records at two separate institutions from 2009 to 2018. The inclusion criteria were patients diagnosed with PJI according to the Musculoskeletal Infection Society (MSIS) criteria (19); patients who underwent the treatment of DAIR protocol; the follow-up time was at least one year unless the clinical failure was diagnosed prior to that time point. If a patient underwent more than one DAIR procedure, the information on the index procedure was included and then categorized into clinical failure after DAIR. Patients were excluded in cases where the index surgery included a revision for PJI or in primary cases of septic arthritis; or megaprosthesis, which replaces part of the femur or tibial, was used to reconstruct hip or knee. The surgeons decided on all the DAIR procedures according to the patients' condition at that time, except that loosening or instability of the prosthesis was an absolute contraindication. In total, 112 patients were identified. After excluding six patients with isolated superficial infection who underwent superficial debridement without arthrotomy and two patients with mega-prostheses, 104 patients were eligible for the current study.

Treatment protocol

There was an infectious disease team in each hospital. Patients were selected for DAIR based on an individualized discussion dependent on each patient's unique situation, including symptoms, soft tissue status, medical comorbidities, and whether prothesis was stable or not. Several fellowship-trained surgeons familiar with the DAIR procedure performed and implemented the protocols at these two institutions, and all patients were treated according to the same therapeutic protocol. A posterolateral approach was utilized for hips, and a midline incision with a medial parapatellar arthrotomy was utilized for knees. If a sinus tract was present, it would be excised intra-operatively. During the procedure, 3–5 samples, including synovial fluid and tissue, were sent for culture and synovial fluid analysis to both confirm an infection and guide antibiotic use after surgery. During the debridement, hydrogen peroxide, saline, iodine, and saline were successively used for joint lavage. The amount of saline utilized was at least 10 L in each case. The treating surgeon decided to retain or exchange the modular components (polyethylene for knees or liner and femoral head for hips) intra-operatively. In most cases, the modular part would be replaced for stability and thorough debridement. However, the modular part would be retained if it is difficult to take out and the joint was stable. We then re-draped the surgical site before inserting the new modular component and suturing the wound.

Given that DAIR is considered an urgent surgery, even we aspirated every joint before DAIR procedure, only 19 of the 104 cases had culture results pre-operatively. Therefore,

sensitive antibiotics were used for positive culture cases before the DAIR procedure, otherwise, vancomycin and a third-generation cephalosporin were combined to cover both gram-positive and negative bacteria initially. We routinely used these broad-spectrum antibiotics prior to culture results returning from the lab. Once the results were received, the antibiotic regimen was narrowed in an organism-specific fashion, except in cases where cultures remained negative (20). Patients received intravenous antibiotics for at least two weeks, then converted to an oral regimen for at least an additional four weeks. Topical antibiotics were given routinely. Sensitive antibiotics were given if the culture was positive before the DAIR procedure, otherwise vancomycin was given topically. Patients were administered antibiotics systemically for no more than three months after the DAIR procedure. If the patient used antibiotics continuously for more than three months, we would check the follow-up medical record. We categorize it as a treatment failure if the patient still has infectious symptoms.

Data collection and outcome assessment

The medical records of all patients were reviewed for information, including gender, age, height, and weight at the time of the DAIR procedure. Comorbidities were assessed using the Charlson Comorbidity Index (CCI), in addition to whether the patients had diabetes mellitus or rheumatoid arthritis. We also collected preoperative laboratory results, including serum C reactive protein (CRP), hemoglobin, albumin, and perioperative culture results. According to current clinical practice and previous studies (21–23), the continuous variables were categorized into groups (age ≥60 years and <60 years; BMI ≥35 kg/m^2 and <35 kg/m^2; CCI ≥4 and <4; CRP ≥115 mg/L and <115 mg/L; hemoglobin ≥110 g/L and <110 g/L and albumin ≥35 g/L and <35 g/L). We also recorded the type of index surgery (primary or revision and hip or knee), whether the patient had a sinus tract, and whether the modular components were retained or exchanged. The duration of clinical symptoms (e.g., fever, swelling, tenderness, wound drainage, etc.) was defined as the number of days from onset until the day that the DAIR procedure was performed. If patients had persistent symptoms after the index surgery, the duration of symptoms was from the date of the index surgery to the DAIR procedure. Acute infection was defined as a time period of <90 days from the index surgery to the DAIR procedure. If the time was >90 days while symptom duration was <3 weeks, this was defined as a hematogenous infection. If the time from the index surgery to the DAIR procedure was >90 days and the duration of symptoms was >3 weeks, then the infection was considered chronic (24). No statistical difference was detected in demographic data between the two institutions (**Table 1**).

Following completion of treatment, patients were encouraged to return for routine follow-up appointments at three months, six months, and 1-year post-operatively, and then annually after that. Treatment success was defined as the eradication of infection without persistent clinical signs or symptoms. We used the treatment failure criteria, as defined by Diaz-Ledezma (25), which incorporated (1) a fistula, drainage, or pain, and infection recurrence caused by the same organism; (2) subsequent surgical intervention for infection after surgery; and/or (3) occurrence of PJI-related mortality.

Statistical analysis

Univariate analyses were performed to identify potential risk factors for the failure of DAIR. Continuous variables with normal distribution were presented as mean and standard deviation (SD) and were compared between groups using the Student's t-test. Non-normally distributed continuous variables were presented as medians and quartiles and were compared between groups using the Mann–Whitney *U* test. Categorical variables were compared between groups using the chi-square test or Fisher exact test. Variables with a *P*-value <0.1 in univariate analyses were then included in the subsequent multivariable analysis.

A multivariable analysis was performed by using the Cox proportional hazards regression model. Given that the most optimal cutoff value for the duration of infectious symptoms was uncertain, a time-dependent ROC (Receiver Operating Characteristic) was applied to assess this with a Kaplan-Meier method (**Appendix Figure A1**). Ultimately, ten days was determined to be the cutoff value at which a difference could be detected, and so this was utilized accordingly.

In addition, Kaplan-Meier survival analysis was utilized to depict overall infection control in this cohort of patients, and Breslow tests were used to compare the success rate of DAIR among acute, hematogenous, and chronic PJI cases.

Significance was set at *P*-value <0.05. All statistical analyses were conducted with IBM SPSS (version 22.0 for Windows; SPSS Inc., Chicago, IL, USA) except for the time-dependent ROC, which was conducted with R software (version 3.6.2; Survival ROC package; R Foundation for Statistical Computing, Vienna, Austria). In addition, a power analysis was conducted by PASS software (version 15.0), primarily based on the analysis of symptom duration, under the assumption of a two-sided type 1 error rate of 5%, and has 80% power to show a clinically significant advantage, the required sample sizes were 40, which is less than our actual sample size. Power analysis for multivariate cox regression showed enough power (0.995).

Results

The median follow-up time for patients in this cohort was 38.6 (interquartile range: 23.5, 90.7) months. Among them, 67 patients achieved treatment success at the final follow-up. Three patients died beyond their respective one-year follow-

TABLE 1 Demographic data between the two institutions.

Variable	Total $n = 104$	Institution 1 $n = 43$	Institution 2 $n = 61$	*P*-value
Age[a], year	62.5 (54, 75)	60 (54, 72)	64 (53, 74)	0.959
Male	45 (43.3%)	18 (41.9%)	27 (44.3%)	0.808
Weight[b], kg	72.2 ± 14.1	70.5 ± 12.7	73.4 ± 15.0	0.306
BMI[a], kg/m^2	26.5 (23.2, 29.4)	25.9 (22.4, 29.8)	27.1 (23.4, 29.8)	0.302
Index surgery				
Primary knee	66 (63.5%)	25 (58.1%)	41 (67.2%)	0.053[c]
Primary hip	19 (18.3%)	8 (18.6%)	11 (18%)	
Revision knee	9 (8.7%)	2 (4.7%)	7 (11.5%)	
Revision hip	10 (9.63%)	8 (18.6%)	2 (3.3%)	
Infection type				
Acute	55 (52.9%)	26 (60.5%)	29 (47.5%)	0.398
Hematogenous	24 (23.1%)	9 (20.9%)	15 (24.6%)	
Chronic	25 (24.0%)	8 (18.6%)	17 (27.9%)	
Success case	70 (67.3%)	28 (65.1%)	42 (68.9%)	0.689

[a]Data with a non-normal distribution are represented with the median (interquartile range).
[b]Data with a normal distribution are represented with mean ± standard deviation; Continuous variables in demographic data (age, weight and BMI) were examined with use of independent t test (if data followed normal distribution) or Mann-Whitney U test (if data did not follow normal distribution) between two institutions. Categorical variables in demographic data (gender, infection type and success) were analyzed with use of either the Pearson chi-square test or the Fisher exact test between two institutions.
[c]Fisher's exact test.

up time points for reasons that were objectively unrelated to infection, and we, therefore, categorized them into the group of treatment success. Thus, 34 patients met the criteria for treatment failure, and the overall success rate was 67.3% at the time of final follow-up. Time to treatment failure ranged from 3 days to 37.2 months post-operatively. The cumulative success rate was 76.9% (95% confidence interval (CI), 69.2%–85.5%) at one year and 64.4% (95% CI, 57.1%–76.6%) at five years follow-up (Figure 1). Among the cases of treatment failure, eight patients underwent no further surgery and were prescribed antibiotic suppression due to medical comorbidity (ies) or a reluctance to accept further surgery. Seven patients received repeat DAIR, and 3 of them failed. A total of 19 patients underwent a one or two-stage revision procedure, of which 13 succeeded.

After a regression analysis model was established, it was identified that a longer duration of symptoms was related to the failure of a DAIR procedure. Univariate analysis revealed that the *P*-values of CRP, modular component exchange, duration of symptoms, and different types of infection were <0.1 for treatment failure and were entered into the Cox proportional hazards regression model (Table 2). Multivariate analysis revealed that only a longer duration of symptoms was identified as an independent predictor of treatment failure. The hazard of failure for a patient with infectious symptoms for more than ten days was nearly 8.5 times the hazard for patients with less than ten days of symptoms. No statistical significance was detected with the other factors (Table 3).

A Kaplan-Meier (KM) survival analysis was further performed to compare results between treatment groups. Patients were sub-grouped by symptom duration, and failure of a DAIR procedure was defined as the endpoint, and results demonstrated that the survivorship of these cases performed more than ten days after symptoms were lower than those performed within ten days ($P = 0.016$; Figure 2). No statistical difference was detected among acute, hematogenous, and chronic cases of PJI ($P = 0.161$; Figure 3).

Discussion

The current study included two centers and more than 100 cases of acute, hematogenous, and chronic infections treated as DAIR procedure with an overall infection control (e.g., treatment success) rate of 67.3% at final follow-up. There was no difference in terms of predicting infection control among different types of infection, and symptom duration of fewer than ten days was more predictive of success.

Infection control is an important priority when surgeons choose to perform a DAIR procedure as a means of managing PJI. Kunutsor et al. performed a systematic review that included 4,897 cases treated with DAIR and reported an overall infection control rate of 61.4%, with a mean follow-up time of 3.6 years (11). This was similar to the infection control rate reported in the current study. However, a subgroup analysis looking at cases performed before or after

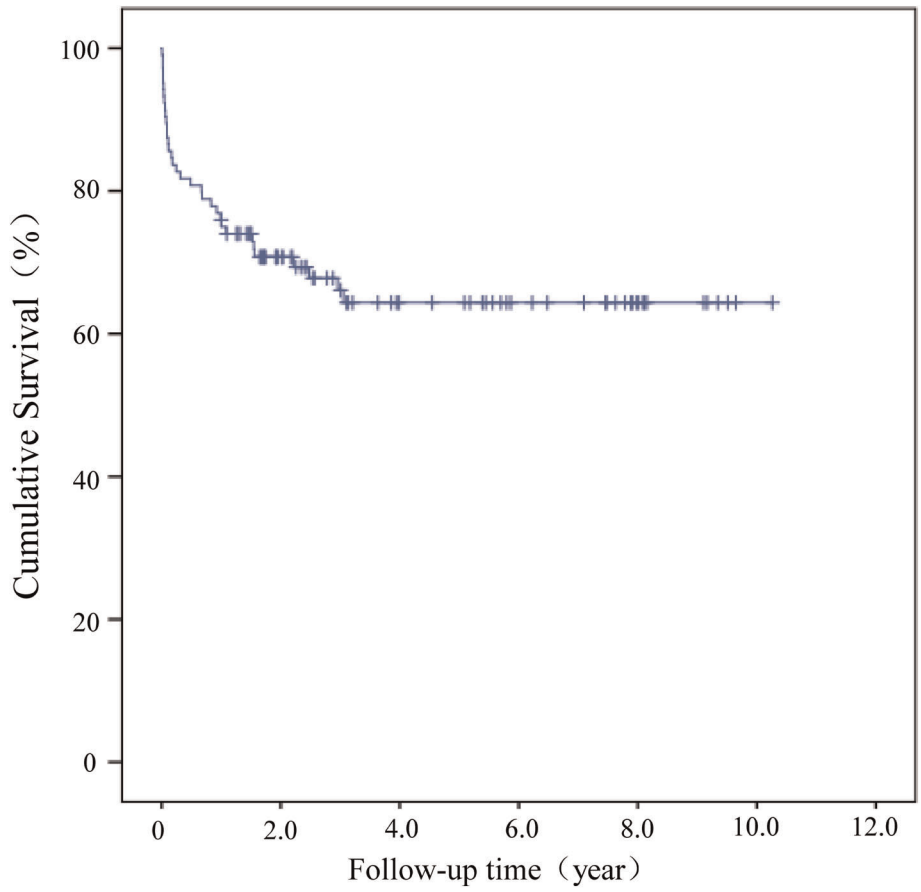

FIGURE 1
Kaplan–Meier (KM) survival analysis for the cohort of patients who underwent a DAIR procedure failure was defined as the endpoint.

the year 2000 revealed a higher infection control rate of 65.0% in the current century as opposed to the prior with an infection control rate of 51.5%. The potential reasons for this observation may be improvements in surgical technique, efficiency in bacterial culture, and optimization in the use of antibiotics. Although most surgeons utilize a DAIR protocol for acute or hematogenous infections, a previous consensus recommendation did not advise against using a DAIR procedure except in cases with evidence of prosthetic loosening (18). As a result, expanding the boundary of indications for DAIR was pursued.

In 2011, Koyonos et al. (17) compared acute, hematogenous, and chronic PJIs treated with DAIR, although no differences were detected among the groups, the infection control rates among all three groups were lower than 50%. Grammatopoulos et al. (26) separately reported a cohort of PJI cases managed with DAIR, including both acute and chronic infections. Their overall infection control rate was 84% and higher than the percentage reported in the current study. In their study, when the cutoff time from the index surgery to the DAIR procedure was between 4 and 13 weeks, the infection control rate revealed no statistical difference. The infection control rates of acute, hematogenous, and chronic PJIs in the cohorts of the current study were 72.8% (40/55), 75.0% (18/24), 48.0% (12/25), respectively, which were without statistical difference. Notably, we also performed a secondary analysis in which we differentiated acute from chronic infections with a cutoff of 4 weeks, and there remained no statistically significant difference among the groups (**Appendix Table A1**).

Identifying the optimal cutoff time for differentiating acute from chronic is difficult, but may help define a paradigm of communication amongst practitioners in the field (16). Fehring et al. reported that the infection control rate of DAIR had no statistical difference when the cutoff was 30 or 90 days (27), to which our results were similar. However, although there was no statistical difference for infection control rate between chronic and acute infection according to different standards. The infection control rate of chronic infection was still lower than that of acute and hematogenous infection. Chronic infection means a longer time of infection which may be related to biofilm formation. That would compromise the results of DAIR (16). While acute and hematogenous

TABLE 2 Comparison of demographics, medical, surgical information and culture results with a univariate analysis.

		Success Rate ($n = 70$)	Failure Rate ($n = 34$)	*P*-value
Demographics				
Age	≥60 years	45 (72.6%)	17 (27.4%)	
	<60 years	25 (59.5%)	17 (40.5%)	0.164
Gender	Male	27 (60.0%)	18 (40.0%)	
	Female	43 (72.9%)	16 (27.1%)	0.165
BMI	≥35 kg/m^2	1 (33.3%)	2 (66.7%)	
	<35 kg/m^2	69 (68.3%)	32 (31.7%)	0.249[a]
DM	Yes	12 (75.0%)	4 (25.0%)	
	No	58 (65.9%)	30 (34.1%)	0.476
Rheumatoid arthritis	Yes	4 (66.7%)	2 (33.3%)	
	No	66 (67.3%)	32 (32.7%)	1.000[a]
CCI	≥4	31 (72.1%)	12 (27.9%)	
	<4	39 (63.9%)	22 (36.1%)	0.382
Preoperative tests				
CRP	≥115 mg/L	22 (81.5%)	5 (18.5%)	
	<115 mg/L	48 (62.3%)	29 (37.7%)	***0.068***
Hemoglobin	≥110 g/L	24 (70.6%)	10 (29.4%)	
	<110 g/L	46 (65.7%)	24 (34.3%)	0.619
Albumin	<35 g/L	23 (67.6%)	11 (32.4%)	
	≥35 g/L	47 (67.1%)	23 (32.9%)	0.302
Surgical information				
Sinus	Yes	32 (62.7%)	19 (37.3%)	
	No	38 (71.7%)	15 (28.3%)	0.331
Modular part exchange	Yes	54 (73.0%)	20 (27.0%)	
	No	16 (53.3%)	14 (46.7%)	***0.053***
Duration of symptoms	≥10 days	50 (60.2%)	33 (39.8%)	
	<10 days	20 (95.2%)	1 (4.8%)	***0.002***
Types of infection	Acute	40 (72.7%)	15 (27.3%)	
	Hematogenous	18 (75.0%)	6 (25.0%)	
	Chronic	12 (48.0%)	13 (52.0%)	***0.060***
Types of index surgery	Primary knee	48 (72.7%)	18 (27.3%)	
	Primary hip	11 (57.9%)	8 (42.1%)	
	Revision knee	6 (66.7%)	3 (33.3%)	
	Revision hip	5 (50.0%)	5 (50.0%)	0.118
Organism	Staphylococcus (MR)	13 (59.1%)	9 (40.9%)	
	Staphylococcus (MS)	5 (62.5%)	3 (37.5%)	
	Gram-negative	7 (63.6%)	4 (36.4%)	
	Polymicrobial	8 (72.7%)	3 (27.3%)	
	Culture negative	24 (68.6%)	11 (31.4%)	
	others	13 (76.5%)	4 (23.5%)	0.903

BMI, body mass index; DM, diabetes mellitus CCI, charlson comorbidity index; CRP, C-reactive protein; MR, methicillin-resistant; MS, methicillin-sensitive.
[a]Fisher's exact test.
The bold values mean it has statistical difference.

TABLE 3 Multivariable analysis for treatment failure following DAIR for PJI cases.

Variables	Category	Hazard Ratio	95% CI	*P*-value
CRP	<115 mg/L	reference		
	≥115 mg/L	1.374	0.510–3.697	0.530
Modular part exchange	Yes	reference		
	No	1.533	0.771–3.051	0.223
Duration of symptoms	<10 days	reference		
	≥10 days	8.492	1.159–62.212	***0.035***
Types of infection	Acute	reference		
	Hematogenous	1.610	0.605–4.290	0.340
	Chronic	1.755	0.832–3.700	0.140

CRP, C-reactive protein.
The bold values mean it has statistical difference.

infection has less bacteria of biofilm form, which is easier to be eradicated. Why we did not find the statistical difference among acute, hematogenous, and chronic infections may be related to the limited number of cases included in this study. At the same time, it may also be that more suitable patients were selected during the selection of DAIR. And the cutoff time is not directly related to bacteria, or host factors. Different patient selection, surgical techniques and/or other confounders may also explain why our study had different infection control rates from others currently available in the literature.

In this study, having a duration of infectious symptoms longer than ten days was the only independent risk factor that was detected for failing to establish infection control with DAIR. Several previous studies have reported that a shorter duration of symptoms was related to the eradication of infection (28–31). Surgical debridement and subsequent continuous antibiotics may remove planktonic bacteria and younger biofilm (32). A longer duration of symptoms theoretically indicates higher rates of biofilm formation and may explain why a longer duration of symptoms infers higher failure from DAIR. However, among these studies, the optimal duration of symptoms in terms of days for DAIR was variable. Fink et al. (31) reported that the target symptom duration was two days, while Narayanan et al. (30) reported that it was two weeks. Limited cases or a lack of reliable statistical methods may explain this difference. Other studies (9, 15, 22) were unable to detect a longer duration of symptoms as a predictor of failure for DAIR. However, all of these studies included only acute or acute hematogenous PJIs, which indicates that the duration of symptoms in all patients was inherently short. The multicenter study from Lowik et al. (15) contained a large cohort of 386 patients, and all had symptom duration of <21 days, thereby preventing any true analysis for symptoms beyond that time point. In contrast, our study combined acute, hematogenous, and chronic infections, each with objectively different durations of symptoms. The statistical method of a time-dependent ROC to identify an optimal cutoff time made our results particularly robust.

Other known risk factors, such as the presence of a sinus tract (15), modular component exchange (26), or staphylococcal infections (13, 17), are reportedly related to the failure of DAIR. Despite that, in the current cohort, although the infection control rates of patients identified with these particular factors were lower than the overall population, we

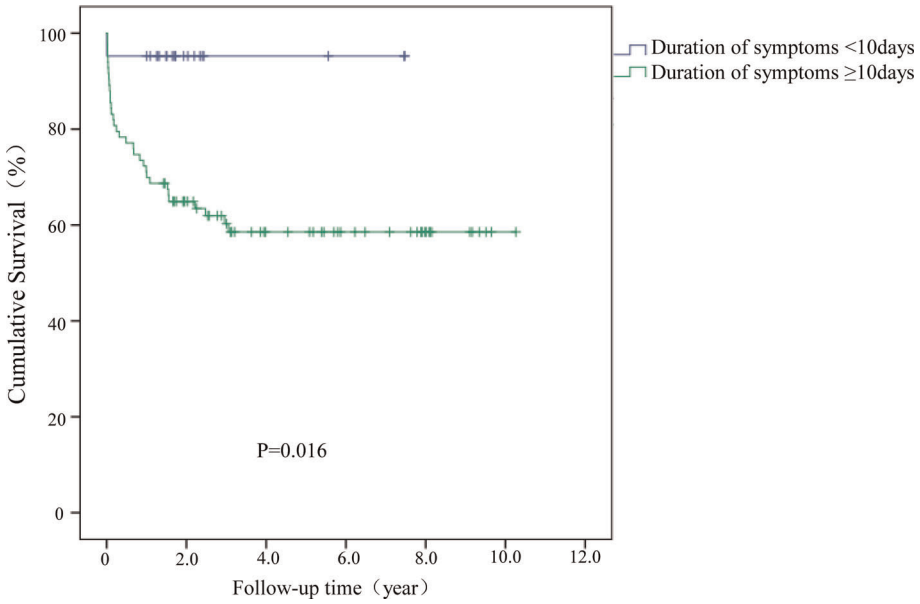

FIGURE 2
Kaplan–Meier (KM) survival analysis for cases with symptom duration greater or less than 10 days.

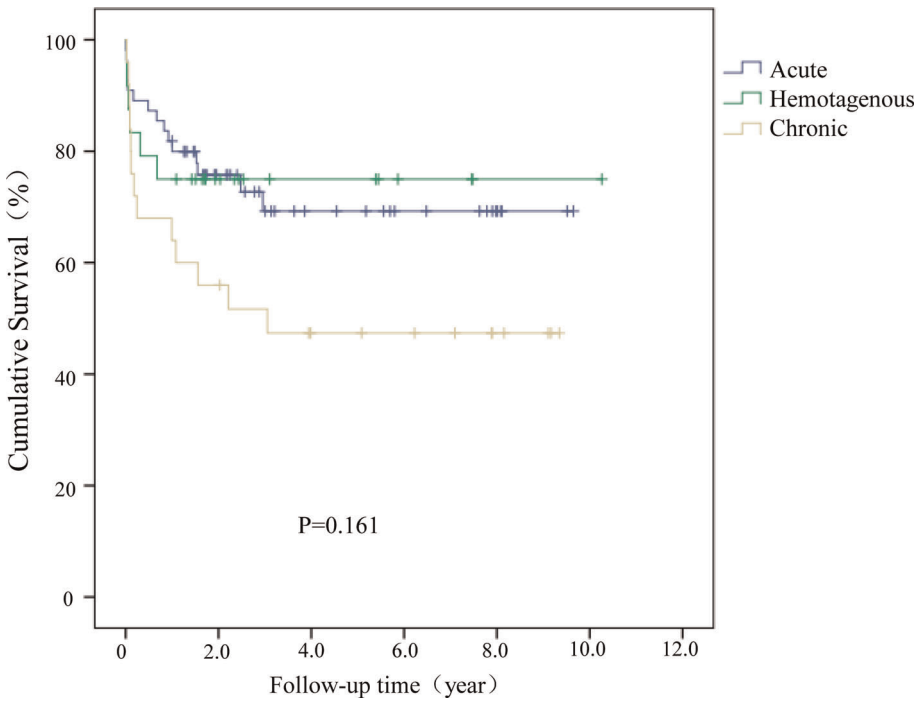

FIGURE 3
Kaplan–Meier (KM) survival analysis for acute, hematogenous, and chronic cases of PJI.

failed to detect statistical significance. The key to the success of DAIR lies in biofilm removed through mechanical and chemical disruption (33). The minimum biofilm eradication concentration (MBEC) is much higher than the minimum inhibitory concentration (MIC) for planktonic bacteria (34). We added local antibiotics intraoperative, which may provide better clinical outcomes (35, 36). Besides that, individual antibiotic selection under the guidance of multidisciplinary

specialists, an improvement in surgical techniques, and strict patient selection can all represent potential reasons as to why the current study had reasonable infection control and was unable to detect differences in these factors.

There are several limitations to be acknowledged in this study. First, it was a retrospective study which indicates inherent weaknesses. However, DAIR is an urgent surgery and, therefore, challenging to organize a prospective study. Both institutions in the current study had an assigned person to crosscheck the data to ensure reliability. Even so, due to the great subjectivity in the selection of DAIR, there was still be some heterogeneity in the data. Secondly, the duration of symptoms was subjective and dependent on the patient's description. Nevertheless, patients were sensitive to symptoms, including fever, wound drainage, swelling, and tenderness, and surgeons were invested in taking a careful patient history. Third, the case number is limited, especially in some demographic factors, including those with a BMI higher than 35 kg/m^2; this may yield type I error. With the exception of registry data, the patient numbers in a study assessing DAIR are unlikely to be significant. The current study reported the largest cohort of data in our region, and further collaborative studies should be pursued. Finally, although some cases had relatively short follow-up time, most cases of failure occurred relatively close to the DAIR procedure itself and are thus still likely to capture our clinical endpoint.

Conclusion

In conclusion, DAIR is a reasonable treatment option for PJI, and chronic infection does not appear to be a contraindication, with a 48% success rate in this cohort of patients. Performing DAIR within a period in which the duration of symptoms was less than ten days achieved a satisfactory clinical result in most cases. Further investigation with a larger number of cases and longer follow-up time points may strengthen these clinical findings.

Data availability statement

The raw data supporting the conclusions of this article will be made available after request and approved by IRB of both hospitals.

Ethics statement

The studies involving human participants were reviewed and approved by The ethical approvals of this study were obtained from the Ethics Committee of Beijing Jishuitan Hospital and Chinese PLA General Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

HS and RL: Contributed substantially to conception and design, acquisition of data, analysis, and interpretation of data; drafted the article; gave final approval of the version to be published; agreed to act as a guarantor of the work. WD: Contributed substantially to the acquisition and interpretation of data; revised it critically for valuable intellectual content; gave final approval of the version to be published; agreed to act as a guarantor of the work. BY: Contributed substantially to the acquisition and interpretation of data; revised it critically for valuable intellectual content; gave final approval of the version to be published; agreed to act as a guarantor of the work. DY, YZ and JC: Contributed substantially to conception and design, acquisition of data, analysis, and interpretation of data; revised it critically for valuable intellectual content; gave final approval of the version to be published; agreed to act as a guarantor of the work. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix

APPENDIX FIGURE A1

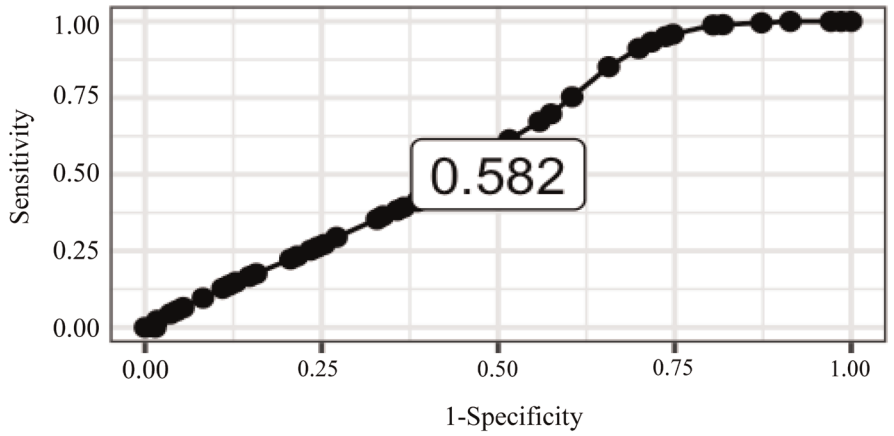

FIGURE A1
Time-dependent ROC to identify the cutoff value for duration of infection symptoms (days). We used 5 years as the predict point of time, the ROC curve got the maximal AUC (0.582) and the cutoff value is reported as 10 days.

