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Reinfection Rate and Its Associated Factors after Two-Stage Revision for Infected Total Knee Arthroplasty

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Abstract

Purpose: Two-stage revision is the gold standard for treatment of infected total knee arthroplasty. The purpose of our study was to evaluate the reinfection rate of two-stage revision and to analyze the factors affecting the prognosis of two-stage revision for infected total knee arthroplasty.

Materials and Methods: One hundred seven cases of two-stage revision for infected total knee arthroplasty were reviewed retrospectively from March 2006 to November 2019. We evaluated possible risk factors between success and reinfection groups. Statistical analyses included multivariable logistic regression analysis to examine the relative contribution of risk factors to the success of two-stage revision.

Results: There were 19 cases of reinfection (17.8%) after two-stage revision in our center. Between the success and reinfection groups, there was a significant difference in history of cancer in univariate analysis (p=0.015). Also, multivariable logistic regression analysis of risk factors demonstrated history of cancer (HR 5.928, p=0.015). There were no statistically significant differences in reinfection relative to other risk factors.

Conclusion: In subjects undergoing two-stage revision for infected total knee arthroplasty, we believe history of cancer should be considered for risk factor of reinfection.

Keywords: Two-stage revision; Infected total knee arthroplasty; Recurrence of infection

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Introduction

Infected Total Knee Arthroplasty (TKA) is the most serious complication of the surgical procedure, and prognosis varies greatly depending on treatment method. This devastating complication is associated with considerable morbidity and economic burden. The incidence of infection following primary TKA ranges from 1% to 2% [1]. There are various treatment options, including chronic antibiotic suppression [2]; Irrigation and Debridement (I & D) with component retention [3]; one-stage revision [4]; two-stage revision [5]; and salvage procedures such as resection arthroplasty, arthrodesis, or amputation [6]. Of these treatment options, two-stage revision is considered the gold standard, with a high rate of infection control ranging from 72% to 100% [7]. However, recurrence of reinfection after two-stage revision occurs in up to 19% of cases [8,9], which elucidates the socioeconomic and individual burden of infected TKA. Previous studies have attempted to identify risk factors associated with reinfection after two-stage revision [10]. However, there were no common risk factors among studies. The purpose of the present study was to evaluate the reinfection rate of two-stage revision and to analyze the factors affecting prognosis of two-stage revision for infected TKA.

Materials and Methods

The design of this retrospective study was approved by the Institutional Review Board (IRB) at the author's hospital, and all patients provided informed consent. One hundred forty-two cases (136 patients) of infected TKA from 2008 to 2019 at a single center were reviewed retrospectively. Among these, 35 cases were successfully treated without need for component removal or antibiotic-loaded cement spacer insertion, and four failure cases required two-stage revision after infection control. Therefore, a total of 107 cases (104 patients) of two-stage revision for infected TKA was analyzed including four failure cases (Figure 1). The following patient demographics were recorded: Age, sex, Body Mass Index (BMI), comorbidities (hypertension, Diabetes Mellitus (DM), heart disease), previous knee surgery, history of cancer, alcohol drinking, smoking, infection interval, laboratory tests (Hemoglobin (Hb), White Blood Cell (WBC), Erythrocyte Sedimentation Rate

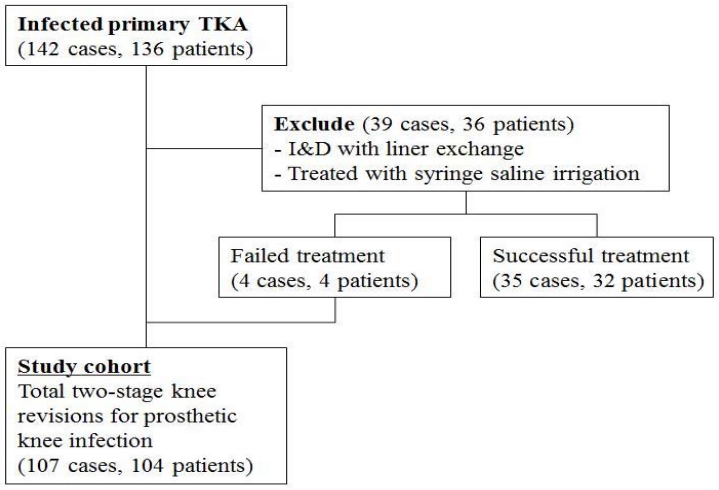

Figure 1: Summary of infected total knee arthroplasty.

