Bone & Joint Research

Supplementary Material

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Contents

1. METHODS 2
1.1. Patient and public involvement 2
1.2. Definition of the at-risk periods 2
1.3. **Time-specific hazard-ratios and model selection** 3
2. SUPPLEMENTARY TABLES 4
3. FIGURES 9

1. METHODS

1.1. Patient and public involvement

Our overall research programme was supported by a dedicated group of patients who had previously had treatment for periprosthetic joint infection (PJI). These patients had been involved in the conduct of all our National Joint Registry (NJR) analyses relating to PJI, including identification of the research questions, study design, conduct, and interpretation of the results. We specifically consulted the group as to what revision outcomes they considered important in the context of this analysis, and we received strong feedback that all revisions used to manage PJI from the point that it is determined that single- or two-stage revision is required should be included. They felt that if repeat first stages before a second-stage procedure were not captured, this would not adequately describe their own lived experience. Quotes from the group include "it is more realistic to include everything", "I had many complications between stages, it was not a straightforward journey between stage 1 and stage 2", and "the middle bit is the worst".

1.2. Definition of the at-risk periods

Patients were followed up from the date of their initial revision surgery for PJI (date of first single-stage or stage 1 of 2 procedure) until the end of the observation period (31 December 2014), date of death, or the date of a re-revision. Patients re-revised with a single stage were therefore followed up until the date of this procedure. Patients re-revised with a two-stage procedure were followed up until the date of the stage 1 surgery. For 54 patients operated with a two-stage procedure, the first procedure (stage 1 of two-stage) was not reported and only the second procedure (stage 2 of two-stage) was recorded (54/165). The date of their stage 1 of two-stage reoperation procedure, and the period they had been at risk of reoperation, were therefore estimated. We initially derived the relative weight of time elapsed between the first PJI revision surgery (date of single-stage procedure or date of stage 2 operation for two-stage procedure) and stage 1 of the two-stage reoperation procedure using patients with complete information: 100 × ([length of time between stage 1 of two-stage reoperation and first PJI revision] / [length of time between stage 2 of two-stage reoperation and first PJI revision]). We then applied this weight to the length of time between the first PJI revision and stage 2 of the two-stage reoperation for those with incomplete information, to estimate the duration between the first stage of their two-stage reoperation and the initial PJI revision surgery.

Patients with incompletely registered two-stage reoperation procedures (n = 54) were comparable to those with both stage 1 and stage 2 reoperation procedures recorded in the NJR (n = 111) in terms of age (≥ 80 yrs: 6% vs 5%; ≤ 60 yrs: 30% vs 34%, p = 0.935), sex (female: 44% vs 37%, p = 0.349), American Society of Anesthesiologists (ASA) Physical Status grade (> P2: 14% vs 15%, P1: 15% vs 19%, p = 0.798) reported at the time of their first revision for PJI (and time of their primary knee arthroplasty; results available on request). They were also comparable in terms of type of primary knee procedure (cruciate ligament retaining and posterior-stabilized: 65% vs 66%; constrained condylar: 28% vs 28%; unicompartmental: 7% vs 5%).

A similar strategy was used to derive the date of the first revision for PJI following the primary knee arthroplasty performed with a two-stage revision, when the stage 1 procedure was not recorded in the NJR. Full details are available elsewhere.[1] Patients with incompletely registered two-stage revision procedures performed for PJI (n =

792) were also comparable from those with complete information for stages 1 and 2 (n = 1,568).

For patients revised for PJI, the time at risk of death was derived from the date of the initial revision surgery for PJI (date of first single-stage or stage 1 of two-stage procedure) until the end of the observation period (31 December 2014) or date of death. For patients with a primary knee arthroplasty never revised, the time at risk of death was derived from the date of primary procedure. For patients with a primary knee arthroplasty revised for a non-septic indication, the time at risk of death was derived from the first revision for non-septic indication.