APPENDIX TABLE A1

TABLE A1 Compare the failure rate of different types of infection with the cut off time as 4 weeks.

	Success ($n = 70$)	Failure ($n = 34$)	p-value
Acute	16 (22.9%)	9 (26.5%)	
Hematogenous	31 (44.3%)	9 (26.5%)	
Chronic	23 (32.9%)	16 (47.1%)	0.198

Acute infection: the time between DAIR and index surgery was less than 4 weeks; Hematogenous infection: the time between DAIR and index surgery was more than 4 weeks while the duration of infectious symptoms was less than 3 weeks; Chronic infection: the time between DAIR and the index surgery was more than 4 weeks while the duration of infectious symptoms was more than 3 weeks.

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Treatment of Periprosthetic Joint Infection and Fracture-Related Infection With a Temporary Arthrodesis Made by PMMA-Coated Intramedullary Nails – Evaluation of Technique and Quality of Life in Implant-Free Interval

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Background: Antimicrobial coating of intramedullary nails with polymethyl methacrylate (PMMA) bone cement promises infection control and stabilization for subsequent bone healing. However, when removing the implant, bone cement can debond and remain in the medullary cavity of the long bones, representing a nidus for reinfection. This work presents a technique comprising reinforcement of PMMA-coated intramedullary nails with cerclage wire to prevent such problems in patients treated for fracture-related infection (FRI) or knee periprosthetic joint infection (PJI) with a static spacer as temporary arthrodesis allowing weight-bearing in the implant-free interval. Outcomes of this surgical treatment were evaluated in terms of (i) associated complications and (ii) patient-reported quality of life.

Methods: In this retrospective case series, 20 patients with PJI ($n = 14$, 70%) and FRI ($n = 6$, 30%) treated with PMMA-coated intramedullary nails reinforced with cerclage wire between January 2021 and July 2021 were included. Quality of life during the implant-free interval was evaluated with the EQ-5D, SF-36, and an ICD-10 based psychological symptom rating and compared with previously analyzed cohorts of successfully treated PJI and FRI patients in whom eradication of infection and stable bone consolidation was achieved.

Results: Complications during the implant-free interval comprised a broken nail in one case (5.0%) and a reinfection in one case (5.0%). Coating-specific side effects and cement debonding during removal did not occur. The mean physical health component score of SF-36 was 26.1 ± 7.6, and the mean mental health component score reached a value of 47.1 ± 18.6. The mean EQ-5D index value was 0.36 ± 0.32 and the mean EQ-5D visual

analogue scale rating was 47.4 ± 19.4. The scores were significantly lower than those in the successfully treated FRI cohort but not in the PJI cohort. The mean ICD-10-based symptom rating scores revealed psychological symptom burden on the depression scale and enhanced levels of anxiety in comparison with healed FRI and PJI patients.

Conclusion: Reinforcement of PMMA bone cement-coated implants seems to be a reasonable treatment option to create a temporary arthrodesis, preventing detachment of the bone cement when the implant was removed.

Level of Evidence: IV.

Keywords: polymethyl methacrylate (PMMA), coated implants, temporary arthrodesis, quality of life, psychological outcomes, periprosthetic joint infection, fracture-related infection

INTRODUCTION

Since the introduction of antibiotic-containing polymethyl methacrylate (PMMA) bone cement to reduce the rate of periprosthetic joint infections (PJI) in arthroplasty by Buchholz and Engelbrecht in the late 1960s, the application of PMMA cement as a local antibiotic carrier for infection prophylaxis and infection therapy has become established in the fields of orthopedics and trauma surgery (1–3). In addition to commercially available antibiotic-containing PMMA chains, local application of PMMA for sheathing osteosynthesis materials has been described (4, 5). The encasement of intramedullary rods with antibiotic-containing PMMA bone cement offers several advantages. In addition to high local antibiotic concentrations, these can provide stability in unconsolidated fractures and thereby, allow fracture-associated infection to heal after surgical debridement. The stability achieved may also allow early weight-bearing of the limb. Meanwhile, PMMA cement-coated implants offer an alternative to external stabilization, which is otherwise necessary in many cases. Such large cement spacers are frequently applied in orthopedic oncology surgery for the treatment of megaprosthesis infection (6). Also, in cases of PJI and fracture-related infection (FRI) - the cement coating of intramedullary rods can serve to create a temporary knee arthrodesis, allowing full weight-bearing as a special type for a static spacer in a two-staged treatment approach (7). While mobile spacers are reported to result in a better range of motion, longtime function after reimplantation of a knee endoprosthesis, and similar infection control, static spacers may allow for pain-adapted weight-bearing without the need for additional braces or casts in the implant-free interval (8). Particularly, in complex revision cases that are not infrequently accompanied by excessive bone loss, mobile spacers are not reasonably implantable, and static spacers are a useful tool to achieve infection eradication and early mobilization of the patient. In addition, when producing custom-made static spacers, the use of PMMA-coated rods or intramedullary nails has several limitations, ranging from difficulties in fabrication to problems with implant removal during follow-up procedures. In the latter, the detachment of the PMMA bone cement from the implant and, thus, the retention of the cement in the medullary canal of long tubular bones poses a challenge. The removal of cement residues deep in the medullary can be surgically complex and time-consuming. Meanwhile, a retention of biofilm-containing infected cement residues can be considered a nidus for reinfection. Therefore, a technique has been presented including reinforcement of PMMA-coated intramedullary nails with cerclage wire to prevent such problems associated with the removal (9). Many studies have focused on comparing mobile and static spacers in terms of infection eradication and knee function after reimplantation of a revision knee prosthesis (8, 10, 11). In general, treatment success is mainly defined from a surgical perspective, and, thus, the inclusion of patient-reported outcome measures plays a major role to comprehensibly determine to what extent PJI or FRI affects the patients. Hereby, especially the quality of life has become an important outcome measure (12). However, in the area of bone and joint infection, such studies are scarce. For instance, a systematic review including 93 studies on FRI outcomes identified only three articles reporting the quality of life (13). Further, most studies assessing the quality of life have incorporated a long-term study design with a follow-up time of several years (14–18). Thus, quality of life in the implant-free interval, which can be regarded as the most critical period for patients suffering from knee PJI or FRI after articular fractures requiring joint arthroplasty, has not been investigated yet. Therefore, the purpose of this study is to first investigate complications in relation to temporary arthrodesis by cerclage wire–reinforced PMMA-coated intramedullary nails. Second, the quality of life of patients in the implant-free interval is assessed.

MATERIALS AND METHODS

Patients

In this retrospective case series (level of evidence: IV), patients treated with PMMA-coated intramedullary nails reinforced with cerclage wire in our department between January 2021 and July 2021 were included. Informed consent was obtained from all individual participants included in the study. The study was approved by the institutional ethics committee of the University Hospital Regensburg according to the Helsinki Convention (file number 20-1681-104). Patient characteristics

were retrospectively retrieved from the hospital's electronic patient files system. Treatment indications included PJI and FRI. PJI was diagnosed according to the EBJIS consensus criteria for the diagnosis of PJI (19). FRI was defined according to the definitions of the FRI consensus group published in 2018 (20). Patient characteristics [sex, age, Charlson Comorbidity Index (CCI)], ASA score, details of orthopedic implant-associated infection such as previous revisions due to infection, reinfection, causing pathogen as well as surgery reports and implant-related adverse events until reimplantation, were assessed by reviewing electronic medical records and post-operative x-rays.

Surgical Treatment and Preparation of Custom-Made Cerclage Wire–Reinforced PMMA-Coated Intramedullary Nails

After removal of the orthopedic implants and thorough surgical debridement and irrigation of bone and soft tissue, in all cases, intramedullary humerus nails were used from the same manufacturer (T2, Stryker, Duisburg, Germany) for arthrodesis. All implants of the T2 humeral nailing system are cannulated and made of Type II anodized titanium alloy (Ti6AL4V) (https://www.stryker.com/us/en/trauma-and-extremities/products/t2-standard-humeral-nail.html). Different other osteosynthesis materials are generally suitable for internal stabilization (21). Manufactured intramedullary humerus nails, however, have several advantages compared with simple smooth intramedullary rods. The used humeral nails have different holes and also a thread at the proximal end. The holes can additionally be used for locking of the nails if necessary. The thread at the proximal end can be used to fix an extraction instrument when nail removal with a forceps is simply not possible. This can save valuable surgical time, and to the best of our knowledge, this a major advantage that outweighs the slightly higher implant costs. All humeral nails have been used due to their availability in small diameters of 7 mm. If intramedullary diameters allow for thicker coated nails, femoral or tibial nails can also be used as an intramedullary device.

With the purpose of reducing the risk of cement debonding from metallic implants when removing the intramedullary implant, an additional cerclage wire was used when coating intramedullary nails (**Figures 1**, **2**). This technique is pretty similar to the reinforcement of concrete in construction. After the bracing of a 1.25 mm cerclage wire to the intramedullary nail, PMMA bone cement can be applied to the nail. In this study, PMMA Copal® (Heraeus Medical GmbH, Wehrheim, Germany) was used in all cases. After mixing the PMMA bone cement, one should wait for 3 min according to the manufacturers' guidance before the bone cement is applied to the nail. Similar to trauma surgery, the nail diameter is adapted to the reamed intramedullary diameter. A gauge is used to measure the diameter of the coated nails. To achieve a sufficient "press fit" insertion of the coated nails, a diameter 1 mm smaller than reamed should be achieved. After hardening of the bone cement, which usually takes about 12 min, the reinforced PMMA-coated nails can be inserted into the corresponding intramedullary canal and fixed "press fit" into the bone. It is of outstanding importance to avoid implanting of still incompletely hardened cement. Immediate cement debonding can occur, and if not, bone cement can be pushed into the cancellous bone, which makes removal of the implants highly difficult in a later surgery. To achieve temporary arthrodesis of the knee, PMMA bone cement-coated nails placed in the medullary canal are overlapped in the bony defect zone of the knee. The knee is held in a flexed position of approximately 10°–15° and in a physiological leg axis. The defect zone is filled with additional PMMA bone cement. Depending on the evidenced pathogens, local antibiotics can be applied to the bone cement. When complete enclosing of the two intramedullary rods is achieved, no further connection between the two encased intramedullary nails is necessary, and patients can be allowed to bear full weight with their new temporary arthrodesis (**Figure 2**).

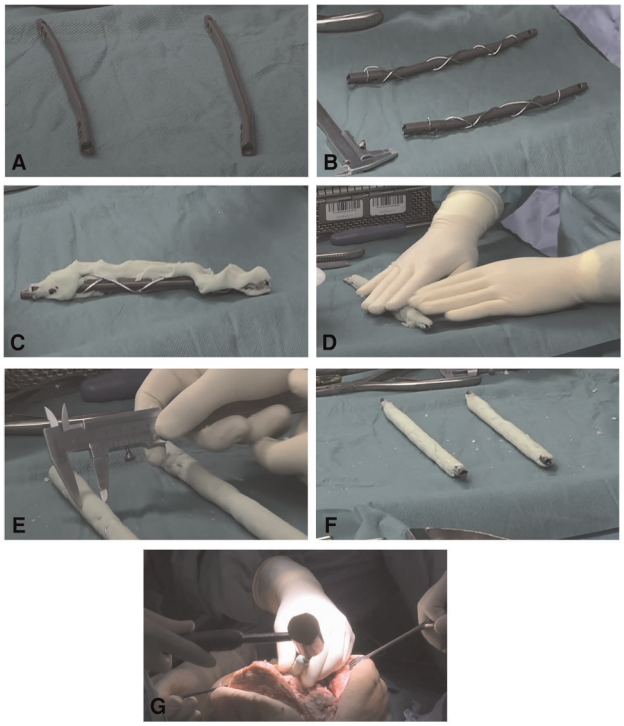

FIGURE 1 | Polymethyl methacrylate (PMMA)-coated intramedullary nails. (**A, B**) 2-Humerus nails (Stryker, Duisburg, Germany) are wrapped with a 1.25- mm steel cerclage wire for reinforcement. (**C, D**) PMMA cement (Copal®, Heraeus Medical GmbH, Wehrheim, Germany) is applied to the nails. The hardening cement is then evenly rolled out on the instrument table. (**E, F**) The diameter is checked with the sliding gauge according to the reamed medullary canal diameter. (**G**) Reinforced PMMA-coated nails are inserted into the corresponding intramedullary canal and fixed "press fit" into the bone.

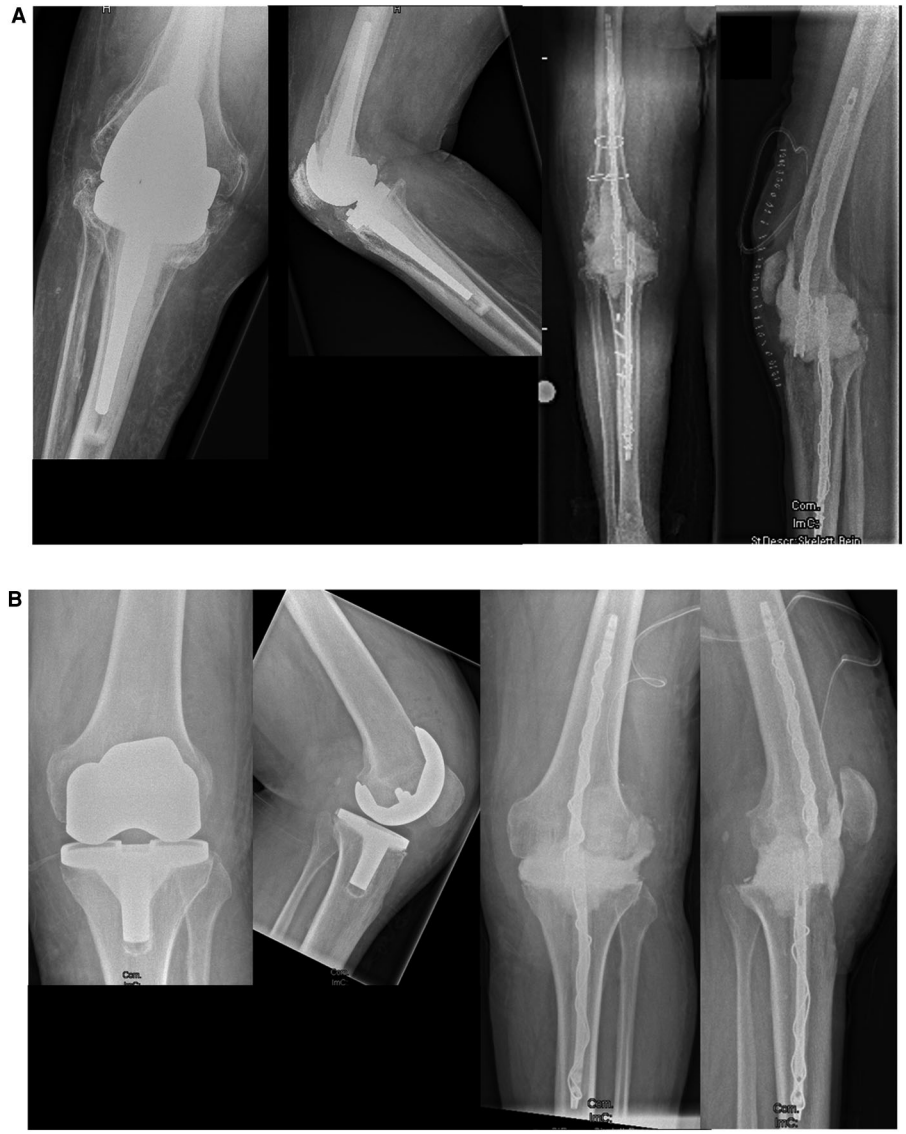

FIGURE 2 | Pre-operative x-rays of (**A**) an infected rotating hinge prosthesis and (**B**) an infected bicondylar surface replacement prosthesis are shown in the left panel. Post-operative images after explantation, debridement, and temporary arthrodesis are shown in the right panel.

Quality-of-Life Assessment

Patient-related outcome and quality of life was assessed using the German Short-Form 36 (SF-36) and EQ-5D scores as well as an ICD-10-based symptom rating (ISR) (22, 23). The latter is an inventory frequently used in psychosomatic anamnesis. It consists of 29 items and covers various mental syndromes with subscales for depression, anxiety, obsessive/compulsive disorders, somatoform disorders, and eating disorders (24). EQ-5D is a well-established generic quality-of-life instrument developed by the EuroQol group comprising five questions concerning the functional domains' mobility, self-care, everyday life activities, pain/discomfort, and anxiety/depression (25). The items were converted into a single EQ index value using German norm data weights (26). Additionally, EQ-5D was evaluated using the visual analogue scale (VAS) method (27). The widely used SF-36 health survey captures the general health status with 36 questions in eight functional domains: physical function, role physical, bodily pain, general health, vitality, social function, role emotional, and mental health. Summary scores for the physical and mental component were calculated using normative data from a German national health interview and an examination survey conducted in 1998 with 7,124 participants (28). Quality of life was compared (1) with scores assessed from $n = 37$ patients after successful treatment, including eradication of infection and stable bone consolidation after long bone FRI

with a follow-up of 4.2 ± 2.7 years after the last surgery (14) and (2) to scores assessed from $n = 36$ patients after successful treatment of knee PJI (mean follow-up of 4.9 ± 3.5 years (15).

Data were analyzed using SPSS statistics version 24.0 (IBM, SPSS Inc., Armonk, NY). Descriptive statistics were calculated for all variables. Continuous variables were expressed as the mean and standard deviation. For comparisons between continuous variables, independent *t*-tests were performed after determining that the distribution was appropriate for parametric testing by Levene's test. The level of significance was set at $p < 0.05$.

RESULTS

In total, 20 patients (9 women, 11 men; mean age 67.3 ± 8.4 years, mean BMI 36.2 ± 9.8 kg/m^2) were included in the analysis (**Table 1**). Indication for surgical treatment was PJI of the knee in $n = 14$ (70.0%) patients and FRI in $n = 6$ (30.0%) patients. The latter comprised FRI at the proximal tibia ($n = 4$) and the distal femur ($n = 2$). Two patients (10.0%) were smokers and nine patients reported to be former smokers (45.5%). The mean CCI was 3.2 ± 1.6 (range: 1–5) and the mean ASA score was 2.5 ± 0.6 (range: 1–3). The quality-of-life assessment took place after an average of 2.6 days after spacer implantation. The mean interval duration was 2.4 ± 1.6 months (range: 0.7–4.4 months).

TABLE 1 | Patient characteristics.

Number	Sex	Age (years)	Indication	Pathogen
1	Male	69	PJI	*Staphylococcus hominis*, *Staphylococcus epidermidis*
2	Female	56	PJI	*S. epidermidis*
3	Male	73	PJI	*Streptococcus agalactiae*
4	Male	83	PJI	*Staphylococcus aureus*
5	Male	74	PJI	*Staphylococcus haemolyticus*, *S. epidermidis*
6	Female	71	PJI	*S. agalactiae*
7	Male	73	PJI	*Streptococcus dysgalactiae*
8	Female	72	PJI	*S. aureus*, *S. dysgalactiae*
9	Male	72	PJI	*S. aureus*
10	Female	62	PJI	*Pseudomonas aeruginosa*, *Streptococcus anginosus*, *Enterococcus faecalis*, *S. aureus*
11	Female	51	PJI	*Candida krusei*, *Serratia*, *E. faecalis*
12	Female	57	PJI	*S. haemolyticus*, *Corynebacterium amycolatum*
13	Male	68	PJI	*S. aureus*
14	Female	67	PJI	*S. aureus*, *Bacillus cereus*
15	Male	71	FRI	*S. aureus*
16	Male	61	FRI	*Enterobacter cloacae complex*
17	Female	79	FRI	*S. aureus*
18	Male	57	FRI	*S. aureus*
19	Female	73	FRI	*S. aureus*
20	Male	63	FRI	*S. epidermidis*, *Enterococcus faecium*

PJI, periprosthetic joint infection; *FRI, fracture-related infection.*

Complications during the implant-free interval occurred in two cases (10%). These comprised a broken nail in one case 21 days post-operatively (Nr. 18, **Table 1**). The patient had a BMI of 40.1 kg/m^2 and was fully mobilized after the surgery. The only comorbidity of the patient was a chronic obstructive pulmonary disease. Subsequently, the spacer was exchanged. Another PJI-patient experienced a reinfection (Nr. 6, **Table 1**). The patient had a BMI of 51.4 kg/m^2 and was fully mobilized with crutches after the surgery. The initial pathogen was a *Streptococcus agalactiae*, which has not been found after the implantation of the spacer. After 71 days post-operatively, *Enterococcus faecalis* and *Klebsiella pneumoniae* were identified, requiring explantation of the spacer. Coating-specific side effects and cement debonding during removal did not occur in any of the patients.

The mean physical health component score (PCS) of SF-36 was 26.1 ± 7.6, and its mean mental health component score (MCS) reached a value of 47.1 ± 18.6. In comparison with the successfully treated cohorts, patients with the temporary arthrodesis scored lower on the PCS than healed FRI patients did, whereas no significant difference was observed in terms of mental health. The subdomain analysis resulted in mean values of 16.6 ± 6.3 for physical function, 4.7 ± 0.8 for physical role, 44.0 ± 23.5 for bodily pain, 63.7 ± 22.4 for general health, 44.2 ± 21.9 for vitality, 73.7 ± 23.7 for social functioning, 61.4 ± 18.9 for emotional role, and 60.8 ± 21.3 for mental health (**Figure 3**). Here, values of the dimension physical function and physical role from the study cohort were lower than the long-term quality-of-life scores from successfully treated PJI as well as FRI patients. Interestingly, general health and social functioning were rated higher in the study cohort than in healed PJI patients, whereas bodily pain and vitality were lower than that in rehabilitated FRI patients.

The mean EQ-5D index value was 0.36 ± 0.32. The mean EQ-5D VAS rating reached 47.4 ± 19.4. The EQ-5D index value, as well as the VAS rating, was significantly lower than that in the successfully treated FRI cohort ($p < .001$ and $p = .006$, respectively) (**Figure 4**). In the subdimensions of EQ-5D, patients showed limitations, especially concerning their everyday life activities. In total, 93.8% of the patients reported problems with mobility, self-care, and pain/discomfort. For all patients, problems with usual activities were noted, and 43.8% of patients reported limitations due to anxiety/depression (**Figure 5**).

The mean total score of the ISR was 0.52 ± 0.20. The mean ISR subdimension scores reached 1.18 ± 0.32 for depression, 0.74 ± 0.22 for anxiety, 0.28 ± 0.16 for obsessive/compulsive disorders, 0.16 ± 0.05 for somatoform disorders, and 0.52 ± 0.15 for eating disorders, respectively (**Figure 6**). On average, the cohort crossed the threshold of mild symptom burden with regard to the scale depression, whereas none of the values of the other syndrome scales met the criteria for caseness, i.e., clinically relevant severity of psychological disorders. Here, depression

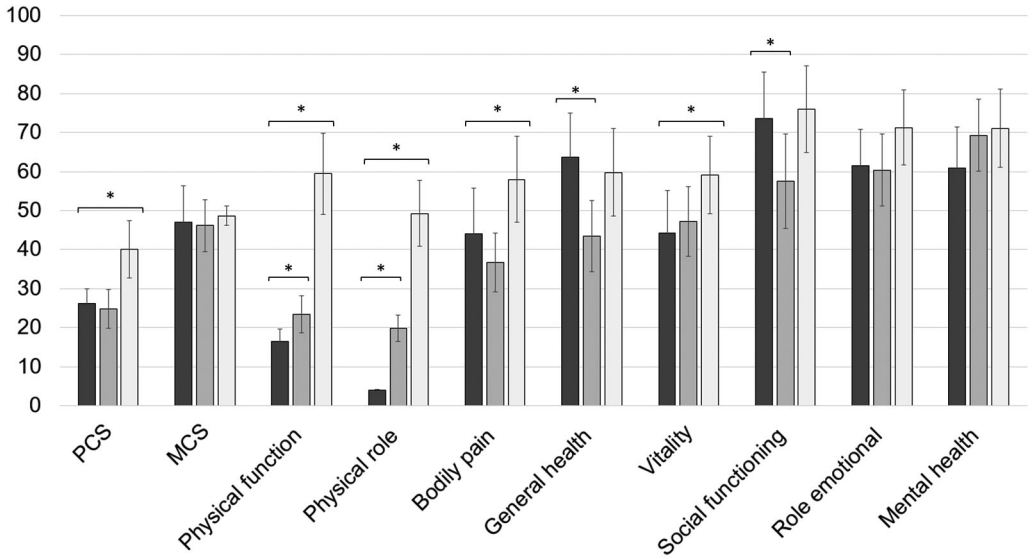

FIGURE 3 | Subdimension scores for patient-related quality of life assessed with SF-36. The results of the study cohort are shown in dark gray. For a comparison, the values of the successfully treated periprosthetic joint infection (PJI) and fracture-related infection (FRI) population are illustrated in gray and light gray, respectively. * illustrates statistical significance on a $p < 0.05$ level determined by an independent *t*-test.

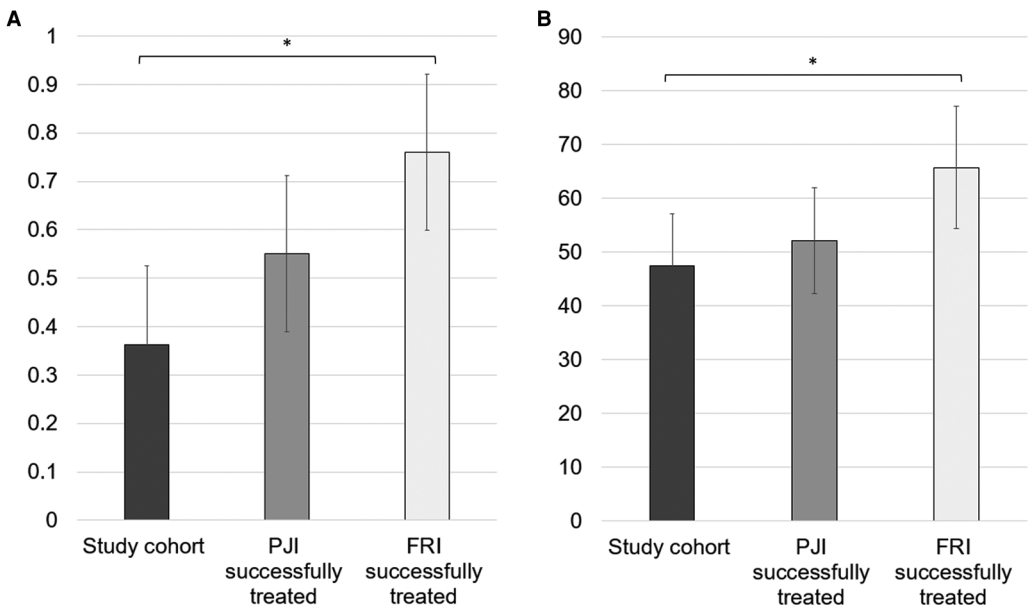

FIGURE 4 | (**A**) Mean EQ-5D index value on a scale 0–1 and (**B**) mean EQ-5D VAS (visual analogue scale) rating on a scale 0–100. For a comparison, the values of the successfully treated PJI and FRI population are illustrated in gray and light gray, respectively. * illustrates statistical significance on a $p < 0.05$ level determined by an independent *t*-test.

scores were significantly higher than those in successfully treated FRI patients ($p < 0.001$), whereas patients treated with the temporary arthrodesis reached enhanced scores for the level of anxiety, as well as for the scale of obsession/compulsion, and somatization compared with healed PJI and FRI patients.

DISCUSSION

In this study, the technique of a temporary knee arthrodesis created with cerclage wire–reinforced PMMA-coated intramedullary nails was introduced and the quality of life

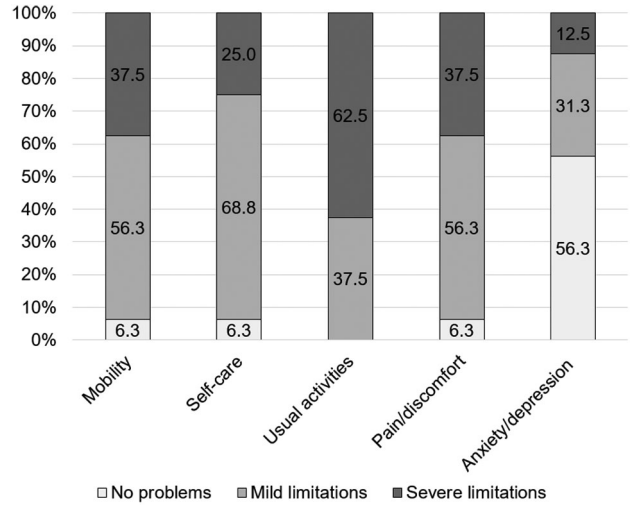

FIGURE 5 | Percentage of patients showing limitations in the mobility, self-care, usual activity, pain/discomfort, and anxiety/depression of the EQ-5D subdimensions. The share of mild limitations is shown in gray, the share of severe limitations is in dark gray, and the share of no limitations is in light gray.