Table 1: Univariate analysis results for demographic characteristics of infected total knee arthroplasty patients.

Variable	All patients (n=107)	Reinfection group (n=19)	Non-reinfection group (n=88)	*p*-value
Age at revision TKA (years)	70.6 (52-83)	70.5 (52-80)	70.5 (54-83)	0.977
Sex*				>0.999
Male	19 (17.8%)	3 (15.8%)	16 (18.2%)	
Female	88 (82.2%)	16 (84.2%)	72 (81.8%)	
BMI (kg/m$^{2)}$*	25.6 (18.3-38.3)	25.4 (18.3-32.0)	25.7 (19.5-38.3)	0.804
Hypertension*	73 (68.2%)	15 (78.9%)	58 (65.9%)	0.268
Diabetes mellitus*	29 (27.1%)	6 (31.6%)	23 (26.1%)	0.628
Heart disease*	3 (2.8%)	1 (5.3%)	2 (2.3%)	0.447
Previous knee surgery*	15 (14.0%)	2 (10.5%)	13 (14.8%)	>0.999
Cancer*	10 (9.3%)	5 (26.3%)	5 (5.7%)	0.015
Alcohol drinking*	2 (1.9%)	0 (0)	2 (2.3%)	>0.999
Smoking*	5 (4.7%)	0 (0)	5 (5.7%)	0.583
Time from primary TKA to infection (m)	34.3 (0-183)	39.3 (1-141)	33.2 (0-183)	0.541
Time from infection to implant removal (w)	20.7 (0-313)	10.4 (0-52)	23.0 (0-313)	0.330
Time from implant removal to revision TKA (w)	6.2 (2-19)	6.9 (4-11)	6.1 (2-19)	0.197
Time from revision TKA to reinfection (m)	.	15.0 (0-61)	.	.
Time from revision TKA to latest follow-up (m)	54.7 (0-151)	62.0 (7-123)	53.1 (0-151)	0.316
Preoperative primary TKA, CRP	0.23 (0.03-1.42)	0.25 (0.03-1.37)	0.17 (0.03-1.42)	0.945
Preoperative primary TKA, WBC	7.6 (4.4-15.5)	7.9 (4.8-12.8)	7.6 (4.4-15.5)	0.684
Preoperative primary TKA, Hb	13.3 (10.3-16.1)	13.0 (10.3-15.4)	13.4 (10.8-16.1)	0.209
Preoperative primary TKA, ESR	22.5 (3-80)	20.83 (10-38)	21.5 (3-80)	0.813
Infected TKA, CRP	8.50 (0.1-43.6)	8.7 (0.4-29.2)	8.45 (0.1-43.6)	0.341
Infected TKA, WBC	9.8 (3.9-21.7)	9.1 (3.9-19.9)	9.9 (5.1-21.7)	0.289
Infected TKA, Hb	11.7 (8.8-16.7)	11.4 (9-14.4)	11.8 (8.8-16.7)	0.312
Infected TKA, ESR	69.8 (2-121)	80.3 (13-112)	67.1 (2-121)	0.921
Revision TKA, tourniquet time (m)	90.0 (45-180)	88.9 (45-110)	90.3 (45-180)	0.851
Type of microorganism*				0.630
MRSA	4 (3.7%)	1 (5.3%)	3 (3.4%)	
DTT	13 (12.1%)	3 (15.8%)	10 (11.4%)	
ETT	90 (84.1%)	15 (78.9%)	75 (85.2%)	

* The values are given as number with percentage in parentheses

Abbreviations: TKA: Total Knee Arthroplasty; BMI: Body Mass Index; CRP: C-Reactive Protein; WBC: White Blood Cell; Hb: Hemoglobin; ESR: Erythrocyte Sedimentation Rate; MRSA: Methicillin-Resistant *Staphylococci aureus*; DTT: Difficult to Treat; ETT: Easy to Treat

Table 2: Multivariable logistic regression analysis of the relative contribution of each variable to reinfection after two-stage revision total knee arthroplasty.