1.3. Time-specific hazard ratios and model selection

The overall, time-averaged hazard ratios (HRs) derived from the Cox shared frailty model to produce findings comparable with the literature were supplemented with time-dependent HRs to capture time-specific disparities between PJI revision procedures. We used Poisson regression (time at risk modelled as an offset) adjusted for age, sex, ASA grade, and type of knee surgery, and modelled the baseline hazard function with restricted cubic splines. The optimum numbers of knots (two degrees of freedom (d.f.)) were identified using the most parsimonious model, minimizing both Bayesian information criterion and Akaike information criterion (Supplementary Table i). We modelled interaction terms between the splines and the main exposure covariate to estimate the time-varying HRs. We computed Huber-White-sandwich robust estimate of variance to account for within-hospital correlation. We used a similar approach to compare the incidence of re-revision for PJI (restricted cubic splines Poisson model with two d.f.) and the risk of mortality (restricted cubic splines Poisson model with five d.f.) between revision procedure types.

2. SUPPLEMENTARY TABLES

The models that minimized the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) criteria were selected to identify the number of optimal knots for the spline function (number of degrees of freedom-1). The log of follow-up time was modelled to obtain better fitting models.

Supplementary Table i. Model selection - Akaike and Bayesian Information Criterions by number of knots used to parametrize the spline function.*

Model	d.f.†	AIC‡	BIC§
All-cause reoperation			
	2	3,106	3,119
	3	3,107	3,122
	4	3,108	3,126
	5	3,109	3,130
Periprosthetic joint infection reoperation-revision			
	2	2,726	2,738
	3	2,725	2,740
	4	2,727	2,746
	5	2,728	2,750
Mortality			
	2	80,703	80,771
	3	80,632	80,711
	4	80,600	80,691
	5	80,586	80,688
	6	80,577	80,691

*In bold, model with optimal number of knots.

†Degrees of freedom; number of knots = df-1.

‡Akaike Information Criterion.

§Bayesian Information Criterion.

Supplementary Table ii. Hazard ratio of all-cause reoperation between single-stage and two-stage revision (reference) performed to manage infected primary knee arthroplasty.

Time*	Unadjusted Analysis			Adjusted analysis†			Sensitivity analysis†‡		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
1 mth	1.93	0.93 to 4.03	0.084	1.86	0.89 to 3.85	0.096	1.25	0.61 to 2.56	0.544
3 mths	1.56	0.98 to 2.51	0.061	1.51	0.95 to 2.41	0.081	1.32	0.81 to 2.13	0.262
6 mths	1.38	0.89 to 2.14	0.151	1.33	0.86 to 2.05	0.204	1.28	0.81 to 2.02	0.293
9 mths	1.28	0.85 to 1.92	0.234	1.23	0.82 to 1.84	0.319	1.22	0.80 to 1.87	0.358
12 mths	1.21	0.84 to 1.75	0.299	1.16	0.80 to 1.68	0.417	1.16	0.79 to 1.71	0.442
24 mths	1.07	0.80 to 1.45	0.634	1.03	0.76 to 1.39	0.867	0.98	0.71 to 1.35	0.911
36 mths	1.00	0.67 to 1.50	0.674	0.95	0.63 to 1.44	0.826	0.87	0.56 to 1.34	0.517
48 mths	0.96	0.55 to 1.65	0.862	0.91	0.52 to 1.58	0.731	0.79	0.44 to 1.40	0.418
60 mths	0.92	0.47 to 1.81	0.801	0.87	0.44 to 1.74	0.697	0.73	0.36 to 1.49	0.384
72 mths	0.90	0.41 to 1.97	0.771	0.85	0.38 to 1.87	0.681	0.69	0.30 to 1.56	0.369

CI, confidence interval; HR, hazard ratio.

*Time from first revision for prosthesis joint infection.

†Adjusted for age, sex, American Society of Anesthesiologists grade, and type of primary knee arthroplasty.

‡Excluding patients with incomplete two-stage revision procedures (n = 792).

Supplementary table iii. Hazard ratio of re-revision for periprosthetic joint infection between single-stage and two-stage revision (reference) procedures performed to manage infected primary knee arthroplasty.