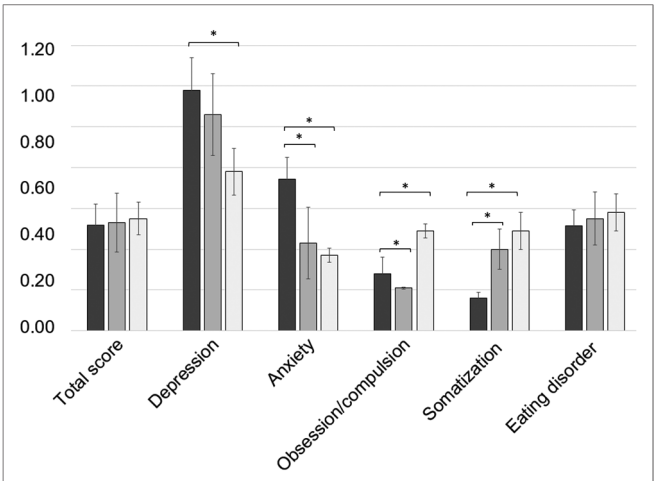

FIGURE 6 | Mean values of the ISR (ICD-10-based symptom rating) total scores and depression, anxiety, obsession/compulsion, somatization, and eating disorder of the subdimensions. The values of the study cohort are shown in dark gray. For a comparison, the values of the successfully treated PJI population are illustrated in gray, and the values of the successfully treated FRI population are in light gray. * illustrates statistical significance on a $p < 0.05$ level determined by an independent *t*-test.

during the implant-free interval was evaluated in a cohort of knee PJI and FRI patients.

Limitations

This study shows several limitations. First, the case series includes patients with PJI and FRI as indications for surgical treatment with comparatively low case numbers. Due to the small sample size, subgroup analysis is not deemed feasible as results may be statistically underpowered. Second, the focus of the study is to evaluate patients' quality of life during the implant-free interval, and, thus, no longer follow-ups and patient-reported outcome assessment after reimplantation or stable bone consolidation are seen. To overcome this limitation, the quality-of life scores were compared with previously analyzed successfully treated FRI and PJI patients.

Here, neither the summary scores of the SF-36 nor EQ-5D values showed a significant difference in comparison with the successfully treated PJI cohort followed up after 4.9 years on average. In line with these findings, it has been shown that patients treated with an arthrodesis showed a difference of only −1.82 points in the PCS and −3.56 points in the MCS of SF-36 in comparison with patients treated with debridement, antibiotics, and implant retention and a one-stage or two-stage exchange and, thus, knee arthrodesis might be deemed as a therapeutic alternative in cases with recurrent infections from a patient perspective (15). Here, 37.5% of the patients reported severe limitations with mobility, which seems low, considering that the scores were assessed 2.6 days on average after spacer implantation surgery and highlights the advantage of possible weight-bearing of the limb during the implant-free interval. In previous studies, functional scores and the range of motion were reported to be significantly better in patients treated with articulating spacers in comparison with patients with a static spacer, whereas the quality of life, as shown by the EQ-5D, was comparable (10).

The explicit psychological screening revealed enhanced levels of depression and anxiety in the study cohort. PJI and especially, a two-staged treatment, puts a high burden on the patients, leading to psychological distress and fears such as losing independency or experiencing a reinfection (29, 30). The need for psychological support has been explicitly reported by PJI patients. However, it should be noted that the psychological impact of PJI treatment is underestimated in the literature, and hitherto, no adequate strategies such as support interventions to address the mental burden of musculoskeletal infections have been investigated (31, 32).

The main benefit of the presented technique is that a variety of antibiotics can be added to PMMA cement according to the susceptibility of the underlying pathogen (33). The application of local antibiotic carriers in the form of implant coating is a feasible approach to bypass the unwanted side effects of systemic antibiotic therapy. Further, high local antibiotic concentrations can be reached, which is particularly required once a mature biofilm is established and persister cells are formed (34). Besides the advantages of the antibiotic coating, also in light of antibiotic stewardship, the temporary arthrodesis provides stability and allows early weight-bearing of the limb. Thus, especially in cases of unconsolidated fractures, the procedure provides an alternative to external stabilization.

For cement-coated intramedullary implants, removal can be highly challenging in follow-up surgeries. Debonded cement residues deep in the medullary can be surgically difficult to remove. This, in general, is time-consuming and the bone is at risk of experiencing an iatrogenic fracture. The complication

of cement debonding was reported in 23 out of 110 cases (21%) with infected nonunions treated with antibiotic cement-coated rods (35). Also, other authors reported problems with removal in 10%–25% of patients (5, 36–39). It has been suggested to remove cement debonds with a J-hook or with sequential reaming and subsequent copious irrigation of the canal using canal tip pulsed lavage in case removal fails. Often, a distal vent channel or bone fenestration is required to completely remove retaining cement (36, 40). Thus, the presented technique of reinforcement of PMMA-coated intramedullary nails with cerclage wire is beneficial for preventing such problems. Also, other techniques for preventing cement debonding have been reported, such as using threaded cores or roughening the nail surface before coating to enhance the adherence of cement (41). To note, no specific guidelines exist with regard to the techniques used to cement-coat implants in a custom-made fashion, and there is a considerable heterogeneity in the reported literature, making it challenging to arrive at a general consensus (21). In the same way, the superiority of reinforced versus unreinforced implants with regard to post-operative complications has yet be proven due to the lack of randomized comparative studies. A broken nail occurred in one case (5.0%), which has also been reported by other authors (5, 21, 37, 42). For instance, Qiang et al. used a self-made antibiotic cement rod for the treatment of intrameduallary infection reporting one broken rod (5.3%) and one complication during removal due to a too large diameter of the rod (5.3%) (36). Paley and Herzenberg performed a preliminary study with $n = 9$ cases treated with a custom-made antibiotic-impregnated cement rod for diverse indications. In one patient with an infected nonunion of the humerus, the rod broke after 2 years (5). In another cohort consisting of 67 patients with an infected arthrodesis, a broken rode (diameter 10 mm) occurred in one case (1.5%) (35).

Here, no coating-specific side effects and cement debonding during removal were observed. Notably, orthopedic surgeons have been hesitant to combine stainless steel and titanium implants due to concerns of galvanic corrosion (43). However, multiple studies have shown no clinical complications or a negative influence when mixing stainless steel and titanium implants for osteosynthesis (44–47). Thus, the reinforcement of bone cement-coated implants seems to be a beneficial option.

CONCLUSION

Reinforcement of PMMA bone cement-coated implants seems to be a reasonable treatment option to create a temporary arthrodesis to prevent detachment of the bone cement when the implant is removed.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the University Hospital Regensburg (file number 20-1681-104). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NW and MR conceptualizd the study, NW, SB, and SL acquired the data, and NW, DS, and JW analyzed the data. MR and VA supervised the project. NW and MR wrote the manuscript, and all authors revised the final version of the manuscript for any important intellectual content. All authors contributed to the article and approved the submitted version.

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Therapy of chronic extensor mechanism deficiency after total knee arthroplasty using a monofilament polypropylene mesh

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Introduction: Lesions of the quadriceps or patellar tendon after total knee arthroplasty (TKA) are a rare but serious complication which, if left untreated, can lead to loss of function of the knee joint. While acute and subacute extensor mechanism disruptions may have several causes, chronic deficiencies are often related to multiple prior revision surgeries for joint infection or aseptic TKA failure. Up to date, biological allograft reconstruction showed unsatisfying results. The use of a monofilament polypropylene mesh is a promising approach for this pathological condition. The aim of the present study was to evaluate clinical, functional and patient reported outcomes of this procedure in patients with chronic extensor mechanism deficiency.

Materials and Methods: Twenty-eight patients with chronic extensor mechanism deficiency (quadriceps tendon rupture $n = 9$, patellar tendon rupture $n = 19$) after TKA were included in this retrospective study. None of the patients were lost to follow-up. Surgical reconstruction was performed at one institution between 2014 and 2020 with a monofilament polypropylene mesh (Marlex Mesh, Bard, Murray Hill, USA). The mean age at the time of surgery was 69 years. Patients presented with a mean BMI of 33 kg/m^2. The mean follow-up period was 23 months.

Results: The 2-year survivorship free of mesh revision was 89% [95% confidence interval (CI): 75% to 100%]. Three patients (11%) had to undergo revision because of mechanical mesh failure and received another polypropylene mesh. No further revisions were performed thereafter. Flexion was 87° (range, 30–120°) on average. The majority of patients (75%, 21/28) had a full active extension. The mean active extension lag after surgery was 4 degrees (range, 0–30°).

Discussion: We observed a substantial improvement of extensor mechanism function. The majority of patients had full extension and showed good clinical results. A failure rate of over 50% has been published for alternative procedures. Thus, the use of the described augmentation technique represents a reasonable treatment option for chronic extensor mechanism disruptions of the patellar tendon as well as the quadriceps tendon after total knee arthroplasty. However, there might be a potentially higher risk for

infection persistence in periprosthetic joint infection cases due to the presence of a foreign material.

KEYWORDS

extensor mechanism disruption, quadriceps tendon, patella tendon, patella fracture, synthetic mesh, marlex mesh, monofilament polypropylene mesh

Introduction

Chronic disruption of the quadriceps or patellar tendon after total knee replacement is a rare but serious complication. These extensor mechanism insufficiencies are often associated with prior revision surgeries due to periprosthetic joint infection or aseptic TKA failure. If left untreated, this leads to substantial knee joint disfunction resulting in gradual patient immobilization. Multiple articles described various techniques for extensor mechanism reconstruction including direct repair, autologous semitendinosus and gracilis tendon grafts, achilles tendon and full extensor mechanism allografts (1–11). An even more invasive technique represents the use of rotational muscle flaps (12, 13). The main drawback of all the previously described techniques is the high failure rate. In 2011, the Mayo Clinic first described the use of a monofilament polypropylene mesh (Marlex Mesh, Bard, Murray Hill, USA) (14, 15). The described mesh has intentionally been utilized in general surgery (e.g. inguinal hernia repair) and gynecological surgical interventions (16–19). It offers substantial tensile strength and decreased foreign-body response compared with other synthetic materials. In contrast to other previously used mesh devices, the polypropylene mesh is completely integrated and intertwined by connective tissue (20, 21).

The initial study included the 3.5-year results of 13 patients with a chronic or subacute patella tendon disruption treated with this new technique. Promising results and good outcomes were reported for extensor mechanism injuries (15). A recent study analyzed 77 patients with subacute or chronic extensor mechanism deficiencies (27 quadriceps tendon disruptions, 40 patellar tendon disruptions, and 10 patella fractures) undergoing the same procedure (14). The survival free of mesh revision was 86% at 2-years. The vast majority (84%) of patients showed excellent functional outcomes. The authors reported a mean improvement in extensor lag of 26°. With regard to periprosthetic joint infection (PJI), Perry et al. reported good clinical outcomes for a group of 16 patients undergoing a two-stage exchange and Marlex Mesh reconstruction for infection after TKA (22). Due to the fact that extensor mechanism disruptions can be differentiated in acute, subacute, and chronic entities, the existing literature reveals a certain kind of heterogeneity, as patient cohorts mostly focus on subacute as well as chronic disruptions (14, 15). However, the vast majority of patients with PJI and extensor mechanism deficiency present with chronic disruptions (22). The aim of the present study was to examine the clinical, functional, and patient reported outcomes of patients with only chronic extensor mechanism deficiencies after TKA treated with a monofilament polypropylene mesh.

Materials and methods

Study design

Retrospective data collection was performed between 2014 and 2020. The study protocol was approved by the local ethics committee (registration number: EA1/035/17) and informed consent was obtained from all individuals who met the inclusion criteria which were chronic extensor mechanism disruption of either the patella- or quadriceps-tendon after previous TKA surgery. Twenty-eight patients were identified and included for further evaluation. Clinical outcomes were assessed by the Knee Injury and Osteoarthritis Outcome Score (KOOS) (23), complications and revisions were documented following an analysis of the medical records. Chronic extensor mechanism deficiency was defined as symptomatic active extension deficit of more than 10° for a time period of greater than 6 months (**Figure 1**). Postoperatively, full extension was defined as an extension lag not greater than 10°.

Surgical technique and rehabilitation protocol

We performed the surgical technique described earlier by Abdel and Hanssen (14, 15, 24, 25). With regard to the different options of mesh fixation, a trough was created in the proximal-anterior aspect of the tibia for the mesh to be cemented in place. Additionally, a lag screw was placed across the mesh and cemented into the host bone for additional fixation (**Figures 2A,B**). The mesh was then passed through a tunnel and incorporated with the remaining aspects of the host patellar tendon. At the level of the joint, it is essential to ensure that the mesh is covered with host tissue. With the limb maintained in full extension, the vastus medialis and vastus lateralis were mobilized and the mesh was sutured to the vastus lateralis, and then the vastus medialis was closed over it. Postoperatively, a stiff knee brace was applied to all patients, with the knee in full extension for 6 weeks. During this period of time, mobilization with passive flexion up to 30° was allowed. Walking was permitted with partial weight-bearing using two crutches in a knee brace locked in full extension. After 6 weeks, the knee brace was changed to an articulating brace with

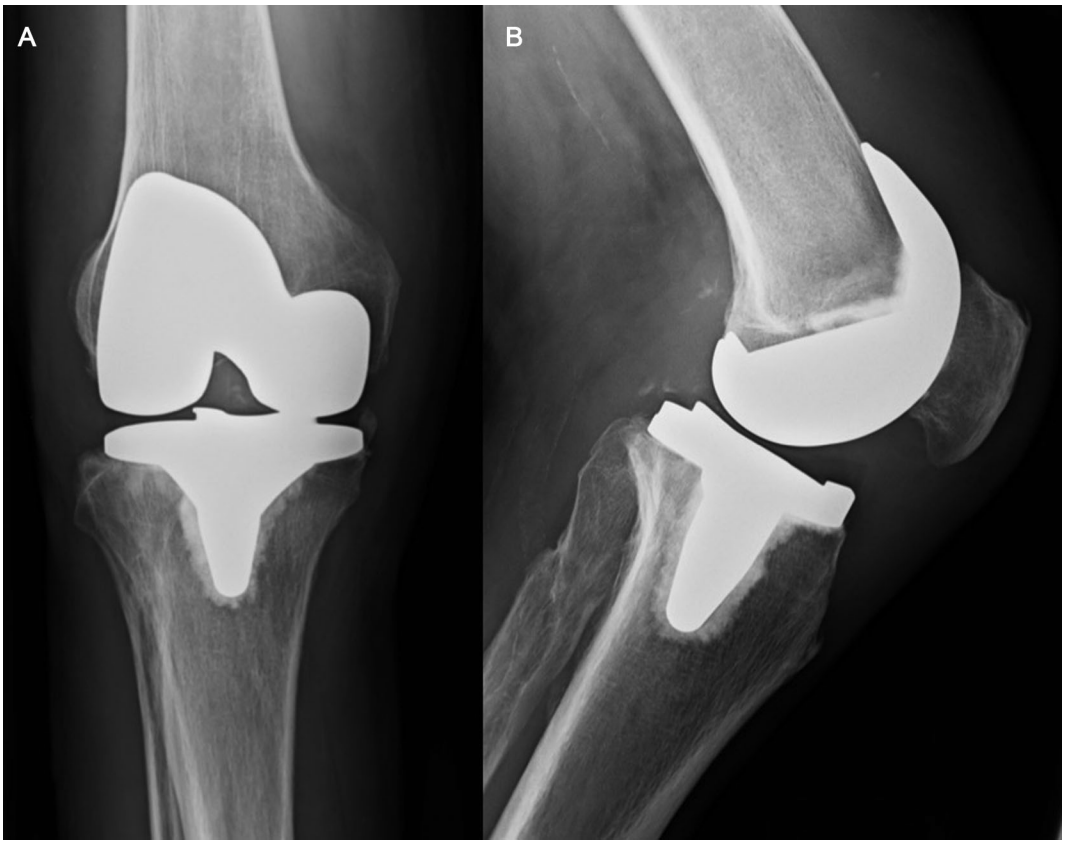

FIGURE 1
(A,B) Chronic quadriceps tendon insufficiency. Antero-posterior (A) and lateral (B) x-ray views of the knee of a patient with a chronic quadriceps tendon insufficiency. The patient sustained a traumatic quadriceps tendon rupture six weeks after primary TKA. Initial attempts of conservative treatment failed and lead to an extension lag of 20°, which was the indication for Marlex mesh reconstruction seven months after primary TKA.

a range of motion from 0 to 30° but still partial weight-bearing using two crutches. Each week, range of motion (of the articulated brace) was increased by 10° until week 12. Full weight bearing was allowed at the twelfth week after surgery.

Statistical analysis

Descriptive statistics are reported as the mean and range, or as the number and percentage. Statistical analysis was performed using SPSS, version 22 (IBM, Armonk, NY). Two-sided P values <0.05 were considered significant. Kaplan-Meier analysis was used to assess survivorship.

Results

Demographics

The study included 28 patients of which 16/28 (57%) were female. The mean age at the time of surgery was 69 years (range, 42–88 years), and the mean follow-up was 23 months (range, 5–71 months). A mean BMI of 33 kg/m^2 (range, 23–50 kg/m^2) was calculated. None of the patients was confirmed to be lost to follow-up. In 20 patients (71%), none of the components was revised at the time of the surgery. Those patients received an isolated reconstruction of the extensor mechanism. In 6 cases (21%), a simultaneous one-stage revision with monofilament polypropylene mesh implantation was performed. Two patients (7%) underwent extensor mechanism reconstruction during TKA reimplantation in the course of a 2-stage reimplantation procedure with previous interposition of a static spacer due to periprosthetic joint infection (PJI). Nineteen (68%) patients underwent surgery due to chronic patellar tendon disruptures, 9 (32%) individuals showed a chronic quadriceps tendon insufficiency. The surgeries were performed by three different high-volume surgeons (PR, TP, CP).

Survivorship and complications

A total of three patients (3/28; 11%) showed a failure of the extensor mechanism reconstruction after 7, 10 and 14 months.

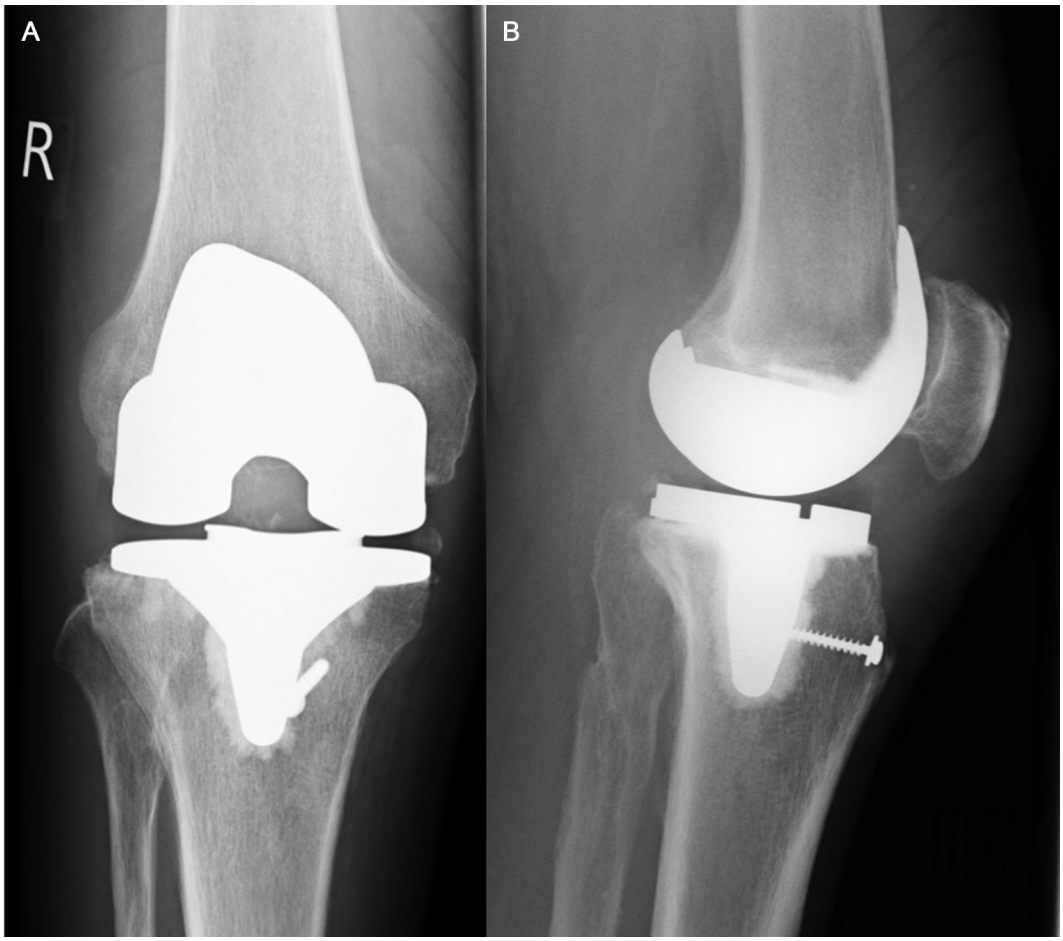

FIGURE 2
(A,B) Marlex Mesh fixation. Postoperative antero-posterior (A) and lateral (B) x-ray views of the knee three months after Marlex Mesh reconstruction. Regarding its distal fixation, a trough was created in the proximal-anterior aspect of the tibia. Additionally, a lag screw was placed across the mesh (as described under "2.2 Surgical Technique and Rehabilitation Protocol").

The reason was a torn-out mesh between the vastus lateralis and the vastus medialis obliquus. All patients underwent revision surgery using the same technique. At most recent follow-up, the revised patients had no further complications and demonstrated satisfactory clinical function. The 2-year survivorship free of mesh revision was 89% [95% confidence interval (CI): 75%–100%]. No periprosthetic joint infection was observed within the study period.

Clinical outcomes

The mean extension lag before reconstruction surgery was 35° (range, 60° to 20°). After surgery, the mean extension lag improved by 31° (range, 0°–30°) to 4° postoperatively. Seventy-five percent of patients (21/28) had full extension (between 0 and 10°) and showed good clincal results. The mean active flexion was 87° (range, 30°–120°). After surgery, patients had a mean KOOS score of 48 (range, 19–84).

Discussion

Apart from the first descriptor's institution, we report the largest series of patients for extensor mechanism reconstruction using a monofilament polypropylene mesh. To date, two major studies investigated the outcomes of this surgical intervention. The original article published in 2011 highlights the results of 13 patients who underwent extensor mechanism reconstruction for subacute or chronic patellar tendon disruption after TKA with an average follow-up of 42 months (15). Browne and Hanssen reported four (30.8%) early failures of graft reconstruction and nine (69.2%) patients with substantial clinical improvement at the time of final

follow-up. While an extensor lag improvement of 26° (36° preoperatively compared to 10° postoperatively) was achieved, knee flexion could be maintained with an average flexion ability of 107° postoperatively. Several studies with various techniques and partly high failure rates focus on extensor mechanism reconstruction after TKA. With regard to a muscle flaps based reconstruction, Whiteside et al. reported about a residual mean extension lag of 22° (11). For allograft reconstruction techniques, a residual postoperative extension lag of 8–30° and failure rates of 15%–38% were described within the short- and medium follow-up period (4, 12, 13). Compared to these techniques, our results suggest a higher rate of successful extensor mechanism reconstruction with a mean improvement of extension lag of 31° (35° preoperatively compared to 4° postoperatively) as well as a substantial lower revision rate of 11% and an average survivorship of 89% after 2 years. These results are in accordance with the largest patient series reported by Abdel et al. (14). The authors evaluated 77 mesh reconstructions and obtained an equal survivorship free of mesh failure of 85% after 2 years. With regard to an average extensor lag improvement of 26° (35° preoperatively compared to 9° postoperatively), similar results compared to our data were documented. However, we observed a decreased active knee flexion (87°) in our study compared to the above mentioned publications [107° (15) vs. 105° (14)]. These differences might be explained by a possibly different surgical technique in terms of a higher degree of mesh tensioning in full extension prior to periarticular soft tissue integration. However, this approach may also contribute to the better extensor function of our patients postoperatively (mean extension lag 4°) compared to the reported data in the literature [mean extension lag 9° (14) and 10° (15)]. Although a marked correlation between mesh tensioning and postoperative flexion ability has so far not been investigated, this hypothesis might account for the observed clinical differences. The latter also might be a reason for the mediocre average KOOS scores (48 points) of our patients. However, these results differ from the described average KSS values of Abdel et al. of 72 points. This thesis is supported by the fact that the lowest PROM scores among our patients were documented in individuals with poor postoperative flexion abilities.

Compared to the above mentioned publications by Browne et al. and Abdel et al., our study highlights three new and important aspects regarding patient age, rehabilitation protocols and chronic extensor mechanism deficiency. First, Browne et al. and Abdel et al. dealt with a mean patient age of 60, and 65 years, respectively. In contrast, our patient population was older (69 years). With regard to the excellent results of the present study, we conclude that despite a higher patient age and the related compromised biological healing potential, synthetic mesh augmentation represents a reasonable treatment option in this group of patients. Second, we applied a different and more progressive rehabilitation protocol within the postoperative course. In our study, a stiff knee brace was applied postoperatively to all patients, with the knee in full extension for 6 weeks. During this period, mobilization with partial weight-bearing and passive flexion up to 30° was allowed. In contrast, Browne et al. described a strict knee immobilization in a long leg cast for six to eight weeks before gradual flexion exercises (15). In the study by Abdel et al. a long leg cast was applied to all patients, with the knee in full extension for even 12 weeks (14). It cannot be denied that a certain amount of immobilization is key for a successful mesh integration leading to an improvement of extensor mechanism function. However, our results reveal that also by the use of a more progressive rehabilitation protocol, excellent results in terms of extensor mechanism function can be achieved. With regard to postoperative immobilization protocols, similar outcomes were observed with either a cast immobilizer or a knee immobilizer (26). Third, this is the first study solely focusing on chronic extensor mechanism deficiencies after TKA. In this regard, the existing literature deals with chronic and subacute extensor mechanism disruptions (12, 14, 26). This raises another important issue, as the definition of chronic extensor deficiency is not consistently defined throughout the literature. Against this background, our interpretation of chronic extensor mechanism deficiency was defined as symptomatic active extension deficit of more than 10° for a time period of greater than 6 months.

PJI of the knee with concurrent disruption of the extensor mechanism is a major challenge in revision surgery. However, especially in cases of periprosthetic joint infection there is a potentially higher risk for infection persistence due to the large surface of foreign material. Perry et al. reported good clinical outcomes for a group of 16 patients undergoing a two-stage exchange and Marlex Mesh reconstruction for infection after TKA (22). At 2 years, survivorship free of PJI was 87%. The mean extensor lag improved from 31° prior to resection to 3° after mesh reconstruction. The authors concluded that two-stage exchange arthroplasty combined with Marlex Mesh reconstruction of the extensor mechanism is a viable alternative to knee arthrodesis or amputation (22). However, especially in cases of difficult-to-treat pathogens, there might be a higher risk for infection persistence due to the large surface of foreign material when using this surgical technique. This study has some limitations starting with the retrospective study design and a limited mean follow-up period of 23 months. A prolonged follow-up might lead to a decreased survivorship of the Marlex Mesh reconstruction. However, a Kaplan-Meier analysis by Abdel et al. revealed an excellent midterm survivorship free of mesh revision of 89% after 2 years which is in line with our results (89%). Second, two different extensor mechanism disruptions (patellar and quadriceps tendon) were treated with the same technique. Although this constitutes a partially heterogeneous cohort, we agree with the above-mentioned authors that this technique can be seen as an

universal surgical approach for any extensor mechanism disruption. Third, a uniform definition of successful extensor mechanism reconstruction as well as a uniform definition of chronic extensor mechanism deficiency after TKA is missing throughout the existing studies. While some authors define a successful outcome as full extension or near-full extension (lag of <10°) (14), others do not consistently quantify their interpretation of treatment success with regard to a certain extensor lag threshold (12, 26, 27). Hence, a standardized and uniform classification is needed to provide a sufficient disease- and outcome-specific comparability between studies. In conclusion, the use of a monofilament polypropylene mesh for reconstructing a chronic extensor mechanism deficiency (quadriceps or patella tendon rupture) after TKA showed a good revision free survivorship. The investigated technique demonstrated substantial functional improvements and revealed a distinct decrease of complications compared to other surgical techniques. However, patients need to be informed precisely about the limited flexion ability after surgery. Additionally, in cases of PJI there might be a higher risk for infection persistence which should further be investigated.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethikkommission der Charité Universitätsmedizin Berlin, Berlin, Germany. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MF: Investigation, data curation, writing (original draft). CG: Formal analysis, consulting, writing (review) NM: Clinical sample acquisition, data acquisition TP: writing (review and editing). CP: Conceptualization, methodology, writing (review) PR: statistics, supervision, writing (original draft). All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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C-reactive protein to lymphocyte ratio as a new biomarker in predicting surgical site infection after posterior lumbar interbody fusion and instrumentation

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Purpose: This study aims to evaluate the potential of C-reactive protein to lymphocyte count ratio (CLR) for the prediction of surgical site infection (SSI) following posterior lumbar interbody fusion (PLIF) and the instrumentation of lumbar degenerative diseases.