Variable	Hazard ratio	95% Confidence interval	*p*-value
Age at revision TKA (years)	0.981	0.911 - 1.055	0.608
Sex, male	0.843	0.219 - 3.244	>0.999
BMI (kg/m$^{2)}$	0.976	0.842 - 1.131	0.749
Hypertension	1.939	0.591 - 6.361	0.268
Diabetes mellitus	1.304	0.443 - 3.832	0.628
Heart disease	2.388	0.205 - 27.780	0.447
Previous knee surgery	0.678	0.139 - 3.292	>0.999
Cancer	5.928	1.517 - 23.160	0.015
Alcohol drinking	0.819	0.748 - 0.896	>0.999
Smoking	0.813	0.741 - 0.892	0.583
Time from primary TKA to infection (m)	1.003	0.992 - 1.014	0.567
Time from infection to implant removal (w)	0.987	0.965 - 1.010	0.289
Time from implant removal to revision TKA (w)	1.122	0.936 - 1.345	0.210
Preoperative primary TKA, CRP	0.770	0.171 - 3.465	0.734
Preoperative primary TKA, WBC	1.037	0.827 - 1.302	0.748
Preoperative primary TKA, Hb	0.728	0.472 - 1.122	0.151
Preoperative primary TKA, ESR	0.994	0.957 - 1.032	0.764
Infected TKA, CRP	1.003	0.951 - 1.058	0.902
Infected TKA, WBC	0.920	0.783 - 1.080	0.310
Infected TKA, Hb	0.817	0.578 - 1.156	0.255
Infected TKA, ESR	1.001	0.984 - 1.018	0.866
Revision TKA, tourniquet time (m)	0.997	0.976 - 1.019	0.820

Abbreviations: TKA: Total Knee Arthroplasty; BMI: Body Mass Index; CRP: C-Reactive Protein; WBC: White Blood Cell; Hb: Hemoglobin; ESR: Erythrocyte Sedimentation Rate

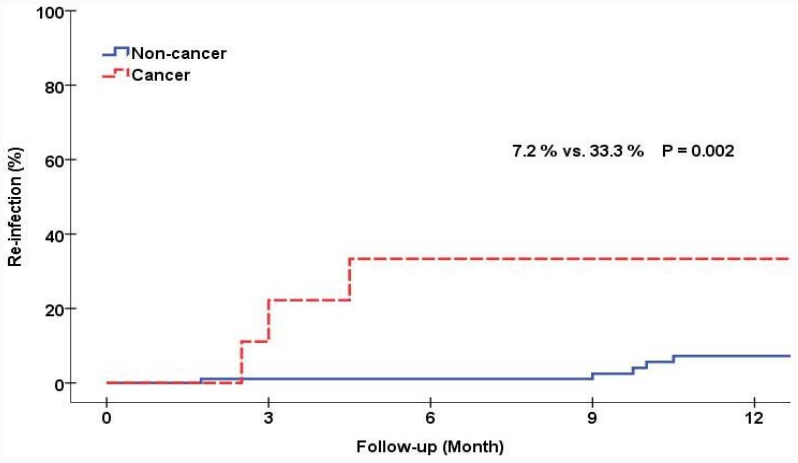

Figure 2: One-year Kaplan-Meier survival analysis of cancer and non-cancer groups after revision total knee arthroplasty.