Time*	Unadjusted analysis			Adjusted analysis†			Sensitivity analysis†‡		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
1 mth	1.81	0.86 to 3.82	0.126	1.78	0.85 to 3.71	0.124	1.17	0.57 to 2.40	0.664
3 mths	1.34	0.80 to 2.25	0.259	1.33	0.80 to 2.20	0.274	1.13	0.67 to 1.93	0.636
6 mths	1.12	0.68 to 1.84	0.646	1.10	0.67 to 1.80	0.694	1.06	0.63 to 1.78	0.826
9 mths	1.01	0.64 to 1.60	0.948	0.99	0.63 to 1.57	0.983	0.99	0.62 to 1.60	0.984
12 mths	0.94	0.62 to 1.43	0.797	0.93	0.61 to 1.40	0.719	0.94	0.62 to 1.44	0.776
24 mths	0.81	0.52 to 1.24	0.328	0.79	0.51 to 1.21	0.279	0.79	0.52 to 1.21	0.277
36 mths	0.74	0.40 to 1.38	0.340	0.72	0.38 to 1.34	0.302	0.70	0.38 to 1.31	0.266
48 mths	0.70	0.31 to 1.57	0.381	0.67	0.30 to 1.53	0.348	0.64	0.29 to 1.46	0.292
60 mths	0.66	0.25 to 1.78	0.412	0.64	0.24 to 1.73	0.381	0.60	0.22 to 1.61	0.324
72 mths	0.64	0.21 to 1.97	0.431	0.62	0.20 to 1.90	0.403	0.57	0.19 to 1.75	0.327

CI, confidence interval; HR, hazard ratio.

*Time from first revision for prosthesis joint infection.

†Adjusted for age, sex, American Society of Anesthesiologists grade, and type of primary knee arthroplasty.

‡Excluding patients with incomplete two-stage revision procedures (n = 792).

Supplementary Table iv. Hazard ratio of mortality between revision procedures performed to manage infected primary knee arthroplasty and other arthroplasty procedures.

Time*	1 stage vs 2 stage (reference)			1 stage vs primary (reference)			2 stage vs primary (reference)			1 stage vs aseptic revision† (reference)			2 stage vs aseptic revision† (reference)		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Unadjusted analysis															
3 mths	1.01	0.51 to 1.98	0.981	3.26	1.77 to 6.01	< 0.001	3.23	2.48 to 4.21	< 0.001	4.24	2.22 to 8.11	< 0.001	4.21	2.94 to 6.02	< 0.001
6 mths	0.45	0.23 to 0.89	0.022	1.12	0.57 to 2.18	0.741	2.49	2.04 to 3.05	< 0.001	1.42	0.72 to 2.78	0.309	3.16	2.43 to 4.10	< 0.001
12 mths	0.21	0.07 to 0.62	0.005	0.38	0.13 to 1.13	0.081	1.81	1.35 to 2.43	< 0.001	0.46	0.15 to 1.40	0.171	2.22	1.57 to 3.14	< 0.001
18 mths	0.31	0.10 to 0.89	0.030	0.51	0.17 to 1.47	0.214	1.66	1.28 to 2.15	< 0.001	0.61	0.20 to 1.78	0.365	1.99	1.50 to 2.65	< 0.001
24 mths	0.79	0.32 to 1.95	0.612	1.33	0.56 to 3.16	0.519	1.68	1.26 to 2.23	< 0.001	1.59	0.67 to 3.78	0.292	2.01	1.47 to 2.75	< 0.001
2.5 yrs	1.20	0.66 to 2.18	0.556	1.79	1.03 to 3.12	0.038	1.50	1.15 to 1.95	0.003	2.15	1.23 to 3.76	0.007	1.80	1.33 to 2.42	< 0.001
36 mths	0.99	0.41 to 2.37	0.981	1.21	0.50 to 2.94	0.678	1.22	0.87 to 1.71	0.246	1.48	0.60 to 3.66	0.389	1.50	1.03 to 2.19	0.034
48 mths	1.00	0.41 to 2.43	0.995	1.27	0.57 to 2.86	0.560	1.28	0.87 to 1.86	0.21	1.73	0.76 to 3.98	0.193	1.74	1.15 to 2.63	0.008
60 mths	1.34	0.40 to 4.88	0.655	3.05	0.94 to 9.94	0.063	2.27	1.36 to 3.81	< 0.001	2.96	0.89 to 9.86	0.077	2.21	1.19 to 4.10	0.012
Adjusted analysis‡															
3 mths	1.14	0.58 to 2.24	0.698	2.93	1.59 to 5.41	< 0.001	2.57	1.96 to 3.35	< 0.001	3.17	1.66 to 6.04	< 0.001	2.77	1.94 to 3.97	< 0.001
6 mths	0.51	0.25 to 1.00	0.049	1.01	0.52 to 1.95	0.984	1.99	1.63 to 2.43	< 0.001	1.06	0.54 to 2.06	0.870	2.09	1.62 to 2.70	< 0.001
12 mths	0.23	0.08 to 0.69	0.008	0.34	0.11 to 1.01	0.051	1.44	1.10 to 1.95	0.009	0.34	0.11 to 1.03	0.056	1.47	1.05 to 2.07	0.025
18 mths	0.33	0.12 to 0.99	0.048	0.46	0.16 to 1.34	0.156	1.35	1.06 to 1.73	0.016	0.45	0.15 to 1.32	0.146	1.33	1.01 to 1.75	0.044
24 mths	0.88	0.35 to 2.18	0.779	1.21	0.50 to 2.94	0.666	1.38	1.05 to 1.83	0.022	1.17	0.48 to 2.85	0.722	1.34	0.98 to 1.82	0.063