Methods: In this retrospective study, we considered patients with a lumbar degenerative disease diagnosis surgically treated by the instrumented PLIF procedure from 2015 to 2021. Patient data, including postoperative early SSI and other perioperative variables, were collected from their respective hospitalization electronic medical records. The receiver operator characteristic curve was constructed to determine the optimal cut-off value for CLR, and the ability to predict SSI was evaluated by the area under the curve (AUC). According to the cut-off value, patients were dichotomized with high- or low-CLR, and between-group differences were compared using univariate analysis. The independent impact of CLR on predicting SSI was investigated by multivariate logistics regression analysis.

Results: A total of 773 patients were included, with 26 (3.4%) developing an early SSI post-operation. The preoperative CLR was 11.1 ± 26.1 (interquartile range, 0.4–7.5), and the optimal cut-off was 2.1, corresponding to a sensitivity of 0.856, a specificity of 0.643, and an AUC of 0.768 (95% CI, 0.737–0.797). CLR demonstrated a significantly improved prediction ability than did lymphocyte count ($P = 0.021$) and a similar ability to predict an infection as C-response protein ($P = 0.444$). Patients with a high CLR had a significantly higher SSI incidence than those with a low CLR (7.6% vs. 0.8%, $P < 0.001$). After adjustment for numerous confounding factors, CLR ≥ 2.1 was associated with an 11.16-fold increased risk of SSI, along with other significant variables, i.e., diabetes, preoperative waiting time, and surgical duration.

Abbreviations

CLR, C-reactive protein to lymphocyte count ratio; PLIF, posterior lumbar interbody fusion; SSI, surgical site infection; CRP, C-response protein; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ASA, American Society of Anesthesiologists; WBC, white blood cell; FBG, fasting blood glucose; SD, standard deviation; ROC, receiver operator characteristic; AUC, area under the curve; OR, odds ratio; H–L, Hosmer–Lemeshow

Conclusion: A high CLR exhibited an improved ability to predict incident SSI and was associated with a substantially increased risk of SSI following instrumented PLIF. After better-design studies verified this finding, CLR could potentially be a beneficial tool in surgical management.

KEYWORDS

posterior lumbar interbody fusion, perioperative management, risk prediction tool, creative protein to lymphocyte count ratio (CLR), surgical site infection

Introduction

Postoperative surgical site infection (SSI) remains a major issue after spinal surgeries, despite adequate prophylactic antibiotics being routinely administered before and after surgery (1). Compared to other approaches, the instrumented posterior lumbar interbody fusion (PLIF) procedure is more likely to be affected by postoperative SSI, and the incidence rate was reported to vary from 1.5% to 7.2% (2–6). SSI is an intractable issue that is resistant to antibiotics in half of the cases, whereby 30% necessitated revision surgery or implant removal (3). Furthermore, even if managed promptly and appropriately, patients with SSI would have greater long-term back pain and less than half of the probability (27% vs. 60%) of achieving a minimum clinically important difference compared to those without (7). Besides, the substantial economic burden from prolonged hospitalization stays, readmission for revision procedures, and nursing care significantly impacted patients and their families (8, 9).

The preoperative identification of patient and clinical factors or biomarkers that effectively predict the postoperative SSI can inform risk evaluation and stratification, facilitating the implementation of targeted prevention measures, which should thus aid in the avoidance of excessive medical resource consumption and the chance of resultant antibiotic resistance. In contrast with patient and clinical factors that are sometimes subjective and obtuse in showing body status (e.g., body's response to tissue injury, inflammatory, and immune status), and SSI, serum biomarkers are more sensitive, objective, and prompt (10). For example, C-response protein (CRP) is a biomarker and is not only a typical acute phase reactant protein in response to inflammation but also an indicator of injury duration in the face of repeated tissue injury (11). The ability of elevated serum CRP concentration to predict SSI after spinal surgeries has been extensively demonstrated in recent studies (12, 13), which was appraised as "more predictive than prehistoric" (13). However, false negatives were often encountered for various reasons, including the low sensitivity in low-virulence-bacterial infections where serum CRP concentration was low (14, 15). Similar observations have also been shown for another biomarker, lymphocyte count (12, 16, 17), which is also particularly important for the immune response state. However, a previous study determined the optimal cut-off of both CRP and lymphocyte to be within the normal reference range, e.g., 4.4 mg/L (reference range, <8 mg/L) for CRP, and 1.2×10^9/L (reference range, $1.1–3.2 \times 10^9$/L) for lymphocyte count, respectively (12), thus limiting their clinical viability. In other words, the "seemingly normal" value for a biomarker is underpowered to alert the treating surgeons to the increased risk of SSI following surgery.

We conducted this study by considering their indicative value of inflammatory/immune status, the demonstrated ability to predict SSI, and their inherent limitations. We hypothesize that CRP to lymphocyte ratio (CLR), derived from both biomarkers, is a better index than predicting SSI after instrumented PLIF. We also hypothesize that high CLR is independently associated with an increased risk of SSI.

Methods

This retrospective study was performed following the Helsinki Declaration. The study protocol was approved by the ethics committee of the local institution, which waived the need for informed consent because of the identification anonymity.

Patient electronic medical records were retrieved to identify those who underwent an instrumented PLIF procedure for a lumbar degenerative disease, i.e., degenerative disc disease, spondylolisthesis, spinal stenosis, or a combination of the above, in our hospital, between January 2015 and December 2021. The inclusion criteria were age ≥18 years and complete medical records. The exclusion criteria were procedures other than an instrumented PLIF, obvious symptoms, signs, or preexisting conditions directly affecting the preoperative CRP concentration or lymphocyte count (e.g., respiratory or urinary tract infection, autoimmune hepatitis, liver cirrhosis, rheumatoid arthritis, tumor, etc.), past surgery at lumbar vertebra, primary or metastatic lumbar tumor, or incomplete medical records.

The instrumented PLIF procedure was performed with total facetectomy and subtotal intervertebral discectomy for adequate posterior decompression, cages with local or allergenic bone graft inserted into the intervertebral space, and fixation of a

fused segment with a screw-rod system. The operations were performed by six orthopedic or spinal surgeons. As per the standard guidelines, prophylactic intravenous single-dose cephalosporins (e.g., cefazolin and cefamandole nafate) were routinely administered 30 min prior to skin incision. For operative procedures exceeding 3 h, an additional dose would be given. After the operation, prophylactic antibiotics were routinely administered. However, the duration relied on the perceived individualized risk of infection, often one to three days and occasionally up to one week, which was at the discretion of their treating surgeons.

Identification of SSI cases

Reviewing the electronic medical records, we identified early SSIs during hospitalization. The US Center for Disease Control and Prevention 2017 was used to diagnose and classify SSI (18). A superficial SSI refers to an infection involving skin and subcutaneous tissues with possible symptoms or signs (i.e., redness, tenderness, heat, and pain over the wound site) and can be resolved by local wound care and antibiotics treatment without the need for surgical intervention. Deep SSI refers to an infection involving the deep issue (i.e., fascia, muscle tissues, or vertebra space), with resultant marked serious symptoms/signs (e.g., fever, pain, tenderness, persistent wound discharge or dehiscence, abscess or gangrenosis), often requiring surgical intervention.

Calculation of CLR and measurements

Blood sampling and testing were performed following the manufacturer's instructions. CLR was calculated by dividing the serum CRP concentration in mg/L by the lymphocyte count in 10^9/L. A preoperative blood sample was extracted to obtain the measurements. For patients with multiple measurements for biomarkers of interest (including CRP, lymphocyte count, and the below-mentioned ones), the one closest to the operation was chosen to minimize the time-dependent effect. Using the manufacturer's recommended cut-offs, these biomarkers were interpreted, and the normal range was <8 mg/L or $1.10–3.20 \times 10^9$/L for CRP and lymphocytes.

Variables of interest

Two researchers (XW and XM) extracted the variables of interest from the medical records. These included socioeconomic features (age, gender, type of insurance), lifestyle (current smoking, alcohol drinking), comorbidities [body mass index (BMI) calculated by dividing body weight in kilograms by square of height in meters, diabetes, hypertension, heart disease, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), renal insufficiency, peripheral vascular disease, past any operation in the lumbar spine], surgery-related variables [preoperative waiting time, American Society of Anesthesiologists (ASA) score, operated levels, surgical duration, intraoperative bleeding, allogeneic blood transfusion, allograft bone use, postoperative prophylactic use of antibiotics], and laboratory test results [albumin, white blood cell (WBC), neutrophil, lymphocyte, red blood cell (RBC) and platelet count, hematocrit, hemoglobin, and fasting blood glucose (FBG)].

Statistical analysis

Continuous data were presented with a mean ± standard deviation (SD), and their normality status was detected employing a Kolmogorov–Smirnov test. A Student *t*-test or Mann–Whitney-*U* test was performed based on the normality status, as appropriate. Categorical data were presented with figures and percentage values, and a between-group comparison was performed by a Chi-square test or Fisher's exact test.

The optimal cut-off value of CLR to predict SSI was determined by the receiver operating characteristic (ROC) curve when the Youden index (specificity plus sensitivity −1) was maximized. The corresponding sensitivity, specificity, and area under the ROC curve (AUC) with a 95% confidence interval (95% CI) were calculated. Additionally, a similar method was used for CRP and lymphocyte count for comparison purposes. The AUCs for three biomarkers were pairwise compared by a Z-test (19), using the MedCalc software version 14.8.1 (MedCalc Software Ltd, Ostend, Belgium).

Based on the above-determined optimal cut-off value of CLR, patients were dichotomized into the high- or low-CLR groups, and the differences were detected by univariate analysis. Variables tested with $P < 0.10$ during univariate analysis were further selected for adjustment in the multivariate logistic regression model, using the "enter" method to minimize the confounding effects. The magnitude of CLR associated with SSI was indicated by odds ratios (ORs) and 95% CI. The goodness-of-fit of the multivariate model was evaluated by the Hosmer–Lemeshow (H–L) test, with $P > 0.05$ indicating an acceptable result and a higher Nagelkerke R^2 value (normal range, <1.0) suggesting a better result. $P < 0.05$ was set as the statistical significance level. The analysis was performed using SPSS 26.0 (IBM, Armonk, New York, USA).

Results

There were 773 patients (348 males and 425 females), with an average age of 51.8 ± 12.8 years. The mean preoperative stay was 3.3 ± 2.4 days, and the operating level was 2.1 ± 1.8. Of the patients, 13.8% (107/773) received an allogeneic bone or bone substitute graft, and 32.7% (253/773) received an intraoperative allogeneic transfusion. The surgical time for the procedure was 175.6 ± 51.1 min, and approximately half (45.8%, 354/773) had a procedure lasting above 3 h. Postoperatively, prophylactic antibiotics use ≥3 days was administered in 21.1% (163/773) of the patients. In total, 26 (3.4%) patients had an early SSI postoperatively, including 12 (1.6%) deep and 14 (1.8%) superficial SSIs.

The preoperative CLR was 11.1 ± 26.1, with a range of 0–215.8 (interquartile range, 0.4–7.5). The ROC curve determined the optimal cut-off as 2.1; the corresponding sensitivity and specificity were 0.856 and 0.643, respectively; the AUC was 0.768 (95%CI, 0.737–0.797). Patients with a high CLR had a significantly higher SSI incidence rate than those with a low CLR (7.6%, 22/289 vs. 0.8%, 4/484; crude OR = 9.2; $P < 0.001$). The optimal value of CRP was 4.0 mg/L, corresponding to the sensitivity, specificity, and AUC of 0.808, 0.651, and 0.759 (95% CI, 0.727–0.789), respectively. Meanwhile, the cut-off value for lymphocyte count was 1.5, and the sensitivity, specificity, and AUC were 0.681, 0.692, and 0.660 (95% CI, 0.555–0.765), respectively (**Figure 1**). The Z-test demonstrated a significantly improved prediction ability of CLR compared to that of lymphocyte count (Z value, 2.309; $P = 0.021$), but was nonsignificant compared to CRP (Z value, 0.765; $P = 0.444$). It was nonsignificantly different from CRP with lymphocyte count (Z value, 1.723; $P = 0.085$).

Patients with a high CLR value were significantly different from those with a low CLR value in terms of age in the form of either continuous ($P = 0.007$) or categorical variables ($P = 0.006$), prevalence of obesity ($P = 0.031$), hypertension ($P = 0.031$), diabetes ($P = 0.036$), peripheral vascular disease ($P < 0.001$), preoperative waiting time ($P < 0.001$), allograft bone ($P < 0.001$), intraoperative bleeding ($P < 0.001$), allogenic blood transfusion ($P < 0.001$), surgical duration ($P = 0.010$), WBC count ($P < 0.001$), albumin <35 g/L ($P < 0.001$), FBG > 6.1 mmol/L ($P < 0.001$), neutrophil count $>6.3 \times 10^9$/L ($P < 0.001$), lymphocyte count ($P < 0.001$), RBC count ($P < 0.001$), hemoglobin ($P < 0.001$), and hematocrit ($P < 0.001$) (**Table 1**).

The multivariate logistic regression analysis, adjusted for the above significant variables and those with $P < 0.10$ (BMI in continuous form, ASA score, and history of any operation), displayed that CLR ≥ 2.1 was associated with an 11.16-fold increased risk of SSI. The other significant variables included diabetes (OR, 3.31; 95% CI, 1.04–9.55), preoperative waiting time in a day (OR, 1.16; 95% CI, 1.01–1.35), and surgical duration in each 30-min increment (OR, 1.24; 95% CI, 1.06–1.59) (**Table 2**). The H–L test showed an acceptable goodness-of-fit of the multivariate model ($P = 0.537$, Chi-square = 6.993; Nagelkerke $R^2 = 0.273$).

Discussion

We verified our previous study reported that preoperative high CLR value (≥2.1) was significantly associated with an 11.16-fold risk of SSI following instrumented PLIF for lumbar degenerative disease. We also found that CLR indicated a better predicting ability, with an AUC of 0.768, a significant difference for lymphocyte count (AUC, 0.660; $P = 0.021$), but nonsignificant for CRP (AUC, 0.759; $P = 0.444$). CLR revealed a higher sensitivity than the original index (CLR, 0.856; CRP, 0.808; and lymphocyte count, 0.681).

SSI is a disastrous complication after spinal orthopedics or other surgeries, and exploring the potential new indexes has been a primary task in clinical research. However, existing risk prediction models based on identified clinical risk factors demonstrated less robustness in predicting postoperative SSI (2, 20–22). The underlying reasons are related to the heterogeneous population and the time-dependent confounding effects of biomarkers. On the other hand, patient self-reported comorbidities as a component of a risk prediction model were a contributor since these self-reported medical conditions may not mirror the true pathophysiological basis. An ideal prediction tool should be readily accessible, easy to use, and rely upon preoperatively routinely measured laboratory parameters. Inflammation/immune biomarkers fit these characteristics well, and more importantly, they are often highly sensitive to the body's pathophysiologic response and have been presenting notable changes before clinical signs or manifestations emerge (23).

During the past decade, numerous derived novel biomarkers have been employed in research and in clinical practice, demonstrating good prognostication for clinical outcomes or complications, including Modified Glasgow Prognostic Score (mGPS), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), CRP to albumin ratio (CAR), systemic immune-inflammation index (SII), fibrinogen to albumin ratio (FAR), lymphocyte to monocyte ratio (LMR), and monocyte to high-density lipoprotein ratio, among others (24–28). As for CLR or lymphocyte to CRP ratio (LCR), the previous studies on surgical tumors (osteosarcoma, gastric cancer, lung cancer, or pancreatic cancer) (29–31) and on infectious events following surgeries (32–34) have demonstrated its effectiveness in providing prognostic information. To the best of our knowledge, this study was the first to apply CLR in spinal orthopedic surgeries to predict the incidence of postoperative SSI.

In this study, CLR demonstrated better predictive ability than the original index, lymphocyte count, or CRP, with AUC

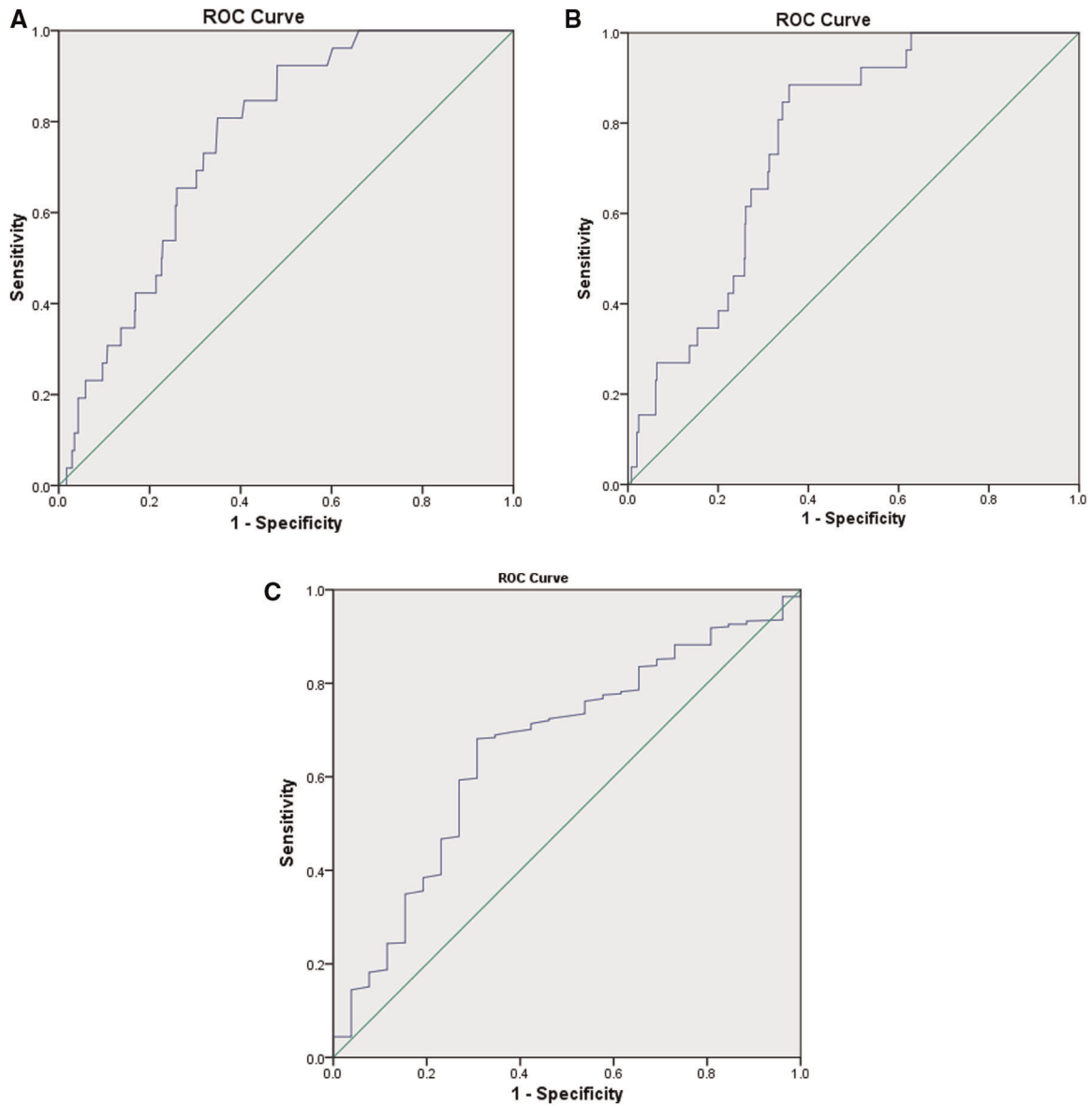

FIGURE 1
The ROC curves were constructed to determine the optimal cut-off values for CLR, CRP, and lymphocyte count. The optimal cut-off of CLR was 2.1, corresponding to a sensitivity of 0.856, specificity of 0.643, and an AUC of 0.768 (95% CI, 0.737–0.797) (**A**). The optimal value of CRP was 4.0 mg/L, corresponding to a sensitivity of 0.808, specificity of 0.651, and AUC of 0.759 (95% CI, 0.727–0.789) (**B**); while for lymphocyte count, the cut-off value was 1.5, and the sensitivity, specificity, and AUC was 0.681, 0.692, and 0.660 (95% CI, 0.555–0.765) (**C**). AUC, area under the curve; CLR, C-reactive protein to lymphocyte ratio; CRP, C-response protein; ROC, receiver operator characteristic.

increasing from 0.660 and 0.808 to 0.868 (*P* value, 0.021 and 0.444). This suggests that the predictive effect of this new biomarker was remarkably strengthened after the division calculation, which was related to the simultaneous uptrend of CRP and downtrend of the lymphocyte count. Most importantly, the predictive effect *via* this cut-off (≥2.1) is, albeit related to CRP and lymphocyte count, incompletely dependent on either one taken individually. In other words, CLR could still exceed the cut-off value even if both biomarkers are simultaneously in reference intervals. The identified optimal cut-off value of CRP and lymphocyte count was exactly within the range of the manufacturer's reference interval (CRP: cut-off, 4.0 mg/L; reference interval, <8 mg/L; lymphocyte count, cut-off, 1.5×10^9/L; reference interval, 1.1 to 3.2×10^9/L). In clinical practice, applying this seemingly normal value as a cut-off for either CRP or lymphocyte count is hardly possible to alert healthcare providers of the substantially increased risk of postoperative SSI. Therefore,

TABLE 1 Univariate analysis of factors associated with CLR.

Variables	Number (%) of patients with CLR ≥ 2.1 (n = 289)	Number (%) of patients with CLR < 2.1 (n = 484)	P
Gender (male)	132 (45.7)	216 (44.6)	0.777
Age (year)	53.3 ± 13.7	50.8 ± 12.2	0.007
<45	67 (23.2)	136 (28.1)	0.006
45-64	158 (54.7)	283 (58.5)	
≥65	64 (22.1)	65 (13.4)	
BMI	25.9 ± 4.0	25.5 ± 3.4	0.095
Obesity (BMI ≥ 28 kg/m^2)	78 (27.0)	98 (20.2)	0.031
Hypertension	93 (32.2)	122 (25.2)	0.036
Diabetes mellitus	50 (17.3)	48 (9.9)	0.003
Heart disease	22 (7.6)	28 (5.8)	0.318
COPD	14 (4.8)	21 (4.3)	0.744
Cerebrovascular disease	23 (8.0)	37 (7.6)	0.875
Peripheral vascular disease	40 (13.8)	22 (4.5)	<0.001
Preoperative waiting time	4.5 ± 3.1	2.7 ± 1.6	<0.001
Total hospital stay	16.1 ± 6.1	12.7 ± 3.9	<0.001
Current smoking	61 (21.1)	93 (19.2)	0.524
Alcohol drinking	87 (30.1)	150 (31.0)	0.796
Previous operation in any site	58 (20.1)	123 (25.4)	0.090
Operated levels	2.2 ± 1.7	2.1 ± 1.9	0.715
allogeneic bone or bone substitute			<0.001
No	210 (72.7)	456 (94.2)	
Yes	79 (27.3)	28 (5.8)	
ASA score			0.076
I	19 (6.6)	50 (10.3)	
II–IV	270 (93.4)	434 (89.7)	
Intraoperative bleeding (ml)	771.2 ± 390.5	546.8 ± 292.8	<0.001
Allogenic blood transfusion	132 (45.7)	121 (25.0)	<0.001
Surgical duration (minutes)	171.8 ± 55.4	162.0 ± 48.1	0.010
Postoperative antibiotic use ≥3 days	57 (19.7)	106 (21.9)	0.473
WBC (>10 × 10^9/L)	146 (50.5)	40 (8.3)	<0.001
Albumin (<35 g/L)	100 (34.6)	5 (1.0)	<0.001
FBG (>6.1 mmol/L)	130 (45.0)	76 (15.7)	<0.001
Neutrophil (>6.3 × 10^9/L)	184 (63.7)	49 (10.1)	<0.001
Lymphocyte (<1.1 × 10^9/L)	109 (37.7)	23 (4.8)	<0.001
Platelet (>300 × 10^9/L)	29 (10.0)	41 (8.5)	0.464
RBC (<Lower limit)	86 (29.8)	16 (3.3)	<0.001
Hemoglobin (<Lower limit)	75 (26.0)	27 (5.6)	<0.001
Hematocrit (<Lower limit)	143 (49.5)	50 (10.3)	<0.001

(*continued*)

TABLE 1 Continued

Obesity, defined as a BMI ≥ 28 kg/m^2, in accordance with the criteria fitted for Chinese adults. RBC reference range: female, 3.5–5.0 × 10^{12}/L; males, 4.0–5.5 × 10^{12}/L; hemoglobin reference range: females, 110–150 g/L; males, 120–160 g/L; hematocrit reference range: females, 35%–45%; males, 40%–50%.
COPD, chronic obstructive pulmonary disease; CLR, C-response protein to lymphocyte ratio; BMI, body mass index; ASA, American Society of Anesthesiologists; FBG, fasting blood glucose; WBC, white blood cell; RBC, red blood cell.

TABLE 2 Multivariate analysis of CLR in association with SSI after adjustment for numerous variables[a].

Variables	OR (95% CI)	P
CLR ≥ 2.1	11.16 (3.71–27.43)	<0.001
Diabetes	3.31 (1.04–9.55)	0.014
Preoperative waiting time (each day increment)	1.16 (1.01–1.35)	0.048
Surgical duration (each 30-min increment)	1.24 (1.06–1.59)	0.029

[a]Multivariate model adjusted for age, hypertension, diabetes, peripheral vascular disease, history of any surgery, preoperative waiting time, allogeneic bone graft, ASA score, allogenic blood transfusion, surgical duration, BMI, albumin, FBG, WBC, neutrophils, RBC, HGB, and HCT.
CLR, C-response protein to lymphocyte ratio; SSI, surgical site infection; OR, odds ratio; CI, confidence interval; BMI, body mass index; ASA, American Society of Anesthesiologists; FBG, fasting blood glucose; WBC, white blood cell; RBC, red blood cell; HGB, hemoglobin; HCT, hematocrit.

CLR can be considered a pragmatic and independent predictive tool.

The other clinical importance of using CLR is guiding postoperative administration. In this study, CLR ≥ 2.1 corresponds to a sensitivity of 0.856, suggesting that patients with a CLR < 2.1 are at low risk (0.8%, 4/484) of postoperative SSI and can thus be considered to execute "no antibiotic strategy" or "less use strategy" postoperatively, to reduce the possibility of multiple drug-resistant bacteria. It is worth noting that CLR's specificity is only 0.643, suggesting a high probability of false positive results. Therefore, a positive CLR result is a determiner of active preventive interventions; combined systemic medical conditions and local operative conditions (i.e., lumbar disease *per se*) should be evaluated for an informed decision.

The results show that preoperative CLR, derived from CRP and lymphocyte count, is a feasible and predictive biomarker for the early incidence of SSI following instrumented PLIF procedures for degenerative lumbar diseases. An elevated CLR $\geq$ 2.1 was independently associated with an 11.15-fold risk of SSI. This value may alert surgeons of the high risk of postoperative SSI, better facilitating the implementation of feasible targeted preventive measures.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: In accordance with the institutional policy, data used in this study are not available publicly but can be obtained from the corresponding author upon justified request for scientific research purposes. Requests to access these datasets should be directed to Xun Ma, xunmadoc1776@126.com.

Ethics statement

This study was approved by the Ethics Committee of the Third Hospital of Shanxi Medical University (No. 2022-095), which waived the need for informed consent because of the identification anonymity.

Author contributions

XM conceived the idea and designed the study. XW and XM inquired about the medical records and collected the data. JZ prepared the figures and tables and CC performed the statistical analyses. All the authors interpreted the data and contributed to the preparation of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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D-lactate is a promising biomarker for the diagnosis of periprosthetic joint infection

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Introduction: Reliable biomarkers for the diagnosis of periprosthetic joint infection (PJI) are of paramount clinical value. To date, synovial fluid leukocyte count is the standard surrogate parameter indicating PJI. As D-lactate is almost solely produced by bacteria, it represents a promising molecule in the diagnostic workflow of PJI evaluation. Therefore, the purpose of this study was to assess the performance of synovial fluid D-lactate for diagnosing PJI of the hip and knee.
Materials and Methods: These are preliminary results of a prospective multicenter study from one academic center. Seventy-two consecutive patients after total hip arthroplasty (THA) or total knee arthroplasty (TKA) were prospectively included. All patients received a joint aspiration in order to rule out or confirm PJI, which was diagnosed according to previously published institutional criteria. Synovial fluid D-lactate was determined spectrophotometrically at 450 nm. Receiver operating characteristic (ROC) analysis was performed to assess the diagnostic performance.
Results: Eighteen patients (25%) were diagnosed with PJI and 54 patients (75%) were classified as aseptic. Synovial fluid D-lactate showed a sensitivity of 90.7% (95% CI: 79.7%–96.9%) and specificity of 83.3% (95% CI: 58.6%–96.4%) at a cut-off of 0.04 mmol/L. The median concentration of D-lactate was significantly higher in patients with PJI than in those with aseptic conditions (0.048 mmol/L, range, 0.026–0.076 mmol/L vs. 0.024 mmol/L, range, 0.003–0.058 mmol/L, $p < 0.0001$). The predominat microogranisms were staphylococci, followed by streptococci and gram-negative bacteria.
Conclusion: D-lactate bears a strong potential to act as a valuable biomarker for diagnosing PJI of the hip and knee. In our study, a cutoff of 0.04 mmol/L showed a comparable sensitivity to synovial fluid leukocyte count. However, its specificity was higher compared to conventional diagnostic tools. The additional advantages of D-lactate testing are requirement of low synovial fluid volume, short turnaround time and low cost.