(ESR), C-Reactive Protein (CRP)), operation tourniquet time, and type of microorganism. The types of organisms were 1) Methicillin-Resistant *Staphylococci aureus* (MRSA); 2) "Difficult to Treat" (DTT) organisms including quinolone-resistant gram-negative bacteria, rifampicin-resistant *Staphylococcus*, *Enterococcus*, and *Candida*; and 3) all other organism summarized as "Easy to Treat" (ETT) including anaerobic bacteria, gram-negative bacteria, culture-negative infection, coagulase-negative *Staphylococcus*, polymicrobial infection, *Staphylococci aureus*, and streptococci [11,12]. The diagnosis of periprosthetic joint infection prior to two-stage revision was confirmed when at least three of the following criteria were met: 1) CRP>1 mg/dl; 2) ESR>30 mm/h; 3) positive culture from joint aspirate; 4) pus at operation; and 5) positive intra-operative culture [13]. Two-stage revision consisted of removal of all prosthetic components, insertion of a vancomycin-impregnated cement (2 g vancomycin per 40 g cement) articulating spacer, and delayed reimplantation. After the first stage, patients underwent physiotherapy to encourage passive knee movement and preserve quadriceps strength. Delayed reimplantation was performed when the wound was healthy and the patient was clinically stable with

Table 3: Summary of reinfection after two-stage revision total knee arthroplasty cases.

Patient No.	Age at revision TKA/sex	BMI (kg/m²)	HT/DM/others	Cancer	Time from primary TKA to infection (m)	Time from infection to implant removal (w)	Time from implant removal to revision TKA (w)	Time from revision TKA to reinfection (m)	Time from revision TKA to latest follow-up (m)	Type of microorganism at infection	Type of microorganism at reinfection	Treatment of reinfection
1	60/F	24.5	Yes/Yes/No	Uterine cancer (TAH), 13 years ago	12	1	7	0	91	No growth	Hafnia alvei	Antimicrobial therapy
2	72/M	19.5	Yes/No/Tuberculosis	No	11	1	9	2	122	*Staphylococcus aureus*	No growth	Antimicrobial therapy
3	71/F	26.1	Yes/Yes/Angina	Gastric cancer (subtotal gastrectomy), 16 years ago	27	5	8	1	10	*Staphylococcus aureus*	No growth	Antimicrobial therapy
4	65/F	26.6	Yes/No/Tuberculosis	No	9	12	11	41	123	Coagulase negative *Staphylococcus*	No growth	re-revision TKA
5	79/F	24.1	Yes/Yes/No	No	22	8	7	34	88	No growth	No growth	I & D
6	73/M	26.9	Yes/Yes/No	Colorectal cancer (cured), 5 years ago	3	2	5	43	99	*Streptococcus pyogenes*	No growth	I & D
7	62/F	27.6	No/No/No	No	3	52	4	0	93	No growth	No growth	re-revision TKA
8	74/F	25.4	No/No/No	No	3	40	4	61	91	No growth	No growth	re-revision TKA
9	75/F	28.8	No/No/No	No	29	1	4	13	76	No growth	Escherichia coli	Antimicrobial therapy
10	79/F	18.3	Yes/Yes/Cerebrovascular accident	No	60	2	6	22	39	*Escherichia coli*	No growth	re-revision TKA
11	69/F	29.6	Yes/Yes/No	No	1	2	10	3	63	No growth	No growth	re-revision TKA
12	78/F	23.4	Yes/No/No	No	137	39	4	0	36	No growth	No growth	Antimicrobial therapy
13	56/F	24.6	No/Yes/No	No	34	13	7	37	42	*Staphylococcus aureus*	No growth	Transfer, f/u loss
14	75/F	27.9	Yes/Yes/No	No	24	0	5	0	67	*Achromobacter xylosoxidans* subsp xylosoxidans	No growth	re-revision TKA
15	75/F	22.2	Yes/Yes/Cardiac insufficiency	No	141	1	11	5	65	No growth	No growth	re-revision TKA
16	52/F	32.0	Yes/Yes/No	No	3	5	6	9	40	Candida albicans	No growth	Transfer, f/u loss
17	74/F	27.4	Yes/No/No	Uterine cancer (cured), 6 years ago	32	1	5	8	12	No growth	*Streptococcus dysgalactiae* ssp equisimilis	I & D
18	80/M	19.8	Yes/No/No	Gastric cancer (subtotal gastrectomy), 20 years ago	129	9	11	6	18	No growth	No growth	Antimicrobial therapy
19	73/F	27.9	Yes/No/No	No	66	2	7	1	7	No growth	No growth	Antimicrobial therapy