2.5 yrs	1.33	0.72 to 2.45	0.360	1.65	0.93 to 2.91	0.084	1.24	0.94 to 1.63	0.120	1.58	0.89 to 2.83	0.119	1.19	0.88 to 1.61	0.255
36 mths	1.11	0.46 to 2.68	0.822	1.12	0.45 to 2.76	0.805	1.01	0.71 to 1.44	0.944	1.10	0.44 to 2.73	0.843	0.99	0.67 to 1.46	0.964
48 mths	1.15	0.47 to 2.77	0.761	1.24	0.55 to 2.79	0.595	1.08	0.75 to 1.58	0.669	1.35	0.59 to 3.07	0.478	1.17	0.78 to 1.77	0.441
60 mths	1.69	0.46 to 6.20	0.427	3.32	1.02 to 10.84	0.052	1.96	1.16 to 3.31	0.018	2.51	0.75 to 8.42	0.135	1.48	0.79 to 2.77	0.216
Sensitivity analysis‡§															
3 mths	0.87	0.45 to 1.68	0.718				3.31	2.56 to 4.30	< 0.001				3.58	2.44 to 4.55	< 0.001
6 mths	0.45	0.23 to 0.89	0.021				2.24	1.79 to 2.79	< 0.001				2.35	2.54 to 5.05	< 0.001
12 mths	0.24	0.08 to 0.73	0.011				1.39	0.97 to 2.00	0.070				1.40	0.94 to 2.10	0.098
18 mths	0.36	0.12 to 1.06	0.064				1.26	0.93 to 1.71	0.139				1.24	0.90 to 1.70	0.193
24 mths	0.87	0.34 to 2.19	0.766				1.40	1.00 to 1.94	0.047				1.35	0.95 to 1.91	0.089
30 mths	1.20	0.64 to 2.24	0.569				1.38	0.99 to 1.90	0.054				1.32	0.93 to 1.87	0.119
36 mths	0.96	0.40 to 2.30	0.919				1.17	0.78 to 1.76	0.447				1.15	0.74 to 1.77	0.536
48 mths	1.13	0.45 to 2.85	0.792				1.10	0.69 to 1.75	0.691				1.19	0.72 to 1.95	0.490
60 mths	1.83	0.46 to 7.30	0.390				1.81	0.91 to 3.59	0.093				1.37	0.65 to 2.87	0.403

CI, confidence interval; HR, hazard ratio.

*Time from first revision for prosthesis joint infection for the “single-stage” and “two-stages” group, from the primary knee arthroplasty for the “primary” group, or from the revision for a non-septic indication for the “aseptic revision” group.

†Aseptic revision: revision surgery performed for other indication than an infection.

‡Adjusted for age, sex, American Society of Anesthesiologists grade, and type of primary knee arthroplasty.