KEYWORDS
biomarker, periprosthetic joint infection, d-lactate, septic revision, diagnostic tool

Introduction

Worldwide, the numbers of total joint arthroplasty revision surgeries are constantly rising (1). One of the main indications for these procedures are periprosthetic joint infections (PJI), which occur in 0.3%–4% of all primary arthroplasties with even higher rates of up to 15% in revision surgeries (2–4). The diagnostic workflow of PJI

evaluation includes various examinations, taking into account individual serum CRP levels, synovial leucocyte cell analyses as well as microbial and histopathological findings (5–7). While the existing PJI classifications lead to fair results, the correct diagnostic assessment of low grade infections in particular is challenging (8, 9). Consequently, current studies focus on the evaluation of new biomarkers in this theme (10–12). However, a single diagnostic tool with sufficient sensitivity and specificity is still missing. An explanation for this might be the fact, that the vast majority of recently investigated synovial biomarkers such as procalcitonin, alpha defensin, IL-1 and IL-6 are linked to the innate immunity (13–15). Therefore, these parameters are not specific for bacterial infections and can also be elevated in patients with systemic inflammatory diseases or within the early postoperative period (16–18). In contrast, the molecule D-lactate is the predominant form of lactate produced by different bacterial species. Due to the fact that it is almost solely produced by bacteria, D-lactate was shown to be a promising marker for the diagnosis of bacterial infections such as meningitis and septic arthritis (19).

Currently, a few studies evaluated the potential of D-lactate as a biomarker for PJI of the hip and knee. In 2019, Yermak et al. conducted a prospective observational study in which the authors reported about a similar performance of synovial fluid D-lactate concentration compared to synovial fluid leucocyte cell count for PJI assessment (20). With respect to the existing classification systems, Karbysheva et al. further reported about a sensitivity of D-lactate between 92%–94% and a specificity of 78%–89% in determining PJI (21). However, considering the defined quantitative thresholds, the three existing studies on this topic reveal significant variations. As such, the described synovial D-lactate cut-off differentiating between septic and aseptic conditions varies from 0.05 to 1.26 mmol/L (20–23). This heterogeneity according to the current state of relevant studies requires further scientific analyses. Therefore, the aim of this study was to evaluate the performance of D-lactate in synovial fluid as an independent diagnostic tool and define the optimal cut-off for diagnosing PJI.

Material and methods

Study design

These are preliminary results of a prospective multicenter study from one academic center. Between 1st of March 2020 and 1st of March 2021, consecutive patients aged 18 years or older who underwent a joint aspiration were considered for study inclusion. The following inclusion criteria were applied: (1) patients with a painful total hip (THA) or knee arthroplasty (TKA); (2) patients with progressive radiolucent lines after THA or TKA; (3) patients with scheduled THA or TKA revision surgery. The study was approved by the local ethics committee (registration number: FSta 40/20). Informed consent was obtained from all patients before participation. A standardized case-report form was used to collect patient history, demographic, clinical, radiological, microbiological, histopathological and laboratory data. All patients were evaluated by an interdisciplinary team consisting of orthopaedic surgeons and infectious diseases specialists. The study was performed in accordance with the Declaration of Helsinki. The D-lactate results were not communicated to the treating physician and thus did not influence individual infection management. A total of 121 participants were screened for study eligibility. Twenty-four synovial samples showed specimen clotting. Nineteen samples had an insufficient synovial fluid volume for laboratory analysis. Furthermore, 6 patients declined study participation. Thus, a total of 72 patients were included for further evaluation.

Sample collection and preparation

Synovial fluid was aspirated under sterile conditions preoperatively in the outpatient department or intraoperatively during revision surgery *via* joint aspiration after skin incision and subcutaneous preparation before opening the joint capsule. Immediately after joint puncture, 1–3 ml of synovial fluid were inoculated into a pediatric blood culture bottles (BacTec PedsPlus/F, Beckton Dickinson and Co, USA) and 1 ml was introduced in a native vial for aerobic and anaerobic culture. An aliquot of 0.5–1 ml synovial fluid was collected in a native vial for D-lactate test, deproteinized and stored at −80°C until analysis. The remaining fluid was used for leucocyte count evaluation (1–2 ml). In cases of revision surgery, 3–5 periprosthetic tissue biopsies were collected intraoperatively from the implant-bone or cement-bone interface for microbiological and histopathological analysis. The explanted prostheses were collected in sterile containers and sent for sonication.

Diagnosis of periprosthetic joint infection

PJI was defined according to previously published institutional criteria (21, 24–26). The different classification-based parameters include clinical features (visible purulence, presence of sinus tract), synovial fluid leukocytes ($>2 \times 10^3/\mu l$), granulocyte percentage (>70%), histopathology, and cultures of synovial fluid, periprosthetic tissue and sonication fluid. Cultures were considered positive if a high-virulent organism grew in ≥1 specimen of synovial fluid, periprosthetic tissue or sonication (*Staphylococccus aureus, Enterobacteriaceae, Streptococcus* spp., *Candida* spp.) or low-virulent organism

grew in ≥2 specimen (*coagulase-negative staphylococci, enterococci, Cutibacterium* spp., *and other bacteria of the skin microbiome*). Sonication was considered positive if ≥1 CFU/ml of a high-virulent organism or >50 CFU/ml of a low- virulent organism grew in sonication fluid. The types of PJI were defined with regard to their temporal context in relation to the primary joint arthroplasty as previously described by Zimmerli et al. (5). Thus, the respective types of PJI were differentiated in early (those that developed less than 3 months after surgery), delayed (3 to 24 months after surgery) and late conditions (more than 24 months after surgery).

Microbiological analysis of synovial fluid, sonication and periprosthetic tissue samples

One to three ml synovial fluid were inoculated in pediatric blood culture bottles and incubated at 36 ± 1°C for 14 days or until growth was detected. Additionally, synovial fluid samples of 0.1 ml aliquots were placed onto tryptic soy agar with 5% sheep blood for aerobic and anaerobic culture. The aerobic cultures were incubated at 37°C and inspected daily for 7 days, and the anaerobic ones were incubated for 14 days. The colonies of microorganism were identified by standard microbiological methods using automated system VITEK 2 (BioMérieux, Marcy L'Etoile, France). Tissue samples were cultured as described above. Sonication was performed according to a previously described protocol (27).

Determination of synovial fluid D-lactate

D-lactate was determined in synovial fluid using D-Lactate Colorimetric Assay Kit (Abcam, Cambridge, UK). Laboratory analysis and sample preparation was performed according to the kit instruction. For the spectrophotometric assay, 40 µl of synovial fluid were used. A calibration curve with D-lactate standard solutions was calculated with each batch. After incubation at room temperature for 30 min, the optical density was measured at absorbance of 450 nm using a Microplate Absorbance Reader (DYNEX Technologies MRX, Chantilly VA, USA) and calculated to molar concentration using a calibration curve. The turnaround time amounts to 2 h.

Statistical analysis

The significance level in all testing procedures was predetermined at $p < 0.05$. Quantitative data were presented as median and range or mean and standard deviation (SD), as appropriate. Statistical significance between the groups was assessed using the Mann–Whitney test. The sample size was calculated on the following assumptions: evaluation of the performance of D-lactate test in synovial fluid, assuming no difference margin of <10%, power 80% and α-risk 5%. Youden's J statistic was used for determining optimal D-lactate cut-off value on the receiver operating characteristic (ROC) curve by maximizing sensitivity and specificity. To compare the respective test performances, the area under the ROC curves were calculated for synovial fluid D-lactate, leukocyte count with granulocyte percentage, histopathology, culture and clinical features. All statistical analyses were performed using MedCalc 16.4.3 (MedCalc Software bvba, Ostend, Belgium). For graphical illustration, the software Prism (version 8.2; GraphPad, La Jolla, CA, USA) was used.

Results

Demographic data and PJI classification

In a total of 72 patients, 39 (54%) were male and 33 (46%) female. Among those, there were 55 patients (76%) with total hip arthroplasties and 17 patients (24%) with total knee arthroplasties. Eighteen patients (25%) were diagnosed with PJI. The majority of septic complications presented as delayed PJI ($n = 9$), followed by early ($n = 5$) and late ($n = 4$) infections. Fifty-four patients (75%) were classified as aseptic failure (AF), Table 1).

TABLE 1 Demographic data and infection characteristics of 72 patients.

Characteristics	All patients ($n = 72$)		
	PJI	AF	*p*-value
No. patients (%)	18 (25)	54 (75)	
Age, years, mean (range)	70 (54–86)	72 (40–90)	0.610
Male sex, No. (%)	11 (61)	28 (52)	0.497
Type of implant, No. (%)			
Knee	12 (67)	43 (80)	0.262
Hip	6 (33)	11 (20)	
Time from last surgery around the affected implant, months, mean (range)	30 (0.2–123)	89 (1–396)	0.008
Type of PJI, No. (%)			
Early (<3 months)	5 (28)		
Delayed (3–24 months)	9 (50)		
Late (>24 months)	4 (22)		
Patients with diabetes, No. (%)	3 (17)	10 (18)	0.859
Patients with underlying rheumatic joint diseases, No. (%)	1 (5)	4 (8)	0.789
Body mass index (kg/m^2), mean (range)	28.9 (18.4–37.6)	29.3 (22.6–37.8)	0.816

AF, aseptic failure; PJI, periprosthetic joint infection.

Performance of synovial fluid D-lactate

Synovial fluid D-lactate showed a sensitivity of 90.7% (95% CI: 79.7%–96.9%) and specificity of 83.3% (95% CI: 58.6%–96.4%) at a cut-off 0.04 mmol/L (**Table 2**). The median concentration of D-lactate was significantly higher in patients with PJI than in those with aseptic failure (0.048 mmol/L, range, 0.026–0.076 mmol/L vs. 0.024 mmol/L, range, 0.003–0.058 mmol/L, $p < 0.0001$) (**Figure 1**).

In 2 patients with PJI, the D-lactate test was false-negative. The diagnosis of PJI in these patients was based on clinical signs in combination with increased synovial fluid leukocyte count, positive histopathological and microbiological analyses (*E. coli* was detected in one patient). In patients with aseptic conditions, D-lactate was false-positive in 6 cases. Four of them had in addition increased synovial fluid leukocyte count which was not considered significant as these patients were diagnosed with periprosthetic fracture or luxation, polyethylene liner wear and one patient had a surgical intervention in the last 6 weeks. In the other two patients with false-positive D-lactate test, the diagnostic puncture was performed due to a painful prosthetic joint and progressive restriction of movement.

Microbiological analysis

The isolated microorganisms mostly were presented by staphylococci, followed by streptococci and gram-negative bacteria (**Table 3**).

Discussion

Defining synovial molecules that enable a reliable diagnostic workup of PJI considering biomarkers solely produced by bacteria is an innovative approach. Synovial fluid analysis determining leukocyte count and granulocyte percentage is the standard preoperative test with a sensitivity between 80%–86% and a specificity around 72%–93% (18, 28, 29). Although this analysis showed high sensitivity, it partially lacks specificity. Synovial fluid leukocyte count and granulocyte percentage may be elevated due to other inflammatory conditions in absence of infection such as periprosthetic fractures, underlying rheumatic diseases or within the early postoperative course. There are several studies evaluating the diagnostic impact of other promising molecules, such as alpha-defensin, leukocyte esterase, interleukin-6 and procalcitonin. However, the elevation of these parameters is not solely associated with bacterial infections. Consecuently, PJI diagnosis remains challenging, especially in patients with low-grade infections (30, 31). Therefore, a pathogen-specific biomarker would be of high clinical significance. The molecule D-lactate is almost solely produced by bacteria and showed a high sensitivity and specificity with regard to the current scientific evidence (20, 21). However, only few studies elucidate it's potential as a biomarker of bacterial infections with described cut-off values ranging from 0.05–1.3 mmol/L (20–23). Yermak et al. reported about a D-lactate cut-off of 1.26 mmol/L with sensitivity of 86.4% and a specificity of 80.8%. In their study, the authors evaluated 44 patients with PJI of the hip, knee or shoulder (20). Another work by Karbysheva et al. compared 2 different definition criteria

TABLE 2 Performance of different diagnostic criteria.

Criterion	Cut-off value	PJI	AF	AUC	Sensitivity, %	Specificity, %	PPV, %	NPV, %
					(95% CI)			
D-lactate, mmol/L	0.04	16/18	6/54	0.92 (0.86–0.99)	90.7 (79.7–96.9)	83.3 (58.6–96.4)	72.7 (55.2–85.2)	96.0 (86.6–98.9)
Purulence around the prosthesis or sinus tract communicating with the joint	–	5/18	0/54	0.64 (0.47–0.80)	27.8 (9.7–53.5)	100 (93.4–100)	100 (–)	80.6 (75.7–84.7)
Synovial fluid leukocytes, $\times 10^3$/µl and granulocytes, %	>2 >70	15/18	11/54	0.90 (0.79–1.00)	93.7 (69.8–99.8)	79.6 (66.4–89.4)	57.7 (44.2–70.1)	97.7 (86.5–99.6)
Histopathology of periprosthetic tissue samples	–	14/16	2/24	0.89 (0.78–1.01)	87.5 (61.6–98.4)	91.7 (73.0–98.9)	87.5 (64.7–96.4)	91.7 (74.9–97.5)
Positive culture samples								
Culture[a]	≥2	13/18	1/54	0.85 (0.72–0.98)	72.2 (46.5–90.3)	98.1 (90.1–99.9)	92.8 (64.6–98.3)	91.4 (83.4–95.7)

Note: If denominator is shown, the test was not performed in all patients.
PJI, periprosthetic joint infection; AF, aseptic failure; AUC, area under curve; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval; CFU, colony-forming unit.
[a]Periprosthetic tissue, sonication and synovial fluid samples.

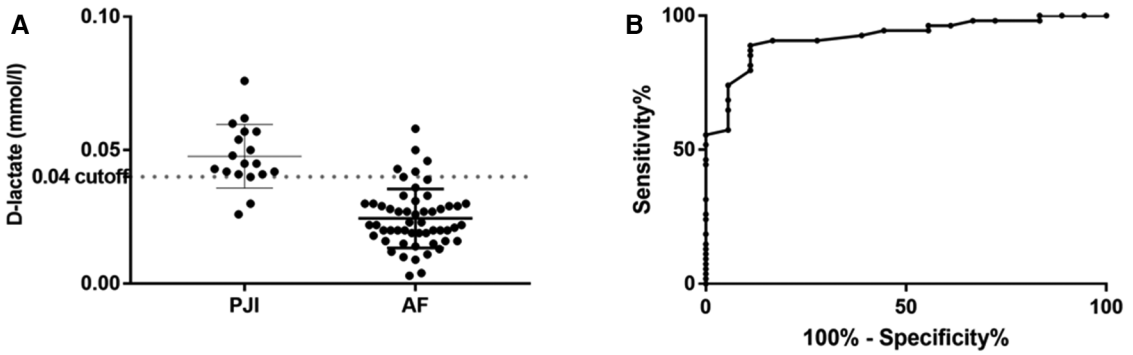

FIGURE 1
Distribution of D-lactate concentration in synovial fluid (A) with corresponding receiver operation characteristic (ROC) curve (B).

TABLE 3 Spectrum of pathogens.

Pathogen	PJI ($n = 18$)
Coagulase-negative staphylococci	4
S. aureus	1
Streptococcus spp.	4
Enterococcus spp.	1
Enterobacteriaceae	4
Pseudomonas aeruginosa	1
Other	–
Culture-negative	5
Polymicrobial infection	2

Table 3 illustrates the positive microbial results in patients with confirmed PJI. Among those, two individuals showed polymicrobial infections.

(Musculoskeletal Infection Society, MSIS criteria and institutional criteria) and determined the optimal threshold of D-lactate for diagnosing PJI of the hip and knee (21). The authors defined a cut-off synovial fluid D-lactate concentration of 1.3 mmol/L, independent of the used definition criteria. The sensitivity of synovial fluid D-lactate was found to be 92.4%–94.3% with a specificity ranging from 78.4%–88.6% for the respective definition criteria. Li et al. conducted a meta-analysis to evaluate the diagnostic accuracy of D-lactate for PJI in which 5 studies were included (32). The pooled sensitivity and specificity of D-lactate for the diagnosis of PJI were 82% and 76%, respectively. However, this meta-analysis focuses on various anatomical locations as well as different PJI definition criteria. In the present study with regard to the diagnostic sensitivity and specificity of D-lactate, we observed similar findings. Synovial fluid D-lactate showed a sensitivity of 90.7% and specificity of 83.3%. Nevertheless, our cut-off of 0.04 mmol/L was substantially lower compared to the above mentioned publications. However, in all previously described studies, the measurement of D-lactate was performed spectrophotometrically by the use of different sample preparation procedures and test protocols. The applied wavelength varied from 340 to 570 nm depending on the study. These differences could partially explain the divergent cut-off values compared to the present results. ROC-curve analysis demonstrated that the AUC of D-lactate was higher or comparable to periprosthetic tissue culture, synovial leukocytes with granulocyte percentage and histopathology ($p = 0.17$, $p = 0.38$, and $p = 0.34$, respectively), but significantly higher than clinical features ($p < 0.01$, Table 2).

In our cohort, D-lactate was false-positive in 6 patients. The majority of these patients had increased synovial fluid leukocyte count due to different disorders other than infection (periprosthetic fracture, dislocation or surgical intervention in the last 6 weeks). These patients had no underlying disease such as severe uncontrolled diabetes or short-bowel syndrome which could lead to an increased D-lactate concentration in blood and body fluids (33). However, Yermak et al. (20) observed a positive correlation between elevated erythrocyte count and D-lactate in synovial fluid using spectrophotometric analysis. This could give an explanation for the false-positive D-lactate results due to a certain contamination of synovial fluid with blood components in patients with periprosthetic fracture, dislocation or within the early postoperative period. Additionally, polyethylene or metal particles in patients with component wear may influence the spectrophotometric analysis since the optical density of the sample is measured to calculate the concentration of analyte. Therefore, other more specific tests such as fluorimetric assay or liquid chromatography should be considered for D-lactate analysis in clinical samples (34, 35).

We are aware that our report has noteworthy limitations and leaves pending issues. First, the lack of patient follow-up examinations limits the value of this study. Second, the information about prior antibiotic use is not complete. Therefore, the effect of any antimicrobial therapy on D-lactate performance could not be reliably assessed. Finally, the small number of the patients included in the preliminary report

leaves a number of questions open, e.g. the usefulness of the D-lactate test in patients with periprosthetic fracture, early postoperative period and liner wear. As our study focuses on preliminary results of a multicenter study, we hope to answer this question more specific in the future. In conclusion, our results reveal that D-lactate bears a strong potential to act as a valuable biomarker for the diagnosis of hip and knee PJI. In our study, a biomarker cutoff of 0.04 mmol/L showed comparable sensitivity to synovial fluid leukocyte count. However, as one may expect of a pathogen-specific biomarker, specificity was higher compared to previously published data of conventional diagnostic standards (36, 37). The main advantages of D-lactate testing are requirement of low synovial fluid volume, short turnaround time and low cost.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethikkommission der Universität Ulm, Germany. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MF investigation, clinical sample acquisition, writing (original draft). MF consulting, writing (review and editing). MRD clinical sample acquisition, data collection. HR supervision, writing (review). PM laboratory work (original draft). AT supervision, writing (review and editing). SK Investigation, laboratory work, statistic analysis, writing (original draft). All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Isolated cryptococcosis of a lumbar vertebra in an immunocompetent patient: A case report and literature review

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Background: *Cryptococcus*, a kind of fungus, can be found in soil, decayed wood, and avian excreta. Immunocompromised patients are prone to infection caused by *Cryptococcus*, and the lungs and central nervous system are the main target organs. Cryptococcosis rarely occurs in the lumbar vertebra or in immunocompetent patients.
Case presentation: A 40-year-old adult male with isolated lumbar vertebra cryptococcosis at the L4 vertebra underwent successful lesion removal surgery performed *via* the posterior approach and postoperative administration of an antifungal agent. At the 12-month follow-up, the patient's pain was relieved, and his motor function had improved. Isolated *Cryptococcus* vertebrae infection is a rare infectious disease.
Conclusions: A needle biopsy can confirm the diagnosis of *Cryptococcus* infection. When patients present with unbearable symptoms of nerve compression, posterior depuration combined with postoperative antifungal agents is a good option.

KEYWORDS

Cryptococcus, spinal infection, lumbar vertebral cryptococcosis, case report, surgery

Introduction

Cryptococcus is a fungus similar to yeast that lives in bird droppings, decaying wood, and soil (1). The respiratory tract is the main route of transmission, and the susceptible population includes people with low immune function. Ninety percent of the cases occur in acquired immune deficiency syndrome (AIDS) patients, which can involve multiple organs throughout the body but mainly involves the central nervous system and lungs

Abbreviations
ELISA, enzyme linked immunosorbent assay; AIDS, acquired immune deficiency syndrome; SPECT, single photon emission computed tomography; MRI, magnetic resonance imaging; CT, computed tomography; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; CAT, cryptococcal antigen test; F, female; M, male; P, positive; N, negative; NA, not available.

(2–5). Skeletal infection caused by *Cryptococcus* is relatively rare, accounting for approximately 5% of all cases of *Cryptococcus* infection (6), and the common sites are the lumbar spine, pelvis, ribs, and skull (7). To the best of our knowledge, only a few studies have reported spinal infections caused by *Cryptococcus*. We report a case of cryptococcosis of the lumbar vertebra in an immunocompetent patient with complete clinical data to raise surgeons' awareness of cryptococcosis of the spine.

Case report

A 40-year-old adult male labourer, who was a construction worker mainly engaged in the handling of construction materials, presented with a more than 4-month history of low back pain, pain radiating to the left limb (visual analogue scale score of 9; Oswestry Disability Index score of 70%), and left limb numbness, without symptoms of tuberculosis, such as fever, night sweats, or cough. A physical examination revealed weakness of the left limb of approximately grade IV, sensory disturbance in the left L4 and L5 area, and difficulty in stretching the left hip. The bilateral Achilles tendon and knee jerk reflexes were normal. There was localised tenderness in the lower lumbar spine. The patient had no medical history of tuberculosis, tumour, AIDS, operations, sarcoidosis, treatment with corticosteroids, or organ transplantation. His close relatives had no history of cancer, tuberculosis, *Cryptococcus*, or other diseases. He denied a past exposure to bird droppings or decaying wood. Therefore, we did not find the source of infection. Lumbar x-ray was performed, which showed that the left pedicle of L4 was unclear and was suspected to be bone destruction. Computed tomography (CT) revealed a lytic lesion at the L4 vertebrae. The entire left half of the vertebral body was involved. The left side of the L4 vertebral body was obviously damaged, and the lesion involved the paravertebral soft tissue. A single photon emission computed tomography (SPECT) scan showed increased uptake in the L4 vertebrae. SPECT did not find any further lesions except the L4 vertebra. Magnetic resonance imaging (MRI) revealed bone destruction in the L4 vertebral body and a portion of the spinal column enclosure. Sagittal T1-weighted MRI of the lumbar spine demonstrated areas of diffuse low signal intensity in L4. Sagittal T2-weighted MRI of the lumbar spine showed a high-intensity zone of oedema around the areas of isointensity in L4. The endplates of the L4 vertebral body were involved, and the upper and lower discs of the L4 vertebra were normal. A transverse MRI scan showed a paraspinal soft tissue lesion that looked like a tumour in L4 (**Figure 1**). Laboratory investigations revealed that the erythrocyte sedimentation rate (ESR) was 57 mm/h. C-reactive protein (CRP) and procalcitonin were normal. Blood counts, liver and renal function, and other serum chemistries were also normal. The enzyme linked immunosorbent assay (ELISA) test for AIDS was negative. We performed a needle biopsy surgery to identify the nature of the lesion. The pathologist found *Cryptococcus* in the lesion; thus, the pathological examination suggested cryptococcal infection. After needle biopsy surgery, we drew a sample of the patient's blood for cryptococcal antigen detection, which was positive. At the same time, the patient was examined by chest CT and brain MRI, and no abnormality was found. We suggested surgical treatment for the patient, but he was concerned about the risk of surgery, refused the operation, and required conservative treatment. The patient was referred to the infection department for antifungal therapy. However, in the course of antifungal treatment with oral fluconazole (400 mg/day) for approximately 2 weeks, the lower limb pain symptoms continued to worsen, so the patient returned to our department for surgical treatment. We performed a posterior approach surgery to remove the lesion and relieve spinal nerve compression.

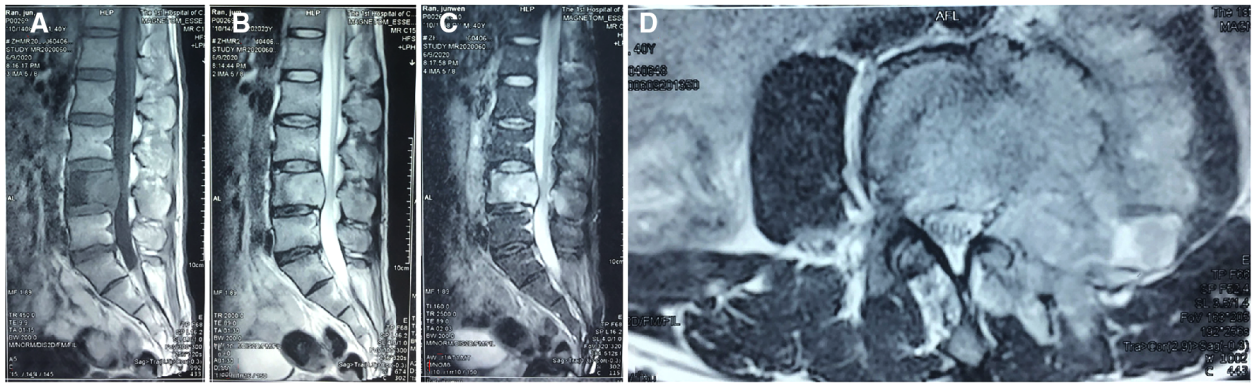

FIGURE 1
MRI scan showing the paravertebral soft tissue mass and the spinal canal stenosis and the pedicle of the fourth lumbar vertebra. (A) T1-weighted images, (B) T2-weighted images, (C) short tau inversion recovery, and (D) transverse section imaging.

This study was performed according to the guidelines of the Declaration of Helsinki and its amendments. Written informed consent was obtained from the patient for the publication of this study and any accompanying images.

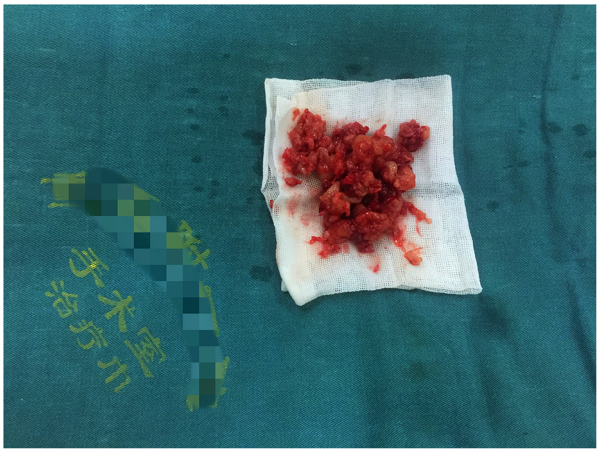

FIGURE 2
The lesions look like jelly.

Under general endotracheal anaesthesia, the patient was placed on the operating table in a prone position. At the affected section of the spine, a standard posterior middle approach was made. Through lateral subperiosteal dissection, the resected levels were exposed to the facet joints in the lumbar region. Pedicle screws were inserted one level above and below the lesion by the freehand technique. When inserting pedicle screws into the L4 vertebra, we found that the accessory structure of the left vertebral body had been destroyed so that pedicle screws could not be placed. Therefore, pedicle screws were not placed on the left side of the L4 vertebral body. After all pedicle screws had been inserted into the centre of the pedicles, the laminae, articular processes, and spinous processes at the level of the lesions were resected. The dura and L4 and L5 nerve roots were then carefully exposed. Then, the lesions were debrided by bone curettes and pituitary rongeurs. The lesions looked like jelly (Figure 2). Simultaneously, 360° decompression around the canal and roots was completed. We filled the lesion with a fluconazole-soaked gelatine sponge to provide local antifungal therapy and used longitudinal beams to connect with the pedicle screws to build a complete internal fixture. The resected lesions were histopathologically examined (Figure 3).

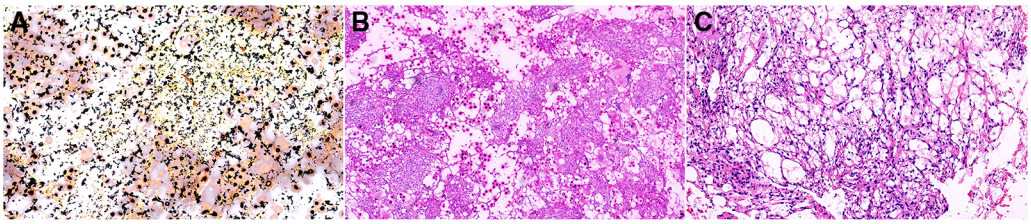

FIGURE 3
Pathological: (A) Ag (×100), (B) PAS (×100), and (C): HE (×100). PAS, Periodic Acid-Schiff stain; HE, hematoxylin-eosin staining.