Abbreviations: TKA: Total Knee Arthroplasty; BMI: Body Mass Index; HT: Hypertension; DM: Diabetes Mellitus; F: Female; M: Male; TAH: Total Abdominal Hysterectomy; I & D: Irrigation and Debridement; f/u: follow-up

normal CRP. Clinical and radiological data from all patients who underwent joint replacement were collected retrospectively from the joint registries of our institutions. Patients had been examined before surgery and at six weeks, six months, and one year after surgery and yearly thereafter. Reinfection was diagnosed by clinical signs, blood work (ESR and CRP), and positive culture of synovial aspiration. The mean follow-up period after revision TKA was 62.0 (7 to 123) months. In the reinfection group, 16 patients were females, three patients were male, and the mean age was 70.5 (52 to 80) years. The mean time from revision TKA to diagnosis of reinfection was 15.0 (0 to 61) months. We evaluated possible risk factors between success and reinfection groups. Differences in continuous variables between the two groups were evaluated using the unpaired t-test or Mann-Whitney rank test. The data are shown as mean (minimum-maximum). For discrete variables, differences are shown as count and percentage and analyzed with reinfection occurred over 15 years of follow-up. Multivariate logistic regression analysis was used to assess the independent impact factor for reinfection. A two-tailed p-value <0.05 was considered statistically significant.

Results

There were 19 cases of reinfection (17.8%) after two-stage revision in our center. Three patients were treated by I & D, and seven patients underwent a two-stage re-revision TKA. Seven patients who were in poor physical condition or refused additional surgical procedures were treated with antimicrobial therapy, and two cases were lost to follow-up. The lost to follow-up patients did not visit the hospital directly, but their condition was checked by telephone interview. The demographic characteristics and univariate analysis of infected TKA patients are shown in Table 1. The mean durations from primary TKA to infection and from infection to implant removal in all patients were 34.3 (0 to 183) months and 20.7 (0 to 313) weeks, respectively. The mean time from revision to reinfection in the reinfection group was 15.0 (0 to 61) months. Between the reinfection and success groups, age, sex, and BMI were similar, and there were no significant differences in hypertension, DM, heart disease, previous knee surgery, alcohol drinking, smoking, time from TKA to infection, time from infection to implant removal, time from implant removal to revision interval, time from revision to latest follow up, preoperative

primary TKA lab values (CRP, WBC, Hb, and ESR), infected TKA lab values (CRP, WBC, Hb, and ESR), revision TKA tourniquet time, and type of microorganism (MRSA, DTT, and ETT). The only significant difference was history of cancer (p=0.015), which remained significant in multivariable logistic regression analysis (HR 5.928, p=0.015) (Table 2). There were no statistically significant differences in reinfection relative to other risk factors. In 19 reinfection cases, those with cancer had a final follow-up period of 3 to 99 months, and those without had a final follow-up period of 0 to 157 months. There was a total of 10 cancer patients: Five were reinfected and five were observed without reinfection. In the reinfection-cancer group, there were two uterine cancers, two gastric cancers, and one colorectal cancer (Table 3). Figure 2 depicts the cumulative survival rates between the cancer and non-cancer groups during a one-year period. There was a significantly higher chance that subjects in the cancer group were reinfected within one year compared to that in subjects in the non-cancer group (33.3% *vs.* 7.2%, p=0.002).