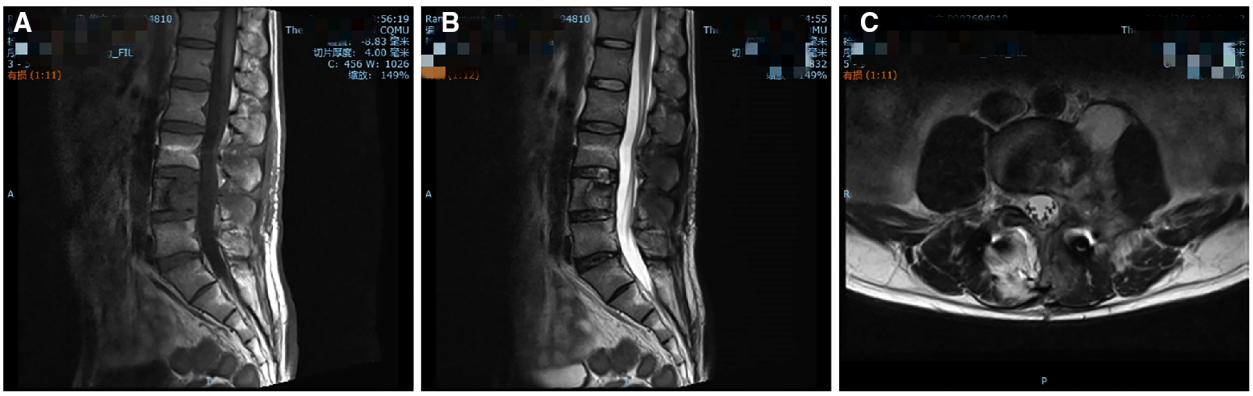

FIGURE 4
Twelve-month follow-up MRI shows a significant reduction of the lesion. (A) T1-weighted, (B) T2-weighted, and (C) axial images.

TABLE 1 General characteristics of 14 literature studies with spine cryptococcosis.

Study	Age (year)/ Sex	Site	Symptoms	CAT	ESR (mm/h)	CRP (mg/L)	Therapy	Medical history	Outcome
Singh and Xess (20)	29/F	L5	Fever, cough, backache, swelling over the sternum	P	110*	NA	Amphotericin B, operation	First-trimester spontaneous abortion	Died
Wang et al. (21)	67/F	T2–T3	Backache and occasional pain radiating bilaterally to the shoulders and chest	P	80*	24.43*	Surgery, voriconazole	No	Curative
Minta (9)	26/M	L4–L5	Backache and pain radiating to lower limbs	NA	NA	NA	Fluconazole, tenofovir–vudine–nevirapine	AIDS	Improve
Al-Tawfiq and Ghandour (11)	34/F	L4	Intermittent fever, low back pain radiating to the right lower	N	89*	8.2*	Nafcillin, flucoconazole, isoniazid, rifampin, ethambutol, pyrazinamide	Pulmonary tuberculosis	Curative
Gurevitz et al. (15)	67/F	L3	Low back pain, fever	P	70*	NA	Biopsy, amphotericin B, 5-fluorocytosine	Lymphadenopathy	Curative
Govender and Charles (13)	9/F	T4	Backache weakness of the lower limbs incontinent of faeces and urine	NA	82*	NA	Surgery, amphotericin B, flucytosine	Pulmonary tuberculosis	Died
Glynn et al. (12)	52/F	L2	Low back pain	P	20*	NA	Biopsy, amphotericin B, 5-flucytosine, ketoconazole	No	Improve
Gupta et al. (14)	24/F	T2–T3	Pain in left shoulder and left chest, paresthesias in both lower limbs, paraparesis and urinary incontinence	NA	NA	NA	Surgery, anti-tubercular therapy, amphotericin B, flucytosine	Tuberculous cervical lymphadenopathy	Died
Jain et al. (16)	72/F	T6	Fever, cough, acute girdle pain at T6 and difficulty in walking	NA	70*	NA	Anti-tubercular therapy, amphotericin B, flucytosine	Diabetic	Improve
Zhou et al. (22)	40/F	L4	Low back pain that had been radiating to the left leg	N	22*	1.45*	Biopsy, fluconazole	Rheumatoid arthritis, scleroderma	Curative
Joo et al. (17)	66/F	L1–L2	Back pain	N	28*	1	Surgery, amphotericin B, fluconazole	Rectal cancer	Curative
Legarth et al. (18)	59/M	T6–T7, 10th rib	Fever, weight loss, a non-fluctuant and tender mass related to the left posterolateral 10th rib	NA	NA	130*	Surgery, voriconazole, fluconazole, itraconazole	NO	Improve
Li et al. (19)	17/F	L1	Fever, back pain, night sweats, headache, nausea	P	NA	NA	Anti-tubercular therapy, hydrocortisone sodium, 5-flucytosine fluconazole, surgery	No	Curative
Adsul et al. (10)	45/F	T4	Back pain, fully paraplegic	NA	38*	18*	Biopsy, surgery, amphotericin B, flucytosine	Type II diabetes	Improve

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; CAT, cryptococcal antigen test; F, female; M, male; P, positive; N, negative; NA, not available.
*Unnormal.

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Mannitol (125 ml/day) and dexamethasone (10 mg/day) were administered intravenously for 3 days following surgery to relieve nerve root oedema and inflammation. The patient was administered oral fluconazole (400 mg/day) as an antifungal treatment. The patient left the hospital approximately 1 week after surgery. Three months following the spinal surgery, the patient reported relief of his symptoms and had returned to his normal preoperative activities. Physical examination revealed that the left limb strength, sensation in his left L4 and L5 areas, and left hip activity had returned to normal. His erythrocyte sedimentation rate was 41 mm/h, which is higher than normal. Twelve months postoperatively, follow-up MRI images of the lumbar spine showed a significant reduction of the lesion (**Figure 4**).

Discussion

Skeleton infection caused by *Cryptococcus* is relatively rare, accounting for approximately 5% of all cases of *Cryptococcus* infection (6). However, cryptococcal spine infections are the most common site of bone infection by *Cryptococcus* (8). We performed comprehensive research *via* PubMed on cryptococcal spine infections, which were reported in a total of 17 articles (**Table 1**). Unfortunately, the full text of three of the articles could not be found. Upon reviewing the 14 published studies, we found 14 cases (9–22). The clinical features of cryptococcal spine lesions were atypical. Fever, cough, pain at the infected site, and radiating pain were the most common symptoms. Incontinence of urine and faeces and full paraplegia occurred in some severe cases (10, 13, 14). The above symptoms are similar to those of spinal tumours and spinal tuberculosis. In our case, the patient presented with low back pain and pain radiating to the left limb. The patient had difficulty straightening the left hip and continually flexed the left lower limb. Paravertebral lesions were considered to have invaded the iliopsoas muscle. During antifungal treatment in the infection department, the patient's lower limb pain symptoms continued to worsen. Surgery was performed, and the patient fully recovered after 1 year of follow-up.

Imaging examinations are essential for the diagnosis of cryptococcal infection of the spine. Plain x-rays can present difficulty in finding lesions (11, 20, 21), as in our case. However, in the case of Joo et al., plain radiographs showed multiple sclerotic lesions (17). Plain radiographs may show scoliosis in patients with tuberculosis of the spine (19). CT may be a good imaging method for the diagnosis of cryptococcal infection of the spine, as it can show osteolytic lesions in the vertebral body (12, 14–19, 21). In our case, the SPECT scan showed increased uptake in the L4 vertebra. This finding is consistent with that of Zhou et al. and Al-Tawfiq and Ghandour (11, 22). MRI may be a good approach to distinguish between cryptococcal infection of the spine, tumours, and tuberculosis. MRI of the spine always presents a paraspinal soft tissue lesion with vertebral erosion at the level of the infection site and intact disc space above and below the lesion (10, 13, 14, 21, 22). Spinal tuberculosis can destroy the disc space above and below the lesion by approximately 70%, while cryptococcosis of the spine does not (14, 23). It is difficult to distinguish vertebral tumours and cryptococcosis of the vertebrae with a simple imaging examination. Needle biopsy may be a good method for resolving the diagnosis. In our case, we highly suspected that the disease was a spinal tumour when the patient first arrived at our outpatient department. The result of the biopsy showed the finding of *Cryptococcus* in the lesion tissues. ESR, CRP, and cryptococcal antigen test (CAT) can be used as primary screening methods. After reviewing the literature, we found that the ESR was abnormal in 10 cases, CRP was abnormal in 4 cases, and CAT was false negative. The accuracy was approximately 66% in immunocompetent patients with cryptococcosis (24). CAT tests were performed in eight cases, among which five were positive and three were negative (**Table 1**). In our case, the CAT test was positive, and ESR and CRP increased.

Antifungal therapy plays an important role in the treatment of spinal infections caused by *Cryptococcus*. We should pay attention to the side effects of antifungal drugs during antifungal therapy. In the case presented by Legarth et al., the patient experienced continuous photosensitivity and pruritus during voriconazole treatment. The complication disappeared after the treatment was changed to fluconazole (18). In our case, the antifungal treatment was oral fluconazole (400 mg daily) until 6 months after surgery. No side effects occurred during the treatment. Oral fluconazole (400 mg daily) may be a good choice for treating spinal infections caused by *Cryptococcus*.

In conclusion, there is no standard therapy regimen to treat cryptococcosis of the spine. We recommend surgery as early as possible when the patient's radiating pain in the lower limbs continues to worsen, combined with antifungal drugs after the operation. This treatment plan can quickly enhance a patient's recovery.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the First Affiliated Hospital of Chongqing Medical University. The patients/participants provided their

written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

All authors contributed to the study's conception and design. Collection and assembly of data, data analysis, and interpretation were performed by ZJ, MT, XZ, XX, WJ, and JH. The first draft of the manuscript was written by ZJ and all authors commented on previous versions of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Development and validation of a diagnostic model for differentiating tuberculous spondylitis from brucellar spondylitis using machine learning: A retrospective cohort study

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Background: Tuberculous spondylitis (TS) and brucellar spondylitis (BS) are commonly observed in spinal infectious diseases, which are initially caused by bacteremia. BS is easily misdiagnosed as TS, especially in underdeveloped regions of northwestern China with less sensitive medical equipment. Nevertheless, a rapid and reliable diagnostic tool remains to be developed and a clinical diagnostic model to differentiate TS and BS using machine learning algorithms is of great significance.

Methods: A total of 410 patients were included in this study. Independent factors to predict TS were selected by using the least absolute shrinkage and selection operator (LASSO) regression model, permutation feature importance, and multivariate logistic regression analysis. A TS risk prediction model was developed with six different machine learning algorithms. We used several metrics to evaluate the accuracy, calibration capability, and predictability of these models. The performance of the model with the best predictability was further verified with the area under the curve (AUC) of the receiver operating characteristic (ROC) curve and the calibration curve. The clinical performance of the final model was evaluated by decision curve analysis.

Results: Six variables were incorporated in the final model, namely, pain severity, CRP, x-ray intervertebral disc height loss, x-ray endplate sclerosis, CT vertebral destruction, and MRI paravertebral abscess. The analysis of appraising six models revealed that the logistic regression model developed in the current study outperformed other methods in terms of sensitivity (0.88 ± 0.07) and accuracy (0.79 ± 0.07). The AUC of the logistic regression model predicting TS was 0.86 (95% CI, 0.81–0.90) in the training set and 0.86 (95% CI, 0.78–0.92) in the validation set. The decision curve analysis indicated that the logistic regression model displayed a higher clinical efficiency in the differential diagnosis.

Conclusions: The logistic regression model developed in this study outperformed other methods. The logistic regression model demonstrated by a calculator exerts good discrimination and calibration capability and could be applicable in differentiating TS from BS in primary health care diagnosis.

KEYWORDS

tuberculous spondylitis (TS), brucellar spondylitis (BS), magnetic resonance imaging (MRI), computed tomography (CT), x-ray, machine learning

Introduction

Tuberculosis (TB) and brucellosis are severe infectious diseases that are threatening human beings. According to the global tuberculosis report (2014), TB remains one of the world's deadliest communicable diseases, and in 2013, approximately 9.0 million people developed TB, among which 1.5 million died from the disease (1), and another recent report showed that 1.6 million people died from TB in 2017 (2). Brucellosis, which is caused by *Brucella melitensis*, is a serious zoonotic disease that causes more than 500,000 human infections worldwide annually (3). Spinal tuberculosis (STB) is not a rare presentation of extrapulmonary tuberculosis. About 1%–2% of all cases of TB are diagnosed as STB, and these patients represent 10%–15% of extrapulmonary TB, of which nearly half involve the musculoskeletal system (4). About 6%–12% of brucellosis cases may suffer a spinal illness, which is the latent reason for the deformities and permanent neurologic deficiencies (5–8). TS and BS are commonly observed in spinal infectious diseases, which are initially caused by bacteremia. They mostly occur in the thoracolumbar segment of the spine. Both TS and BS present several similar clinical performances, such as low-grade fever, including dull pain or discomfort of the dorsum, and elevated inflammatory mediators; hence, distinguishing TS from BS is challenging and BS is commonly misdiagnosed as TS. Currently, the most effective and accurate method for distinguishing TS from BS is based on biopsy and the isolation, culture, and identification of mycobacteria from patient specimens, but it is laborious and time-consuming (9). Hence, developing rapid, cost-effective, and accurate diagnostic methods is urgently desired and of great clinical significance. In this study, we report the development and validation of a machine learning algorithm-based diagnostic model to differentiate betweenthe acute and subacute stages: TS and BS. The predictive model presented in this article follows the TRIPOD Checklist (10).

Materials and methods

The research was conducted under the approval of the ethics committee of Xinjiang Medical University Affiliated First Hospital, Urumqi, and individual agreements for this retrospective analysis were waived.

Patients

Patients admitted to the Department of Spine Surgery between January 2018 and December 2021 and considered as spinal TS ($n = 275$, primary cohort: 612) or BS ($n = 135$, primary cohort: 209) (**Table 1**) were included in this population-based retrospective cohort study with ethical approval of the ethical review committee board of Xinjiang Medical University Affiliated First Hospital. Patients included in this study met the following criteria: (1) diagnosed with spinal tuberculosis or brucellar spondylitis in the acute and subacute stages; (2) accepted surgery therapy; (3) the collected information, especially imaging materials, was complete and available; and (4) age ≥18 years. Patients who met the following exclusion criteria were excluded from analysis: (1) diagnosed with malignant cancer, hematological diseases, and hepatology disease; (2) spine out of alignment; (3) revision spinal surgery; (4) scoliosis deformity; (5) pyogenic spondylitis; (6) spinal hydatid; (7) age <18 years; and (8) patients with missing data were ≥10%.

The diagnosis, referred to as a response variable in our research, was obtained from symptoms, signs, laboratory tests, and imaging features. TS and BS share similar clinical presentation along with the systemic constitutional manifestation, characterized by sweating, fever, local pain, fatigue, etc. Imaging revealed mild or severe vertebral destruction, intervertebral disc height loss, cold abscess, etc. Laboratory tests included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and routine blood tests, which are considered nonspecific. Specific tests comprised positive results of enzyme-linked immunospot assay (T-SPOT.TB), the presence of *Mycobacterium tuberculosis* based on acid-fast bacilli in Ziehl–Neelsen-stained smears, growth in cultures, and/or biopsy examination for TS and *Brucella* agglutination titer test (1:160 or higher) and isolation of *Brucella* species from blood, bone marrow, or other tissues for BS.

TABLE 1 Baseline characteristics of patients.

Variables	Total ($N = 410$)	BS ($N = 135$)	TS ($N = 275$)	p-Value
Age (years)	51.6 ± 16.1	51.8 ± 12.2	51.4 ± 17.7	0.780
Gender				**<0.001**
Female	166 (40.5%)	36 (26.7%)	130 (47.3%)	
Male	244 (59.5%)	99 (73.3%)	145 (52.7%)	
Ethnicity				0.181
Han	126 (30.7%)	52 (38.5%)	74 (26.9%)	
Kazak	33 (8.05%)	10 (7.41%)	23 (8.36%)	
Mongolian	7 (1.71%)	1 (0.74%)	6 (2.18%)	
Others	23 (5.61%)	6 (4.44%)	17 (6.18%)	
Uygur	221 (53.9%)	66 (48.9%)	155 (56.4%)	
BMI (kg/m^2)	23.1 ± 3.03	23.61 ± 2.86	22.8 ± 3.09	0.011
Fever				**<0.001**
High	73 (17.8%)	43 (31.9%)	30 (10.9%)	
Low	337 (82.2%)	92 (68.1%)	245 (89.1%)	
Pain severity				**<0.001**
Moderate	192 (46.8%)	41 (30.4%)	151 (54.9%)	
Severe	218 (53.2%)	94 (69.6%)	124 (45.1%)	
History of weight loss				0.483
No	259 (63.2%)	89 (65.9%)	170 (61.8%)	
Yes	151 (36.8%)	46 (34.1%)	105 (38.2%)	
Past history of tuberculosis in other solid organs				0.181
No	324 (79.0%)	101 (74.8%)	223 (81.1%)	
Yes	86 (21.0%)	34 (25.2%)	52 (18.9%)	
WBC (×10^9/L)	6.56 ± 2.15	6.62 ± 2.10	6.53 ± 2.17	0.667
ESR (mm/h)	45.60 ± 17.61	44.4 ± 15.4	46.1 ± 18.6	0.327
CRP (mg/L)	44.30 ± 37.00	30.9 ± 23.31	50.8 ± 40.5	**<0.001**
Hb (g/L)	126 ± 17.7	130 ± 16.6	124 ± 18.0	**0.004**
TG (mmol/L)	1.25 ± 0.54	1.37 ± 0.62	1.19 ± 0.49	**0.003**
TC (mmol/L)	3.95 ± 0.92	4.15 ± 0.86	3.85 ± 0.93	**0.002**
HDL-C (mmol/L)	1.00 ± 0.31	0.97 ± 0.30	1.02 ± 0.31	0.155
LDL-C (mmol/L)	2.69 ± 0.77	2.79 ± 0.69	2.65 ± 0.81	0.058
ALB (g/L)	37.8 ± 5.71	37.1 ± 6.08	38.1 ± 5.49	0.093
AST (U/L)	24.0 ± 17.5	27.0 ± 17.0	22.5 ± 17.5	0.012
ALT (U/L)	25.9 ± 27.6	34.3 ± 29.0	21.8 ± 26.0	**<0.001**
GGT (U/L)	51.9 ± 45.4	55.8 ± 43.1	50.0 ± 46.5	0.215
ALP (U/L)	103 ± 42.8	108 ± 39.7	101 ± 44.0	0.072
Location				
C	10 (2.44%)	7 (5.19%)	3 (1.09%)	
C + T	2 (0.49%)	1 (0.74%)	1 (0.36%)	
L	233 (56.8%)	90 (66.7%)	143 (52.0%)	
L + S	52 (12.7%)	27 (20.0%)	25 (9.09%)	
S	1 (0.24%)	0 (0.00%)	1 (0.36%)	
T	90 (22.0%)	6 (4.44%)	84 (30.5%)	
T + L	22 (5.37%)	4 (2.96%)	18 (6.55%)	
Segment	2.48 ± 0.96	2.29 ± 0.66	2.57 ± 1.07	**0.001**
MRI spinal stenosis				**0.001**
No	273 (66.6%)	106 (78.5%)	167 (60.7%)	
Yes	137 (33.4%)	29 (21.5%)	108 (39.3%)	
MRI paravertebral abscess				**<0.001**
No	169 (41.2%)	85 (63.0%)	84 (30.5%)	
Yes	241 (58.8%)	50 (37.0%)	191 (69.5%)	
MRI psoas abscess				0.116
No	259 (63.2%)	93 (68.9%)	166 (60.4%)	
Yes	151 (36.8%)	42 (31.1%)	109 (39.6%)	
MRI epidural abscess				0.973
No	320 (78.0%)	106 (78.5%)	214 (77.8%)	
Yes	90 (22.0%)	29 (21.5%)	61 (22.2%)	
CT vertebral destruction				**<0.001**
Mild (≤1/3)	129 (31.5%)	68 (50.4%)	61 (22.2%)	
Severe (>1/3)	281 (68.5%)	67 (49.6%)	214 (77.8%)	
CT marginal osteophytes				0.429
No	186 (45.4%)	57 (42.2%)	129 (46.9%)	
Yes	224 (54.6%)	78 (57.8%)	146 (53.1%)	
CT endplate sclerosis				0.022
No	267 (65.1%)	77 (57.0%)	190 (69.1%)	
Yes	143 (34.9%)	58 (43.0%)	85 (30.9%)	
CT spinal stenosis				**0.005**
No	317 (77.3%)	116 (85.9%)	201 (73.1%)	
Yes	93 (22.7%)	19 (14.1%)	74 (26.9%)	
CT paravertebral abscess				**0.001**
No	198 (48.3%)	81 (60.0%)	117 (42.5%)	
Yes	212 (51.7%)	54 (40.0%)	158 (57.5%)	
CT epidural abscess				0.737
No	366 (89.3%)	122 (90.4%)	244 (88.7%)	
Yes	44 (10.7%)	13 (9.63%)	31 (11.3%)	
X-ray intervertebral disc height loss				**<0.001**
No	166 (40.5%)	84 (62.2%)	82 (29.8%)	
Yes	244 (59.5%)	51 (37.8%)	193 (70.2%)	
X-ray endplate sclerosis				**<0.001**
No	248 (60.5%)	53 (39.3%)	195 (70.9%)	
Yes	162 (39.5%)	82 (60.7%)	80 (29.1%)	
X-ray osteophytes				**<0.001**
No	251 (61.2%)	63 (46.7%)	188 (68.4%)	
Yes	159 (38.8%)	72 (53.3%)	87 (31.6%)	

BMI, body mass index (kg/m^2); WBC, preoperative white blood cell (× 10^9/L); ESR, preoperative erythrocyte sedimentation rate (mm/h); CRP, preoperative C-reactive protein (mg/L); Hb, preoperative hemoglobin (g/L); TG, preoperative total triglyceride (mmol/L); TC, preoperative total cholesterol (mmol/L); HD-C, preoperative high-density lipoprotein cholesterol (mmol/L); LDL-C, preoperative low-density lipoprotein cholesterol (mmol/L); ALB, preoperative operative albumin (g/L); AST, preoperative aspartate aminotransferase (U/L); ALT, preoperative alanine aminotransferase (U/L); GGT, preoperative gamma-glutamyl transferase (U/L); ALP, alkaline phosphataseU/L; C, cervical spine; T, thoracic spine; T + L,thoracolumbar spine; L, lumbar spine; L + S, lumbosacral spine.

Collection of data

Demographic, clinical, and imaging data were collected for each case, including age, gender, location that can be used to estimate the disease epidemiology characteristic (map source: http://datav.aliyun.com/portal/school/atlas/area_selector) (as is shown in **Figure 1**), the body mass index (BMI), the level of pain degree divided into two categories based on the visual analog scale (moderate, VAS ≤ 5; severe, VAS > 5), the fever grade measured at the patient's first visit also divided into two categories (low, <38.5°C; high, ≥38.5°C), preoperative ESR, preoperative CRP, preoperative white blood cell (WBC) count, preoperative hemoglobin, history of weight loss, history of tuberculosis in other solid organs, preoperative low-density lipoprotein cholesterol (LDL-C), preoperative high-density lipoprotein cholesterol (HDL-C), preoperative total cholesterol (TC), preoperative total triglyceride (TG), preoperative albumin (Alb), preoperative gamma-glutamyl transferase (GGT), preoperative alanine aminotransferase (ALT), preoperative aspartate aminotransferase (AST), preoperative alkaline phosphatase (ALP), the level of involvement, the number of affected vertebra, magnetic resonance imaging (MRI) findings including abscess (paravertebral abscess, epidural abscess, psoas abscess) and spinal stenosis, and computed tomography (CT) findings including vertebral destruction, marginal osteophytes, endplate sclerosis, spinal stenosis, paravertebral abscess, and epidural abscess. We defined severe vertebral destruction as one-third or higher vertebral damage. X-ray findings included intervertebral disc height, osteophytes, endplate sclerosis, and bone bridge. All images used in this study were reviewed and analyzed by a chief physician blinded to clinical and laboratory results. We imputed the missing data (<10%) using the MICE package (version 3.14.0) (11).

Feature selection

We identified candidate predictors through the least absolute shrinkage and selection operator (LASSO) model owing to its attribution of compression estimation algorithms in high-dimensional regression and the importance score of each predictor via the permutation importance approach using the random forest classification model. After applying the LASSO regression model and permutation feature importance method to the training set, respectively, we initially screened variables (12). We chose the top 10 variables according to their importance arranged by the model, which simultaneously were selected in the LASSO method. Then, a multivariable logistic regression analysis was conducted. Variables with a two-sided p-value ≤0.05 and frequently used in routine clinical practice were included in the model along with their odds ratios (ORs), associated 95% confidence intervals (CI), β-coefficients, and corresponding p-values.

Machine learning model construction

Regarding machine learning, we used six risk algorithms to develop a predictive model for TS: logistic regression (LR),

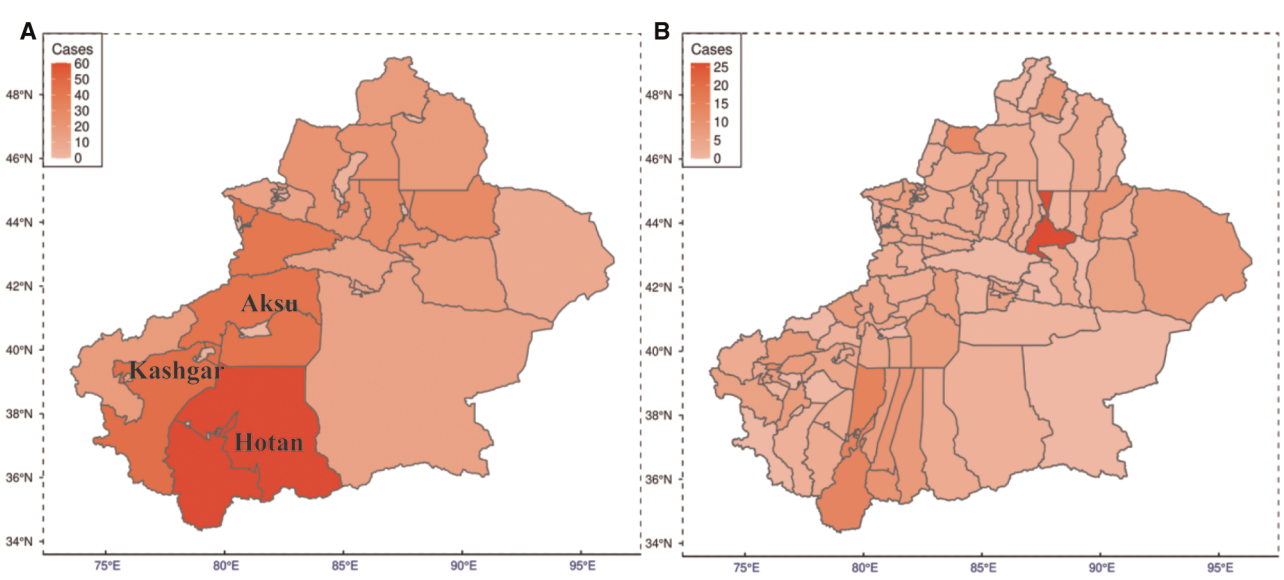


FIGURE 1
Prevalence of TS and BS among northwestern Chinese residents. (**A**) Prevalence map of the regional level. (**B**) Prevalence map of the county level. TS, tuberculous spondylitis; BS, brucellar spondylitis.

neural network (NN) (13), random forest (RF) (14), decision tree (DT) (15), Gaussian naïve Bayes (Gaussian NB) (16), and K-nearest neighbor (KNN) (17). LR is basically a classification algorithm that comes under the supervised category. DT is a nonparametric supervised learning algorithm consisting of upside-down trees that make decisions based on the conditions present in the data. RF is a combination of a multitude of decision trees that can be constructed for prediction when facing regression tasks. NN is one of the supervised machine learning methods that simulates the way the human brain processes information. NB is a method based on Bayes theorem mainly used for classification. KNN is a nonparametric classification approach widely used in real-life issues (18–22).

Once the features were inputted, these algorithms enabled predictions regarding important signs for the diagnosis of TS in a sample of patients with TS or BS. R programming software (version 4.1.2) was used to build the predictive models.

Evaluation and improvement of model performance

The data used in this study were randomly divided into two groups including a training set and a validation set with a ratio of 7:3. Model establishment consists of some unavoidable processes: data preprocessing, training the model with tuned hyperparameters (also called model performance improvement), evaluating the model performance, and testing the model on unknown data. However, previous research studies present an error-prone manipulation, which is reporting the performance estimated in the tuning procedure as model performance, which is somehow biased and overestimated (23). Evaluating the model performance should not be carried on the same datasets used for tuning since this kind of operation would cause biased performance during evaluation. Thus, we adopted a nested resampling strategy (nested cross-validation) to obtain an unbiased score. It used outer and inner loops to separate resampling optimization from model performance evaluation. The model was fitted on the outer training data set using the tuned hyperparameter configuration obtained by inner resampling. Repeated k-fold cross-validation (KCV, $k = 10$, $n = 10$, n is the number of repeats) was used as the outer resampling strategy, and k-fold cross-validation (KCV, $k = 5$) was the inner resampling method to tune the hyperparameters of each model. In the process of KCV, $k-1$ folds of the data were used as the training set and the reserved part of data was used as the testing set to evaluate nine metrics, namely, sensitivity, specificity, accuracy, precision, positive predictive value (PPV), negative predictive value (NPV), F1 score, area under the curve of the receiver operating characteristic curve (AUROC), and the precision–recall curve (AUPRC) iteratively until every fold experienced inner validation. The whole process was repeated 100 times. This was believed to reduce the probability of overfitting and underfitting in a tiny data set and would help to reflect its practical performance.

Ultimately, the values of AUROC and AUPRC from the six models were compared to decide the best performing model. The opted model, logistic regression (LR), was constructed as a scoring system using the entire training data, and it was validated using the validation data set. The ROC and PRC

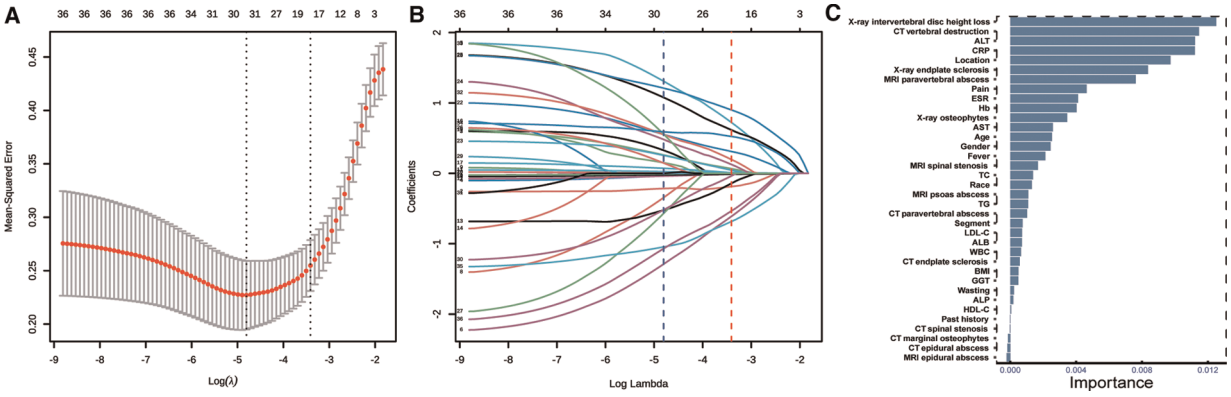


FIGURE 2
Feature selection. (A) Optimal parameter (lambda) selection in the LASSO model using 10-fold cross validation via minimum criteria (the left dotted vertical line) and the 1–SE of the minimum criteria (the right dotted vertical line). (B) LASSO coefficient profiles of the 36 features. A coefficient profile plot was produced against the log (lambda) sequence. Nineteen features with nonzero coefficients were selected by the optimal λ. (C) Features selected using permutation importance *via* random forest ordered by their importance score. LASSO, least absolute shrinkage and selection operator.

analyses were carried out utilizing the R package: ModelMetrics (version 1.2.2.2) (24).

Scoring system development and validation

The logistic regression model, selected after the aforementioned individual models were evaluated based on the required criteria, is displayed as a scale system embedded into Excel (Microsoft, USA), which is convenient to use (25). We estimate the discrimination performance of the scale system with AUROC and the calibration curve in the training and validation sets, respectively. At last, decision curve analysis (DCA) was used to examine the clinical efficiency of the model to quantify the benefits and the area under the curve to be appraised (26).

Statistical analysis

We performed all statistical analyses by using R software 4.1.2. The normality of the data with the *Q–Q* plots of all data was assessed. Continuous variables were presented as mean ± standard deviation (SD) in the case of normal distribution; otherwise, they were presented as median values (quartiles). Student's *t*-test was used to compare two mean values of continuous data considered normally distributed after normality evaluation. Otherwise, the Mann–Whitney *U*-test was performed. Categorical variables were expressed as frequency (percentage). The chi-square test or Fisher's exact test was used to compare two frequencies.

Results

Epidemiology of cases enrolled in this study

Regional distributions of patients diagnosed with TS or BS enrolled in this study are shown in **Figure 1**. For each region, the darker shade represents a higher incidence of disease. As can be seen, in general, the southern part of Xinjiang China, especially the Hotan region, reveals a higher prevalence.

Patients

A total of 410 patients ($n = 275$ TS patients and $n = 135$ BS patients) were enrolled; 70% of them were included in the training set ($n = 292$), and the remaining patients were included in the validation set ($n = 118$). The differences in all baseline demographic characteristics and predictors, including clinical personation, laboratory tests, and radiology findings between the TS and BS, are given in **Table 1**. Patients with TS had higher CRP levels, ESR, and proportion of lower pain, while patients with BS showed higher WBC count. In additon, most imaging-related data showed significant differences between patients with TS and BS.

Feature selection

Thirty-six variables were reduced to 19 predictors with the LASSO method (**Figures 2A,B**). The top 10 variables with relative importance score selected by the LASSO method were CRP, ESR, Hb, ALT, pain severity, CT vertebral destruction, x-ray intervertebral disc height loss, x-ray endplate sclerosis, MRI paravertebral abscess, and location (**Figure 2C**). Multivariate analysis was conducted based on the above results. Predictors associated with the TS patients included pain severity, CRP, x-ray intervertebral disc height loss, x-ray endplate sclerosis, CT vertebral destruction, and MRI paravertebral abscess (**Table 2**).

TABLE 2 Prediction factors for TS from study population by multiple logistic regression model.

Characteristic	OR	95% CI	*p*-Value
Pain severity			
Moderate	—	—	
Severe	0.37	0.20, 0.66	**<0.001**
CRP (mg/L)	1.02	1.01, 1.03	**<0.001**
Hb (g/L)	0.97	0.95, 0.99	0.008
ALT (U/L)	0.99	0.98, 1.00	0.045
ESR (mm/h)	0.99	0.97, 1.01	0.2
X-ray endplate sclerosis			
No	—	—	
Yes	0.20	0.11, 0.36	**<0.001**
X-ray intervertebral disc height loss			
No	—	—	
Yes	3.31	1.87, 5.98	**<0.001**
CT vertebral destruction			
Mild (≤ 1/3)	—	—	
Severe (>1/3)	3.21	1.78, 5.87	**<0.001**
MRI paravertebral abscess			
No	—	—	
Yes	3.05	1.72, 5.51	**<0.001**
Location			
C	—	—	
C + T	1.92	0.04, 102	0.7
L	4.46	0.89, 26.9	0.079
L + S	3.95	0.69, 26.8	0.13
T	38.6	6.15, 292	**<0.001**
T + L	16.5	1.93, 171	0.013

OR, odds ratio; CI, confidence interval; CRP, preoperative C-reactive protein (mg/L); Hb, preoperative hemoglobin (g/L); ESR, preoperative erythrocyte sedimentation rate (mm/h); ALT, preoperative alanine aminotransferase (U/L); C, cervical spine; T, thoracic spine; T + L, thoracolumbar spine; L, lumbar spine; L + S, lumbosacral spine.

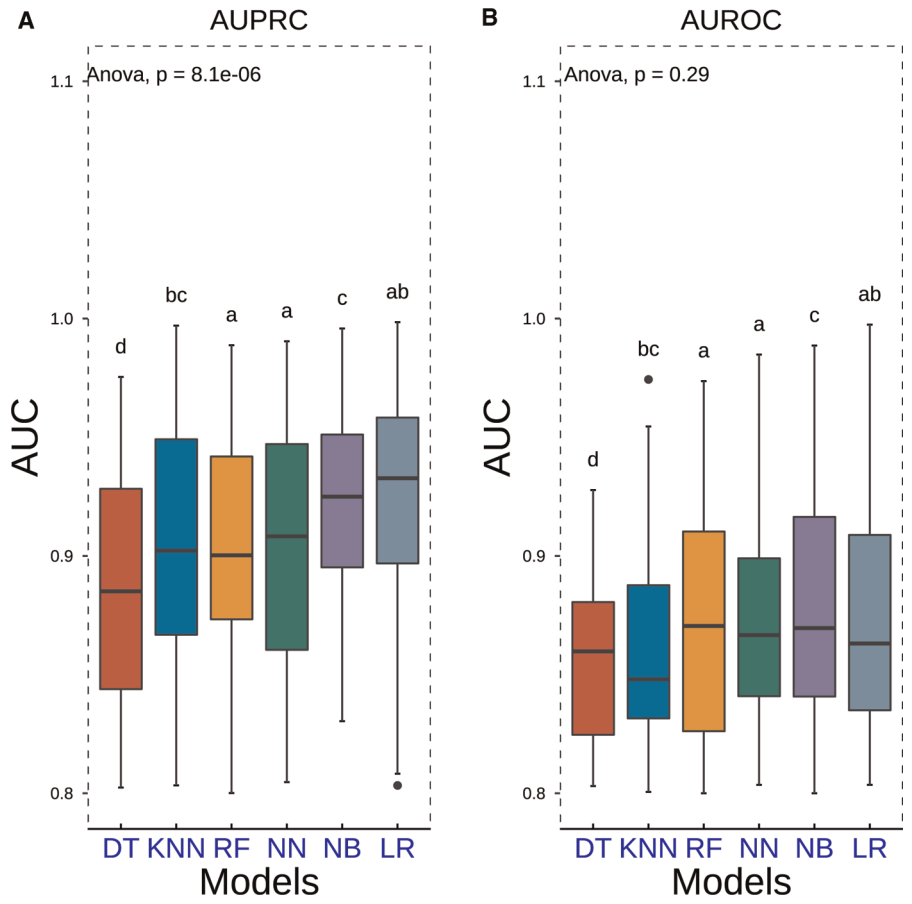


FIGURE 3
Boxplots of AUPRC and AUROC measurements of model performance using the nested resampling strategy for six different machine learning algorithms. *P*-values were calculated through one-way analysis of variance with Tukey's *posthoc* test. AUPRC, area under the curve of the receiver operating characteristic curve; AUPRC, area under the curve of the precision–recall curve.

Evaluation of model prediction capability

Repeated 10-fold cross-validation was carried out in the outer loop to assess model performance with ROC and PRC analyses. This process was repeated 10 times. We discovered that DT was related to relatively lower AUROC and AUPRC values. However, LR, NN, and NB methods exhibited higher AUROC and AUPRC values (**Figure 3**). Furthermore, seven popular metrics (sensitivity, specificity, accuracy, precision, F1 score, PPV, and NPV) were also used to assess the performance of these models (**Table 3**). As LR shows higher specificity than NN and NB and has best accuracy and F1 score, it is the most commonly used algorithm with its convenience displaying high accuracy with lower standard deviance. This indicated that the LR model did possess an outstanding ability to be implemented into clinical decision-making.

Establishment of the scoring system

Based on the candidate predictors screened on the training set, a scale calculator, which comprised six major features, was developed for predicting the probability of TS. Each factor in the calculator was assigned a unique score in light of the value of the corresponding factor. The sum of all scores computed by rounding up the scores of all predictors can be used to compute the probability of TS (**Figure 4**). For details, please refer to **Table S1**.

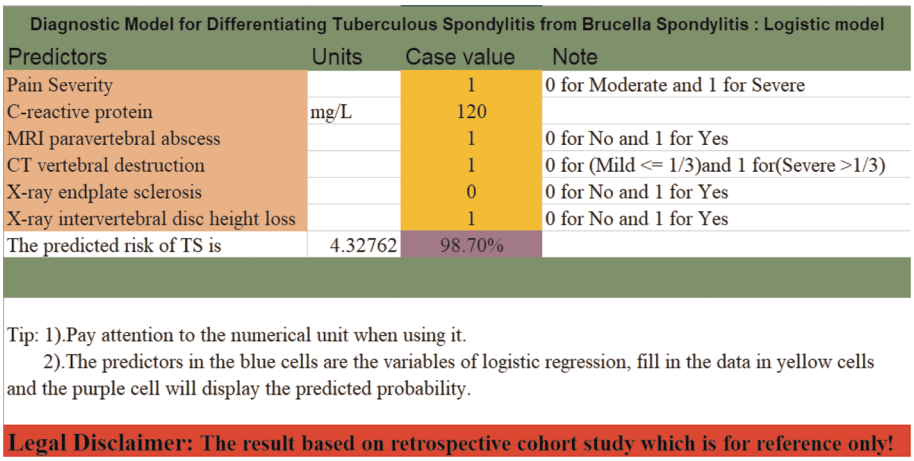
Model performance and validation

We validated the differentiation capacity of the model in the training set and validation set, respectively. The C-statistics and AUC of the model to predict the diagnosis of TS were 0.860

TABLE 3 Predictive performance of each model.

Model	Sen.	Spe.	Acc.	Pre.	P.P.V.	N.P.V.	F1
LR	0.88 ± 0.07	0.58 ± 0.18	0.79 ± 0.07	0.82 ± 0.08	0.82 ± 0.08	0.69 ± 0.19	0.85 ± 0.06
NN	0.87 ± 0.08	0.56 ± 0.2	0.77 ± 0.07	0.81 ± 0.09	0.81 ± 0.09	0.68 ± 0.17	0.84 ± 0.06
RF	0.89 ± 0.08	0.56 ± 0.17	0.79 ± 0.08	0.82 ± 0.08	0.82 ± 0.08	0.71 ± 0.18	0.85 ± 0.06
DT	0.86 ± 0.08	0.53 ± 0.19	0.75 ± 0.08	0.8 ± 0.09	0.8 ± 0.09	0.64 ± 0.18	0.82 ± 0.06
NB	0.84 ± 0.09	0.64 ± 0.15	0.77 ± 0.07	0.83 ± 0.08	0.83 ± 0.08	0.66 ± 0.17	0.83 ± 0.06
KNN	0.86 ± 0.06	0.62 ± 0.17	0.78 ± 0.07	0.83 ± 0.08	0.83 ± 0.08	0.67 ± 0.15	0.84 ± 0.05

Sen., sensitivity; Spe., specificity; Acc., accuracy; Pre., precision; P.P.V., positive predictive value; N.P.V., negative predictive value; LR, logistic regression; NN, neural network; RF, random forest; DT, decision tree; NB, naïve Bayes; KNN, K-nearest neighbor.



Diagnostic Model for Differentiating Tuberculous Spondylitis from Brucella Spondylitis : Logistic model			
Predictors	Units	Case value	Note
Pain Severity		1	0 for Moderate and 1 for Severe
C-reactive protein	mg/L	120	
MRI paravertebral abscess		1	0 for No and 1 for Yes
CT vertebral destruction		1	0 for (Mild <= 1/3)and 1 for(Severe >1/3)
X-ray endplate sclerosis		0	0 for No and 1 for Yes
X-ray intervertebral disc height loss		1	0 for No and 1 for Yes
The predicted risk of TS is	4.32762	98.70%	

Tip: 1).Pay attention to the numerical unit when using it.
2).The predictors in the blue cells are the variables of logistic regression, fill in the data in yellow cells and the purple cell will display the predicted probability.

Legal Disclaimer: The result based on retrospective cohort study which is for reference only!

FIGURE 4
Selected models presented as logistic regression equations in this Excel (USA) document.

(95% CI, 0.814–0.900) (Figure 5A) and 0.857 (95% CI, 0.778–0.920) (Figure 5C). The calibration curve showed that the model excellently predicted actual probabilities (Figures 5B,D).

Clinical efficiency of the model

We implemented DCA to confirm whether it could bring benefit to clinical practice. It can be found that the model had a prominent ability to improve clinical efficiency in predicting TS, as shown in Figure 6.

Discussion

Machine learning has been widely used in many types of research on diseases. As per our best knowledge, this is the first report on exploiting different machine learning algorithms to develop a diagnostic model with noninvasive clinical indices to differentiate between TS and BS. ML approaches vary their performance depending on various hyperparameters, which play a significant role in decision-making. Finding a set of configurations of hyperparameters is called tuning. It is realized that performance evaluation and tuning are strongly correlated. The nested resampling method we implemented in this research could combined these two procedures to minimize the bias occurring in the whole process. Moreover, the opted model has been visualized as a calculator embedded into an Excel document to encourage further study of its clinical utility. All distinctive predictors selected in the prediction model were basic clinical appearance, laboratory tests, and different imaging data, allowing for routine accessibility in clinical practice. The results displayed that our model possessed excellent discrimination and calibration capacity in two data sets, with AUC values of 0.860 in the training set and 0.857 in the validation set. However, we can find from the above results that the model has the likelihood of misclassification. We assume that this is because of the instability of data. In addition, it somehow depends on the interpretation of the radiologist evaluating the image of patients because the five predictors are related to radiological manifestations.

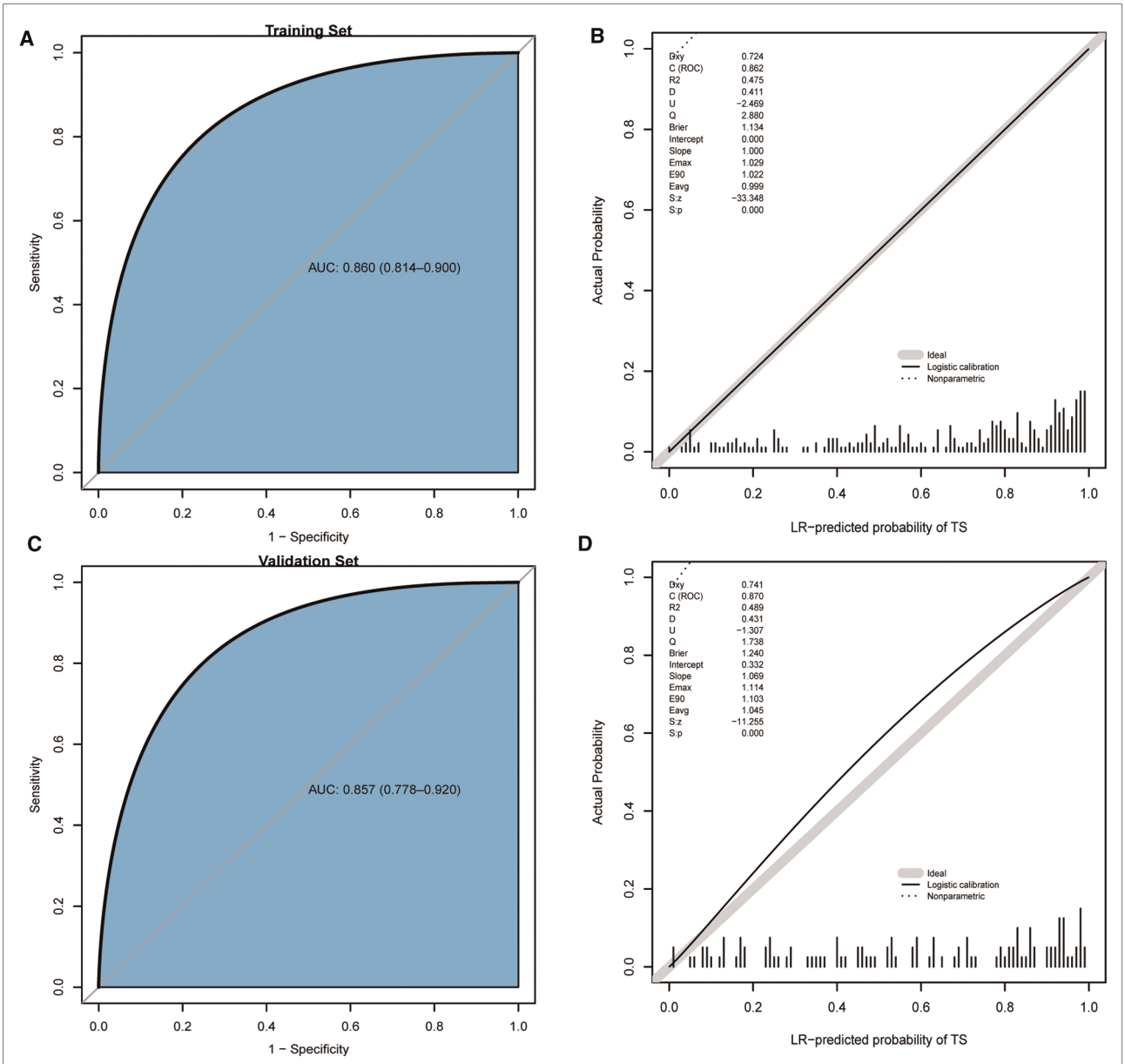


FIGURE 5
ROC curves and calibration curves of the training set, validation set, and scoring system. (A) ROC curve of the training set. (B) Calibration curve of the training set. (C) ROC curve of the validation set. (D) Calibration curve of the validation set. ROC, receiver operating characteristic.

Both tuberculosis and brucellosis are systemic diseases and remain to be considered public health issues, especially in developing countries, showing higher incidence in the northwest part of China than the other parts of China (27). TS has been mainly discovered in less developed regions because of low income and hygienic status (28). Xinjiang has the second highest incidence of human brucellosis, according to data from the China Public Health Data Center, where patients are mainly pastoralists and veterinarians (29). Previous studies have shown human brucellosis is associated with contact with animals and consumption of uncooked milk and products from goat and sheep (30–32). In addition, there are other factors also connected to brucellosis like high temperatures, air pollution, wind speed, etc. (33). However, the aforementioned factors can be found in Southern Xinjiang, China. Our statistical results based on the patients enrolled in this study displayed that the southern part of Xinjiang, China shows a higher incidence than the northern part, which agrees well with previous research studies. The clinical diagnosis of spinal tuberculosis usually comprises clinical manifestations, laboratory studies, and imaging data (34). The gold standard for diagnosing spinal TB or BS is

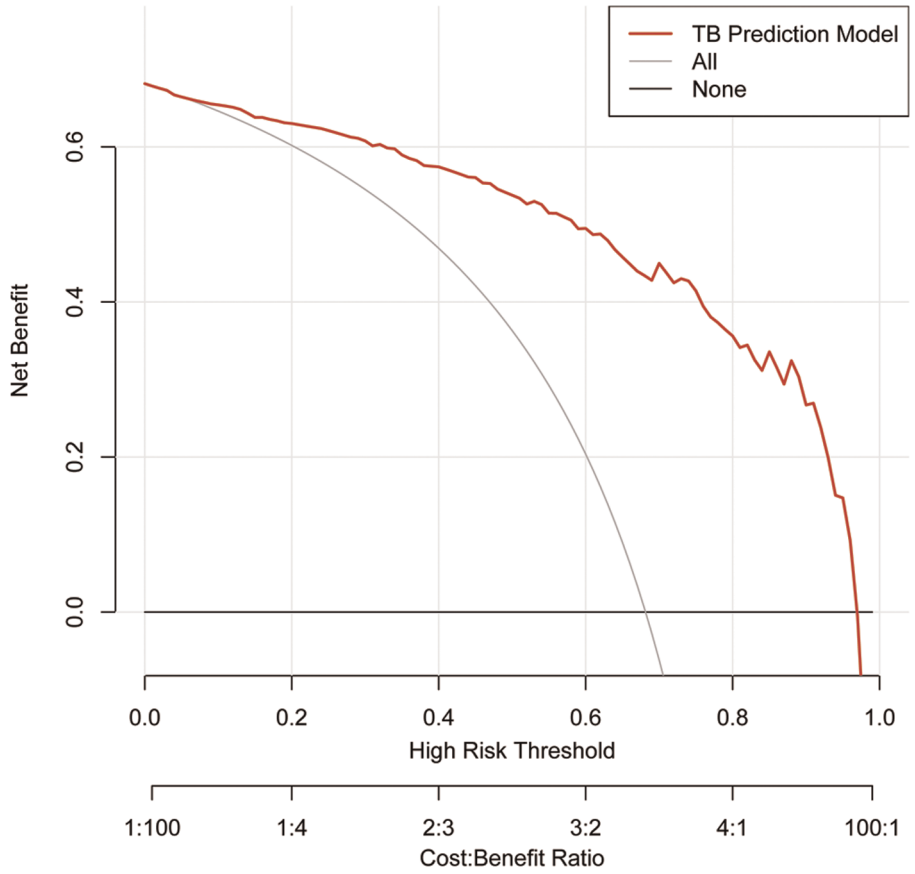


FIGURE 6
Decision curve analysis for the TS prediction model in the training set. The red line represents the TS predictive model. The thin solid line represents the assumption that all patients are considered to be diagnosed with TS. The thick solid line represents the assumption that no patients suffer from TS. The decision curve analysis indicated that using this TS prediction model could gain net benefit when the threshold probabilities >4%. TS, tuberculous spondylitis.

bacterial isolation (culture) from blood, bone marrow, or tissues (35, 36). Nevertheless, confined to the low positive rate of mycobacteria culture or isolation, diagnosis commonly incorporates clinical symptoms, physical examinations, radiographic findings, tissue a microbiological culture, polymerase chain reaction (PCR), and gene detection (37). Due to the resemblance in the clinical manifestation laboratory tests and imaging findings, many patients may be misdiagnosed during the primary phase of the sickness due to delays from insufficient knowledge (38). Early recognition and effective cure are critical in preventing devastating complications (39). Thus, it is urgent to investigate the related features, develop a convenient and sensitive prediction model, and help primary health care clinicians in less developed areas.

In this article, we select six predictors strongly associated with TS, including pain severity, CRP, x-ray intervertebral disc height loss, x-ray endplate, CT vertebral destruction, and MRI paravertebral abscess. To minimize the heterogeneity of the model to differentiate TS from BS, we chose to acquire features based on the first blood test. We believe that this measure can reduce heterogeneity and boost the model performance.

Patient complaints in TS or BS may initially be effortful to discriminate because of the nature of the illness. Patients with BS often report moderate fever, sweating, malaise, back pain (local pain), and anorexia, whereas patients with TS report back pain, evening pyrexia, generalized body ache, fatigue, body weight loss, neurological abnormalities, and night sweats. Unfortunately, one or more of these symptoms are shown in merely 20%–38% of patients with skeletal tuberculosis (40, 41). Back pain is considered the most frequent complaint of TS. It can be axial pain or radicular pain, which is believed to be the result of the damage to the anterior spinal bodies and mass effect by cold abscess or instability of the spine, nerve root compression, and vertebral body collapse (41, 42). In

clinical practice, pain severity showed variance between TS and BS, and the latter can be found with severe pain degrees the former, which is concordant with previous findings. The result of multivariate logistic regression also proved that point (OR: 0.37, 95% CI, 0.20–0.66, $p < 0.001$). Fever types of the two diseases also show differences in that brucellosis appears to be a moderate (≥38.5°C) fever, while tuberculosis is low (<38.5°C) fever with sweats ($p < 0.001$). However, it was not included in our model. Given the wide range among the patients, their age, gender, and ethnicity, to some degree, may affect the result. However, gender shows a great difference between TS and BS, which might be the result of sampling bias. None of these were selected as predictors in ML models because the training set cannot be represented with a small number of samples. Thus, we maintained that there were no significant differences in demographic characteristics, including ethnicity, gender, history of weight loss, history of tuberculosis in other solid organs, and age, between the BS and TS patients after the scientific and precise analysis of our data, which is in line with previous studies (43).

Clinical laboratory tests, such as WBC count, ESR, and CRP level, which are all nonspecific in showing infectious processes and linked to spondylitis in the majority of cases, are a significant part of clinical diagnoses (40, 42, 44, 45). It can be easily found from our result that CRP levels were higher in TS patients than those in BS patients ($p < 0.001$), which was similar to the results reported in previous studies (46–48). At the same time, contrary to the findings, we did not find a significant difference in WBC count and ESR between patients with TS and BS.

Radiological findings are the keystone of the diagnostic process (49). Plain radiography is usually examined first in patients suspected to have TS or BS, and plain radiography images may exhibit no positive result at the early stage of the disease (50). CT has high sensitivity for early diagnosis. In addition, the identification of the extent of the inflammatory process can also be evaluated in time. Moreover, CT has unreplaceable merits of better visualization of the bony details of irregular lytic lesions, sclerosis, disc collapse, and damage to vertebral circumference (51, 52). Previous findings suggest that the diagnosis and differential diagnosis based on MRI of spondylitis patients was qualitative (53, 54). TS and BS are the results of *M. tuberculosis* and *B. melitensis* infections, respectively, which can cause vertebral edema and abscesses, which is reflected by increased T2 values. The lesion level and segments of spinal disease are known to vary according to its etiology. It has been observed that thoracic involvement and multifocal involvement were generally associated with TS (55, 56), a finding consistent with our result. Previous studies have demonstrated that paravertebral abscess, severe bone destruction, and intervertebral disc height loss were suggestive of TS, while local bone damage and confined paravertebral involvements were suggestive of BS, which can be proved by our results (57). In addition to that, endplate sclerosis and osteophytes are more common in BS than in TS, while disc height loss is more frequent in TS, which is in agreement with previous studies (37, 58, 59).

A previous study indicates no sign of predicting the benefit of ML over LR for clinical prediction models (60). The LR model showed good performance with AUROC, AUPRC, and specificity and no significant difference when compared to SVM and NB. Thus, we selected the logistic regression model to differentiate TS from BS. Previous research studies have largely used nomograms exhibiting predictive models. It is not precise enough and somewhat rough to use, and some factors in this model cannot be computed directly, so a scaling system is chosen to visualize the model (25).

Limitations

There are several limitations of this research. First, this analysis was based on data acquired from electronic medical records in a single center, and it would be more convincing to use multicenter clinical data. Second, it was hard to determine the phase of disease in this series. In addition, as a retrospective design, the research has a few innate demerits compared to a prospective study. What is more, further prospective studies to validate its efficacy with a larger sample size are still needed.