Discussion

Infection remains one of the most serious complications of TKA. Two-stage revision is the standard treatment of infected TKA and seems to eradicate infection and provide a functional outcome. This case-control study aimed to evaluate the reinfection rate of two-stage revision and to analyze the factors affecting prognosis of two-stage revision for infected TKA. The most important finding of our study is that history of cancer was the only risk factor for reinfection after two-stage revision for infected TKA. There was a significantly higher chance that a subject with cancer would be reinfected within one year than a subject without. To find out the cause of this result, it is necessary to check the recurrence of cancer or immunotherapy, chemotherapy and radiotherapy in the cancer group. In our study, there were 19 cases of reinfection (17.8%) after two-stage revision. This is similar to previous studies that showed a 10% to 12% incidence of reinfection after two-stage revision [14,15]. Several studies have reported risk factors and reinfection rate of two-stage revision for infected TKA. Sabry et al. reported the following as preoperative predictors of failure following two-stage revision: Duration of symptoms, time from index surgery, number of previous surgeries, high markers of inflammation levels (CRP, ESR, and peripheral WBC count), lower hemoglobin and hematocrit, need for soft tissue coverage, time to reimplantation, previous infection in the same joint, higher the American Society of Anesthesiologists (ASA) score, DM, anemia, heart disease, and infection with a gram-negative organism in the absence of malignancy [16]. Kubista reported chronic lymphedema, revision between resection and definitive reimplantation, and intravenously administered cefazolin as the strongest positive predictors of treatment failure [17]. Fashingbauer et al. reported revision during or after a two-stage exchange, number of surgeries, and alcohol abuse as risk factors for recurrence, and that recurrence rates did not differ among organisms [10]. Fehring reported repeat two-stage exchange arthroplasty for periprosthetic knee infection is dependent on host grade (Musculoskeletal Infection Society, MSIS) [18]. Also, Vadiee found a higher incidence of failure in those patients with poor general health based on MSIS score, inadequate soft tissue envelope and resistant bacteria [19]. Kao reported that low periprosthetic knee joint infection rates and high 5-year relative survive rates indicate the feasibility of TKA in cancer patients despite a higher mortality rate in the first year following TKA [20]. Previous studies attempted to identify risk factors associated with reinfection after two-stage revision [10,17]. However, little information is available concerning the prognosis and risk factors in reinfection after two-stage revision for infected TKA. In this study, that undergoing revision operation for infected TKA with history of cancer (10 patients) showed a relatively high re-infection rate of 50% (5 patients). This result seems similar to host grade MSIS of previous studies, but the strength of our study is to identify the history of cancer as a risk factor. Assessment of a total knee arthroplasty patient with a history of cancer should start with a thorough review of cancer with an emphasis on treatment modalities, dosages, and timing of treatments. The patient's medication profile should also be examined for potential medication interactions. The most effective way to reduce complications is to make sure that patient is in optimal health before the surgery is scheduled. Surgeons should not hesitate to delay elective joint arthroplasty in the event that the patient's condition is yet to be optimized [21]. This study had some limitations. First, it was retrospectively designed and may have introduced bias when data were not accurately reported in the medical chart. In particular, medical history was recorded through patient statements. Second, in the cancer group, we could not assess cancer recurrence or immunosuppressant use during the follow-up period. Third, we could not analyze antibiotics used due to individualization of treatment regimens without a standardized protocol. Fourth, the finding that there was no organism-dependent difference in reinfection after two-stage revision conflicts with the current literature [22-24]. One possible reason for this discrepancy is that our study had an insufficient number of cases to achieve adequate power analyses. Nevertheless, our study says that history of cancer might be especially important among systemic host compromising factors and significantly higher chance that subjects in the cancer group were reinfected within one year compared to that in subjects in the non-cancer group.

In conclusion, patients with identified history of cancer undergoing revision operation for infected TKA showed worse outcomes. Therefore, staged revision arthroplasty in patients with history of cancer should be closely observed to minimize re-infection, and these patients should be informed of the high probability of infection.

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