Conclusions

The model established in this research revealed better discrimination and calibration capability, and internal cross-validation disclosed that this model can still maintain stability when facing diverse tasks. Then, this model was visualized by a calculator that can quickly identify individuals at risk of TS and help physicians in primary health care in less developed areas with a higher incidence of TS or BS in time.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**; further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the ethics committee of Xinjiang Medical University Affiliated First Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MM designed the study. PY collected and analyzed the data and wrote the manuscript. MM, TX, XC, YFA, TW, WS and MM reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.955761/full#supplementary-material.

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Is long time to reimplantation a risk factor for reinfection in two-stage revision for periprosthetic infection? A systematic review of the literature

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The two-stage revision arthroplasty is a common treatment option for chronic periprosthetic infection (PJI). The time to reimplantation (TTR) reported in the literature varies substantially from a few days to several hundred days. It is hypothesized that longer TTR could be associated with worse infection control after second stage. A systematic literature search was performed according to Preferred Reporting items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, in Pubmed, Cochrane Library and Web of Science Core Collection in clinical studies published until January 2023. Eleven studies investigating TTR as a potential risk factor for reinfection met the inclusion criteria (ten retrospective and one prospective study, published 2012–2022). Study design and outcome measures differed notably. The cutoff points above which TTR was regarded as "long" ranged from 4 to 18 weeks. No study observed a benefit for long TTR. In all studies, similar or even better infection control was observed for short TTR. The optimal TTR, however, is not yet defined. Larger clinical studies with homogeneous patient populations and adjustment for confounding factors are needed.

KEYWORDS

periprosthetic joint infection, two-stage exchange, revision arthroplasty, time to reimplantation, spacer interval, TKA, THA

Introduction

Periprosthetic joint infection (PJI) is a feared complication in orthopedic surgery that requires complex surgical procedures and long systemic treatments aiming at infection control. This is an enormous burden for affected patients and results in high costs for the health care system (1). The infection risk after primary total hip or knee arthroplasty is 1%–2% (2), but the risk for recurrence of infection can reach up to 50% in complex cases after multiple revisions (3–6). The current gold standard for chronic PJI is the two-stage revision arthroplasty (7, 8). A temporary polymethyl methacrylate (PMMA) spacer fills the debrided joint space, bridges bony defects, stabilizes the joint and ideally maintains the length of the extremity. In addition, local anti-infective substances mixed in the PMMA are released into the surrounding, reaching very high local concentrations, with little risk of systemic side effects (9). However, surgeons in clinical practice are confronted with the issue of timing second stage reimplantation surgery. From a patient's perspective, a short interval appears preferable to regain the ability to use the affected limb in

everyday life. Yet, various factors such as comorbidities, clinical examination, laboratory results and organizational factors influence the time to reimplantation (TTR) (10). A widely adopted classification by Trampuz and Zimmerli defines intervals of two to four weeks (short interval) and six to eight weeks (long interval) until reimplantation (11). Other authors suggest four to six weeks (12), or nine weeks between the stages (13). However, spacer intervals reported in clinical studies often exceeded the time periods of guideline recommendations. They range from a few days to several hundred days, but mostly an average interval around 80 to 100 days is reported (4, 7, 14–22),. This heterogeneity in clinical practice indicates that an optimal interval period between the stages, has not been conclusively defined. In this study, we systematically searched the literature for studies that described two-stage revision arthroplasty of the hip and knee and analyzed the outcome "reinfection" in relation to the TTR.

Methods

The preferred reporting items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the Cochrane Handbook for Systematic Reviews of Interventions were followed (23, 24).

Data sources

Electronic searches were performed in the databases PubMed (including MEDLINE; 1970 to 2023), Cochrane Library (1970 to 2023), and Web of Science Core Collection (1970 to 2023) to identify relevant studies. For PubMed and the Cochrane Library, index terms (MeSH-terms) were included and combined with free text words to search in title, abstract, and keywords. We used four concepts (1. Arthroplasty, 2. Infection, 3. Treatment, 4. Humans). These four concepts were combined with the Boolean operator "AND". The operator "NOT" was used to exclude case reports and reviews. The search was performed on January 1, 2023. The full search strategy is available in the **Supplementary Material**.

Study selection

After identification of 6,010 publications, duplicates were removed and eligible studies were selected by the authors in three phases, resulting in eleven included studies (**Figure 1**). Eligibility criteria were set as follows: 1) population: Adult humans with chronic PJI of hip and knee, 2) intervention: treatment with completed two-stage revision arthroplasty 3) outcome: reinfection after the second stage; and 4) study design – retrospective cohort studies, prospective cohort studies and Randomized Controlled Trials (RCT). Technical notes were excluded. Only studies providing information on the time to reimplantation (TTR) after the first stage of a completed two-stage revision arthroplasty were included. We excluded the following studies: studies of paediatric patients; studies not involving endoprostheses of the hip and knee; treatment of septic arthritis of native joints, treatment of PJI with one-stage revision arthroplasty, DAIR procedure (Debridement, antibiotics, implant retention) or only partial removal of prosthesis components; studies that did not provide sufficient information on the surgery, experimental or animal studies; and studies written in languages other than English. After removal of duplicates, 5,659 titles and abstracts were screened. A total of 65 clinical studies evaluated the outcome of two-stage revision arthroplasty and reported on the time to reimplantation (TTR). The full-text analysis lead to the exclusion of 54 articles. Eleven studies met the inclusion criteria and were included in the analysis (**Figure 1**).

Data analysis

A descriptive analysis was performed by comparing the risk of reinfection in the observation period after completed second stage, in relation to the time to reimplantation (TTR: time interval between first and second stage). In addition, potential sources for bias were identified.

Results

Study characteristics

The included studies and their main characteristics are summarized in **Table 1**. All were published between 2012 and 2022 and reported on a total of 1,552 patients treated between 1996 and 2019. Ten studies were retrospective, and one was a prospective cohort study.

Reinfection after two-stage revision arthroplasty and time to reimplantation (TTR)

Kubista et al. compared risk factors from 58 patients with reinfections after two-stage exchange of total knee arthroplasty (TKA) with 58 patients they randomly selected from a cohort without reinfection (25). The median TTR in their study was 66 days in the reinfected group and 61 days in control group. They also considered TTR as a continuous variable and calculated a hazard ratio for additional 30 days TTR of 1.14 ($p = 0.03$). However, they included a relevant proportion of patients that required additional revision and spacer exchanges before reimplantation ($n = 26$, 22%; $n = 17$ in the reinfected group and $n = 9$ in the group without reinfection $p = 0.01$). This could be a confounding factor as these revisions likely prolonged the TTR and are considered themselves a risk factor for reinfection (34–36).

Sabry et al. identified TTR as an independent risk factor among 314 patients with knee PJI undergoing a two-stage exchange with a median of 124 days until reimplantation in the reinfected group vs. 96 days in the group without reinfection ($p = 0.015$) (17). Again,

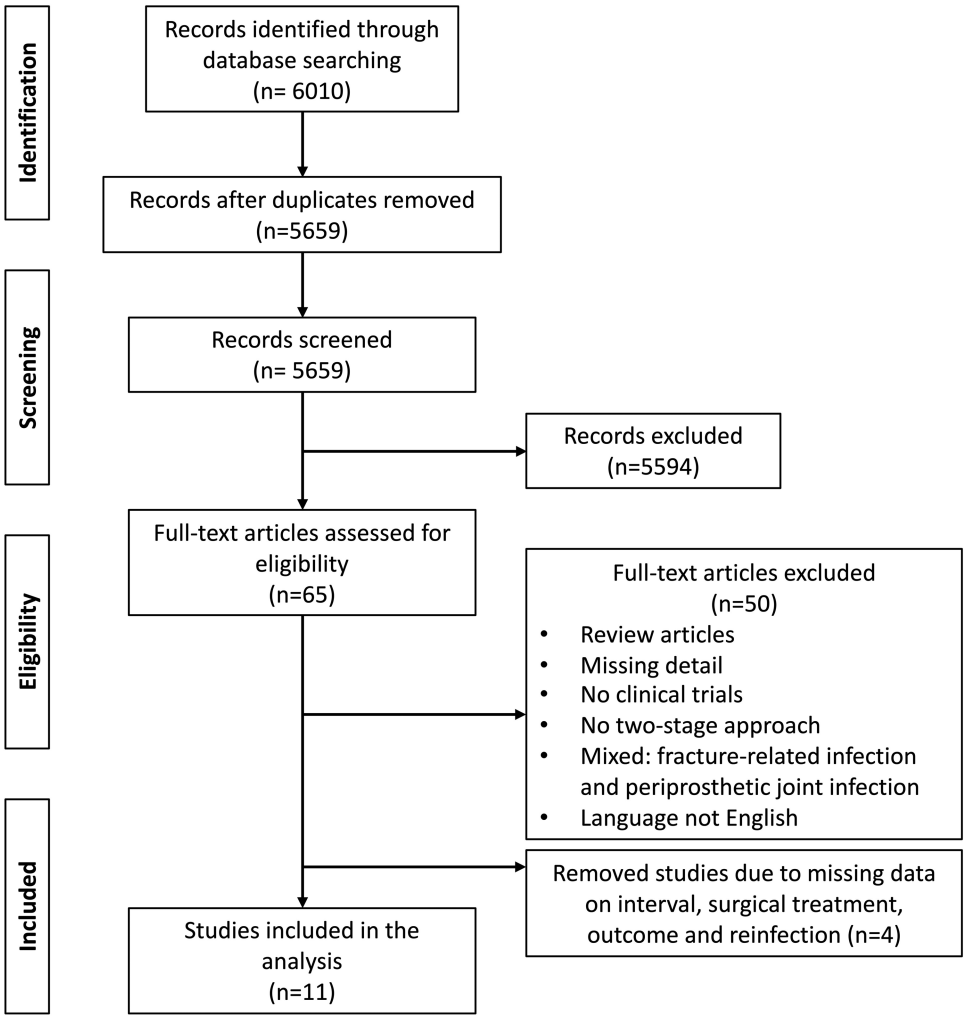

FIGURE 1
Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram: eligibility assessment.

patients requiring a spacer exchange in between the stages were not excluded from the analysis.

Winkler et al. published a small series of patients with hip and knee PJI receiving reimplantation either within four weeks ($n = 19$) or thereafter ($n = 19$) (14). Cases with difficult to treat microorganisms and patients with critical soft tissues were excluded. On average the short interval group had a mean of 17.9 days compared to 63 days in the long interval group. Only one reinfection was observed in this cohort in the long interval group, therefore the authors suggested that the shorter interval might at least achieve similar infection control compared to longer intervals.

Akgün et al. from the same group published a cohort of 18 patients with hip PJI in 2019 with an interval of less than 6 weeks and 66 patients with a longer interval (26). Mean time interval of all patients between stages was reported 60.9 days (8.7 weeks, range: 1–25). Girdlestone resection arthroplasty without the use of cement spacers was the preferred treatment approach. Thirteen patients required revision surgery between the stages due to infection persistence and were kept in the analysis. Reinfection was observed in none of the patients in the shorter interval group and in nine patients in the longer interval group, however this difference was not significant.

Hipfl et al. reviewed 97 cases of knee PJI with static spacers and reported an average TTR of 66 days for all patients (mean ± Standard Deviation: 9.4 ± 3.5 weeks) (27). Fifteen patients had a reinfection and their average TTR was 71 days (10.2 ± 4.0 weeks) compared to 64 days (9.2 ± 4.0 weeks) in uninfected patients, however this difference was not significant ($p = 0.393$). The lack of statistical validation may be due to the considerably small number of patients.

Tan et al. investigated the association of the antibiotic holiday with the risk for reinfection after two-stage revision in a large retrospective cohort of 409 patients in two institutions over 14 years from 2000 to 2014 (28). All patients that had additional surgery in the interim period between the stages were excluded. No association with the duration of the antibiotic holiday was found, but with TTR. When graphed alongside the treatment failure rate a steep increase of the treatment failure rate was observed after 100 days TTR. The average TTR for patients

TABLE 1 Overview of eleven studies assessing the association of the time to reimplantation (TTR) and the risk of reinfection after two-stage revision arthroplasty.

Study	Year	Study design	Population	Outcome	Results	Limitations and potential bias
Kubista *et al.* (25)	2012	Retrospective Study period: 1998-2006 Follow-up interval: 6-2,853 days	116 patients with knee PJI, completed two-stage exchange	1. TTR in a cohort with reinfection compared to controls without reinfection 2. TTR as continuous variable regarding outcome reinfection.	1. Median TTR 66 days (reinfection) vs. 61 days (no reinfection) 2. Additional 30 days TTR: Hazard ratio: 1.14 ($p = 0.03$)	• Retrospective • 26 patients had additional revision and/or spacer exchanges between stages (not excluded). • No information on spacer type
Sabry *et al.* (17)	2014	Retrospective Study period: 1996-2010 Follow-up interval: mean: 1,215 days (range, 59–4,202 days	314 cases of knee PJI, completed two-stage exchange	TTR in a cohort with reinfection compared to controls without reinfection	Median TTR 124 days (reinfection) vs. 96 days (no reinfection) ($p = 0.015$)	• Retrospective • different spacer types were used • no adjustment for potential confounding factors (comorbidities) • cases with additional revision and/or spacer exchanges between stages were not excluded (no exact number)
Winkler *et al.* (14)	2019	Prospective, quasi randomized to short and long interval in two different time periods Study period: Jan-Dec. 2013 Follow-up interval: Minimum follow-up: n.a., Mean follow-up: 3.3 years	38 patients with hip or knee PJI, completed two-stage revision TKA. Reimplantation within 4 weeks (short interval, $n = 19$) or ≥4 weeks (long interval, $n = 19$)	Reinfection rate	One patient with reinfection in the long interval group, no patients with reinfection in the short interval group	• Small cohort • no information on missing data/drop-out • no adjustment for comorbidities
Akgün *et al.* (26)	2019	Retrospective Study period: 2013-2015 Follow-up interval: Minimum follow-up: 2 years, Mean follow-up: 33.1 months	84 patients with two-stage revision THA Reimplantation within 6 weeks (short interval, $n = 18$) or > 6 weeks (long interval, $n = 66$)	1. Kaplan-Meier Infection free survival 2. Reinfection rate	1. All patients: infection free survival: 3 years 89.3% (95% CI, 80% to 94%) with 30 patients at risk Reinfection: 0 patients in short interval group vs. 9 patients in long interval group ($p = 0.02$)	• Retrospective • Small cohort • 13 patients had additional revision and/or spacer exchanges between stages (not excluded).
Hipfl *et al.* (27)	2019	Retrospective Study period: 2014-2015 Follow-up interval: Minimum follow-up: 2 years, Mean follow-up: 41 months	97 patients with knee PJI, completed two-stage exchange using static spacers	Time to reimplantation (TTR) in a cohort with reinfection ($n = 15$) compared to controls without reinfection ($n = 82$)	Median TTR 71 days (reinfection) vs. 64 days (no reinfection) ($p = 0.393$)	• Retrospective • Small cohort • 9 patients had additional revision and/or spacer exchanges between stages (not excluded).
Tan *et al.* (28)	2018	Retrospective Study period: 2000-2014 Follow-up interval: Minimum follow-up: 1 year, Mean follow-up: n.a.	409 patients with knee PJI, completed two-stage exchange, Patients in need of revision surgeries between stages were excluded.	1. Reinfection rate (association with duration of antibiotic holiday and TTR) 2. Time to reimplantation (TTR) in a cohort with reinfection compared to controls without reinfection	1. association of reinfection risk with TTR (but not with antibiotic holiday). Notable increase of reinfection risk for TTR >100 days. 2. Median TTR 113 days (reinfection) vs. 88 days (no reinfection) ($p = 0.037$)	• Retrospective data over 14 years from two institutions with varying surgeons and protocols • different spacer types were used • only graphical presentation of increased risk for TTR >100 days. • No adjustment for confounding factors (regarding TTR)

(*continued*)

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TABLE 1 Continued

Study	Year	Study design	Population	Outcome	Results	Limitations and potential bias
Sigmund *et al.* (29)	2019	Retrospective Study period: 2006-2014 Follow-up interval: Minimum follow-up: 1 year, Mean follow-up: 3.6 years	93 patients with hip PJI; completed two-stage exchange with resection arthroplasty (no spacer) Reimplantation within 10 weeks (short interval, $n = 49$) or > 10 weeks (long interval, $n = 44$)	Kaplan-Meier Infection free survival	Infection free survival at 12 months: 94% (short) and 91% (long); at 24 months: 94% (short) and 86% (long) (log-rank test, $p = 0.223$)	• Retrospective • no adjustment for comorbidities (BMI sign. different)) • additional revision and/or spacer exchanges between stages were not excluded. • small cohort (Reinfection in only nine patients)
Vielgut *et al.* (30)	2015	Retrospective Study period: 2005-2010 Follow-up interval: Minimum follow-up: n.a., Mean follow-up: 20.5 months	76 patients with acute and chronic hip PJI with intended two-stage exchange.	optimal TTR cutoff with maximally selected log-rank statistic	Calculated cutoff-points: Increased rate of reinfection before 4 weeks (5/5) and after 11 weeks (11/23). Patients with TTR 4-11 weeks had lowest rate of reinfection (36/40) ($p = 0.014$)	• Retrospective • 13 patients had additional revision and/or spacer exchanges between stages and eight patients did not reach second stage reimplantation • No difference was made between acute and chronic infections • No adjustment for confounding factors • Small cohort. Only five patients in the group with reimplantation within 4 weeks
Vielgut *et al.* (31)	2021	Retrospective Study period: n.a. Follow-up interval: Minimum follow-up: n.a., Mean follow-up: 24.5 months	77 patients with knee PJI, completed two-stage exchange using static spacers	1. Kaplan-Meier Infection free survival and optimal TTR with maximally selected log-rank statistic 2. TTR as continuous variable regarding outcome reinfection.	1. Calculated cutoff-point: 83 days (12 weeks). Kaplan Meier estimate of reinfection rate at five years was 13.7% for shorter TTR and 46,9% for longer TTR. 2. Hazard ratio was 6.1 (95% CI: 1.6-22.9, $p = 0.007$) if TTR was longer than 12 weeks	• Retrospective • 17 patients had additional revision and/or spacer exchanges between stages (not excluded). • No adjustment for confounding factors • Small cohort • patients had additional revision and/or spacer exchanges between stages
Borsinger *et al.* (32)	2022	Retrospective Study period: 2011-2018 Follow-up interval: Minimum follow-up: 2 years Mean follow-up: n.a.	90 patients with hip or knee PJI, completed two-stage exchange (after excluding 11 patients with revision between stages)	Treatment failure at two years (reoperation or death)	If TTR was >18 weeks the risk for reinfection was significantly increased (Odds ratio: 4.12, CI 95%: 1.18-15.37, $p = 0.029$) Adjusted for health status (ASA Score and number of prior revisions)	• Retrospective • cutoff-point (18 weeks) was chosen arbitrarily • different spacer types were used • small cohort
Hartman *et al.* (33)	2022	Retrospective Study period: 2008-2019 Follow-up interval: Minimum follow-up: 2 years, Mean follow-up: 3.4 years	158 patients with hip and knee PJI; with completed two-stage exchange and articulating spacers if possible	1. Reinfection rate 2. TTR in group with reinfection compared to group without reinfection	1. Reinfection rate: 19.6% (31/158) 2. Median TTR 141 days (reinfection) vs. 109 days (no reinfection) ($p = 0.055$)	• retrospective • no information on revisions between stages • no adjustment for comorbidities • no adjustment for multiplicity, no information on missing data/drop-out

ASA Score: American Society of Anesthesiologists Score; TTR: time to reimplantation; n.a.: not applicable/not reported.

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without treatment failure in their study was reported 87.9 days and 112.8 days for patients with treatment failure ($p = 0.037$).

Sigmund et al. in 2019 defined ten weeks as a cutoff between a short and a long TTR interval in a retrospective cohort of 93 patients with hip PJI (29). The infection free survival after one year amounted to 94% for the group with the short interval and 91% in the long interval group. At 24 months the survival was 94% (short interval) and 86% (long interval). However, these differences were not significantly different (log-rank test, $p = 0.223$), potentially due to the small number of only nine patients with observed reinfections.

Vielgut et al. analyzed 76 patients with acute and chronic hip PJI that were treated with two-stage exchange arthroplasty from 2005 to 2010 (30). Most patients in their cohort received spacers that consisted of a femoral stem with metal head, wrapped in antibiotic-loaded cement. Reimplantation of a prosthesis was planned once the infection was considered eradicated. This required a regular clinical and laboratory examination, three negative joint aspirates and a normal leukocyte scintigraphy. Intraoperative frozen sections and local status at the second stage determined, whether an endoprosthesis was reimplanted or the spacer was exchanged. Thirteen cases required spacer exchange. On average TTR amounted to 12.6 weeks. A TTR-threshold was calculated using the maximally selected log-rank statistic by Hothorn and Lausen (37). This method calculates a cutoff where the survival data yields the biggest difference between two groups. A significantly higher reinfection rate was observed when TTR was less than four weeks or more than eleven weeks. The authors concluded that the optimal TTR, therefore, lies within this timeframe. However, the <4 weeks group contained only five patients, that were all reinfected during the observation period, thus limiting validity. In addition, eight patients that were not fit for second stage surgery due to other preconditions and thirteen patients that required spacer exchange were not excluded from the analysis. Therefore, the authors conclude that the association of TTR with reinfection might be biased by worse overall health condition in the group with longer TTR.

A more recent publication of the same group from 2021 analyzed 77 patients with knee PJI (31). Using a similar methodology, they calculated an optimal cutoff of 83 days (11.8 weeks) for this cohort. The risk for reinfection after the second stage was increased sixfold for patients with a longer interval. In contrast to the patient cohort with hip PJI no second cutoff was identified. Again, patients with spacer exchanges in the interval period were not excluded and no adjustment for the host status was performed, although both factors were identified as significant predictors for reinfection.

In 2022 Borsinger et al. reported an increased rate of reinfection after two years for patients with TTR of more than 18 weeks [Odds ratio, CI 95%: 4.12 (1.18–15.37)] (32). Adjustment for comorbidities and previous revision surgeries was done in a cohort of 90 patients with hip and knee PJI (after excluding eleven patients with spacer exchange or Girdlestone resection arthroplasty in the spacer interval). Another group (TTR: 12–18 weeks) had higher odds of treatment failure compared to a group with TTR <12 weeks (odds ratio, CI 95%: 1.89 (0.67–5.77), although not significantly different. The cutoffs at 12 and 18 weeks were defined arbitrarily resulting in groups of similar group size. The calculation of an optimal cutoff with the method by Hothorn and Lausen (37) and additionally a consideration of TTR as a continuous variable would have been interesting. The patient cohort was heterogenous as hip and knee PJI was reported together and the type of knee spacer was inconsistent (static and mobile, prefabricated and handmade, some containing polyethylene tibial components in the PMMA).

Hartman et al. in 2022 reported on a retrospective cohort of 158 patients with hip and knee PJI that underwent both stages with mainly articulating spacers (33). The overall reinfection rate was reported as 19.6% (31/158) and the median TTR in the group with reinfection was 141 days compared to 109 days in the group without reinfection, although not statistically significant ($p = 0.055$). No information on potential revision surgeries between stages was reported.

Discussion

Few studies have systematically analyzed the potential association of outcomes with TTR in the concept of two-stage revision arthroplasty. However, this topic has recently received increasing attention. This is reflected by the fact that seven of the included eleven studies were published after 2019. The identified studies showed that shorter intervals can achieve comparable or even better infection control compared to longer TTR. In Borsinger's study, this difference was still significant even after adjustment for potential confounding factors and exclusion of all patients with additional surgeries in the interim phase (32).

In chronic PJI, pathogens had long time to penetrate deep into tissue and form mature biofilms on surface areas. Recent findings have shown that *S. aureus* is able to invade deep into the bone *via* the osteocyte lacuno-canalicular network (38). This highlights the need for a radical debridement during the first stage in order to reduce the bacterial load. However, it is difficult to clearly identify infiltrated bone and define "clean" resection margins (39). In the concept of the two-stage exchange arthroplasty, any remaining bacteria after the first stage should be completely eradicated by antibiotic therapy. In addition to systemic therapy, the use of local antibiotics is well established. In many cases antibiotic loaded temporary cement spacers are a preferred treatment concept for chronic PJI (7, 8). The spacer has the task of filling the dead space, stabilizing the joint, maintaining the length of the extremity and releasing local anti-infective substances. Nevertheless, elution decreases over time and the amount of this decrease depends on various factors such as surface size, dosage, mixing technique and choice of antibiotic among other factors (40–43). Without relevant antibiotic elution the spacer acts as a foreign body that could be recolonized by remaining bacteria as observed after sonication of retrieved spacers (21, 44, 45). To avoid this situation, it seems reasonable to keep TTR as short as possible. Additional modern drug delivery systems are commercially available, such as calcium sulfate, that can deliver antibiotics over the time the carrier

substance is resorbed (46). Other drug delivery systems such as anti-infective microspheres with high bone affinity are currently being investigated (47).

Another possible explanatory approach for the phenomenon of increased risk of reinfection after long TTR could be the following. The interim phase before reimplantation often means immobilization for elderly patients, especially if static spacers are used and weight bearing is not recommended. Immobilization promotes major complications, including pressure ulcers, pneumonia, urinary tract infection and thromboembolic events (48). Besides a significant reduction of muscle mass in elderly patients (49), negative effects of bed rest are also observed for the immune system (50, 51). It therefore seems plausible that patients with a deteriorated immune system after long immobilization periods could be more prone to reinfection.

These considerations suggest that there is a strong case for shorter spacer intervals. Following this line of reasoning, one could question the value of the two-stage exchange compared to the increasingly propagated one-stage exchange (52, 53). However, It has become accepted that certain conditions are regarded as contraindication for the one-step exchange, such as severe immunocompromise, significant soft-tissue or bony compromise and acute sepsis (54). Therefore, a certain minimum duration of TTR seems justified, but it is still not clear whether this is in the range of 2–4 weeks or longer. The optimal TTR probably depends on various patient specific factors. This circumstance demands a great deal of experience from the surgeons, which confirms that septic revision arthroplasty should be performed at specialised centres with a high caseload.

The question arises why, in clinical trials with large patient cohorts, the reported TTR has so far been significantly longer than known guidelines recommend (4, 7, 14–22). An important factor currently preventing the introduction of short spacer intervals seems to be rules in hospital payment systems (55–57). Many countries, including the United States, Germany and the United Kingdom, have introduced rules that make another surgery for the same diagnosis financially unattractive within a certain period after discharge, which is usually 30 days (58, 59). These measures, which were supposed to improve quality of care by penalizing inappropriately early discharges, have the potential of nudging surgeons to schedule second stage reimplantation later. The consideration of the second stage as a separate case becomes evident in economic analyses, where the second stage reimplantation is classified as an “aseptic” revision case (56, 57). This leads to the situation that the second stage competes for scarce capacity with other surgeries considered “elective”. In the context of a general shortage of hospital capacity, aggravated by the Covid-19 pandemic it is to be expected that implementing shorter TTR will become even more difficult (60, 61). The potential future increase in waiting times for the second stage reimplantation should be closely monitored in registries. The interpretation of the second stage reimplantation as an “aseptic” elective revision case appears inappropriate and should rather be considered as “ongoing infection treatment” that ends only after the antibiotics have been completed after reimplantation. A reasonable consideration to address this barrier seems to be for insurers and health policy makers to provide financial incentives for reimplantation to occur during one inpatient stay or shortly thereafter, as this could reduce the societal costs associated with long-term immobilized patients (62) and could achieve, at least, similar infection control.

This systematic review has substantial limitations. Thus, the results should be interpreted with caution. The most important limitation is the compromised comparability of the studies due to different study designs, small sample size, different definition of treatment success and statistical approaches. Most studies did not evaluate TTR as the primary outcome. Rather, it was one parameter among many to identify potential risk factors as part of an exploratory approach. Although the studies report a measure of the overall health status of patients, it is certainly possible that other factors that were not considered in most studies, such as the virulence of microorganisms, soft tissue condition, nutritional status, wound healing, treatment adherence, or other patient-specific factors, had a relevant impact on TTR and infection control. Spacer exchanges or wound revisions in the interim period prolonged the TTR and this is considered a risk factor for reinfection. But most studies did not exclude these cases. In addition, patients who a surgeon believes might be at a higher likelihood of treatment failure based on clinical experience may have been monitored longer before reimplantation in order to detect persisting infection or reinfection. Only the study by Winkler et al. included patients in two different time periods, quasi randomized, to longer or shorter TTR, however the cohort of 38 patients was small and reinfection was observed only once in the whole cohort (14). Because of this variety, a meta-analysis of the results is currently not possible. We suggest for future studies to exclude all patients that require surgery between the stages and to perform adequate adjustment for confounding factors.

Conclusion

The optimal time to reimplantation within the concept of two-stage revision arthroplasty is not yet defined conclusively. Current evidence suggests that short time to reimplantation might be associated with similar or even better infection control compared to long intervals, although cohorts in the existing literature are still rather small and inhomogeneous. This hypothesis should be investigated in larger clinical studies with standardized outcome parameters and adequate adjustment for potential confounding factors.

Author contributions

All authors conceptualized this systematic review, analyzed current literature, drafted the initial manuscript and revised the

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2023.1113006/full#supplementary-material.

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