§Excluding patients with incomplete two-stage revision procedures (n = 792).

3. FIGURES

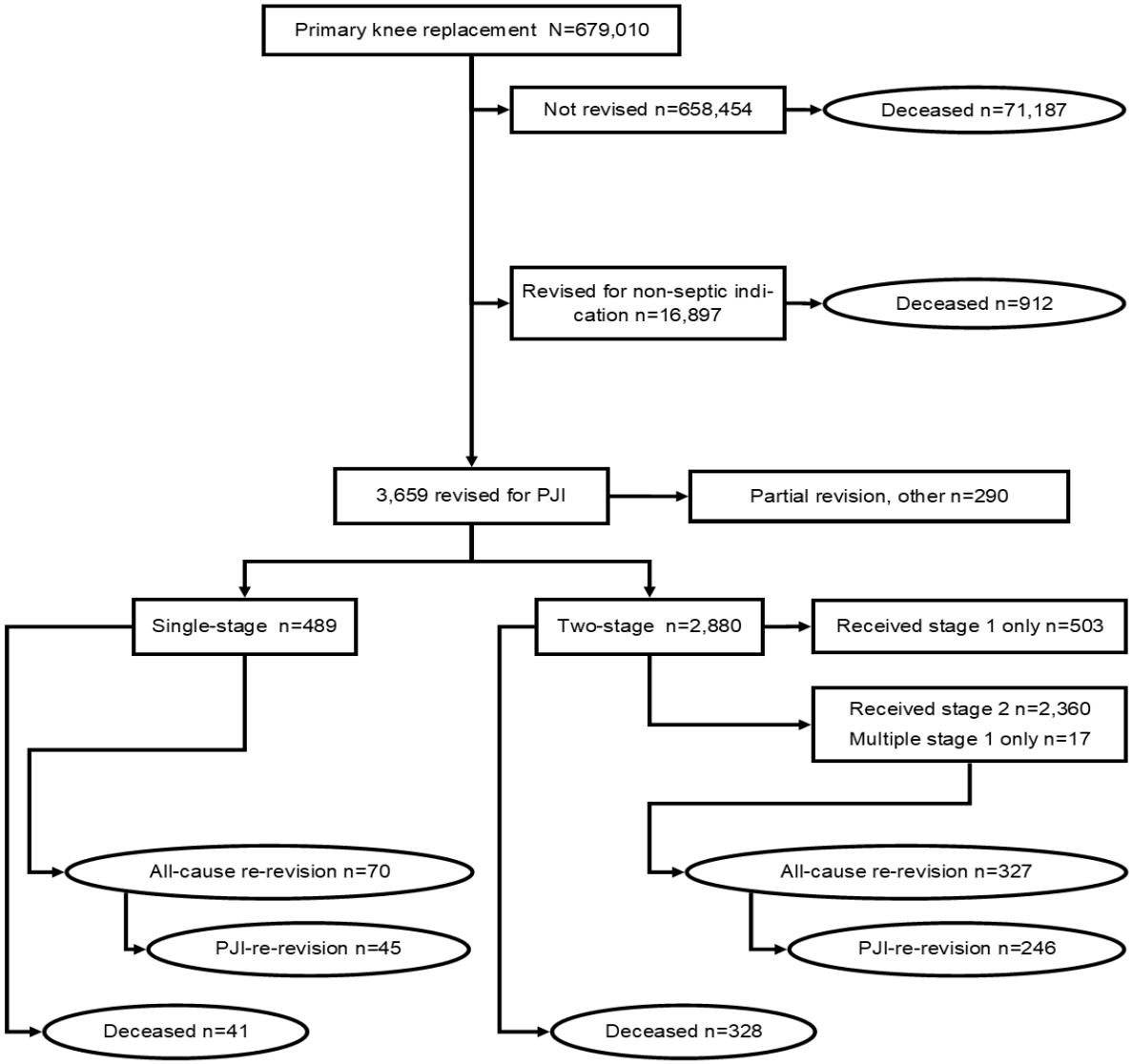


Fig a. Participants flow diagram. PJI, periprosthetic joint infection.

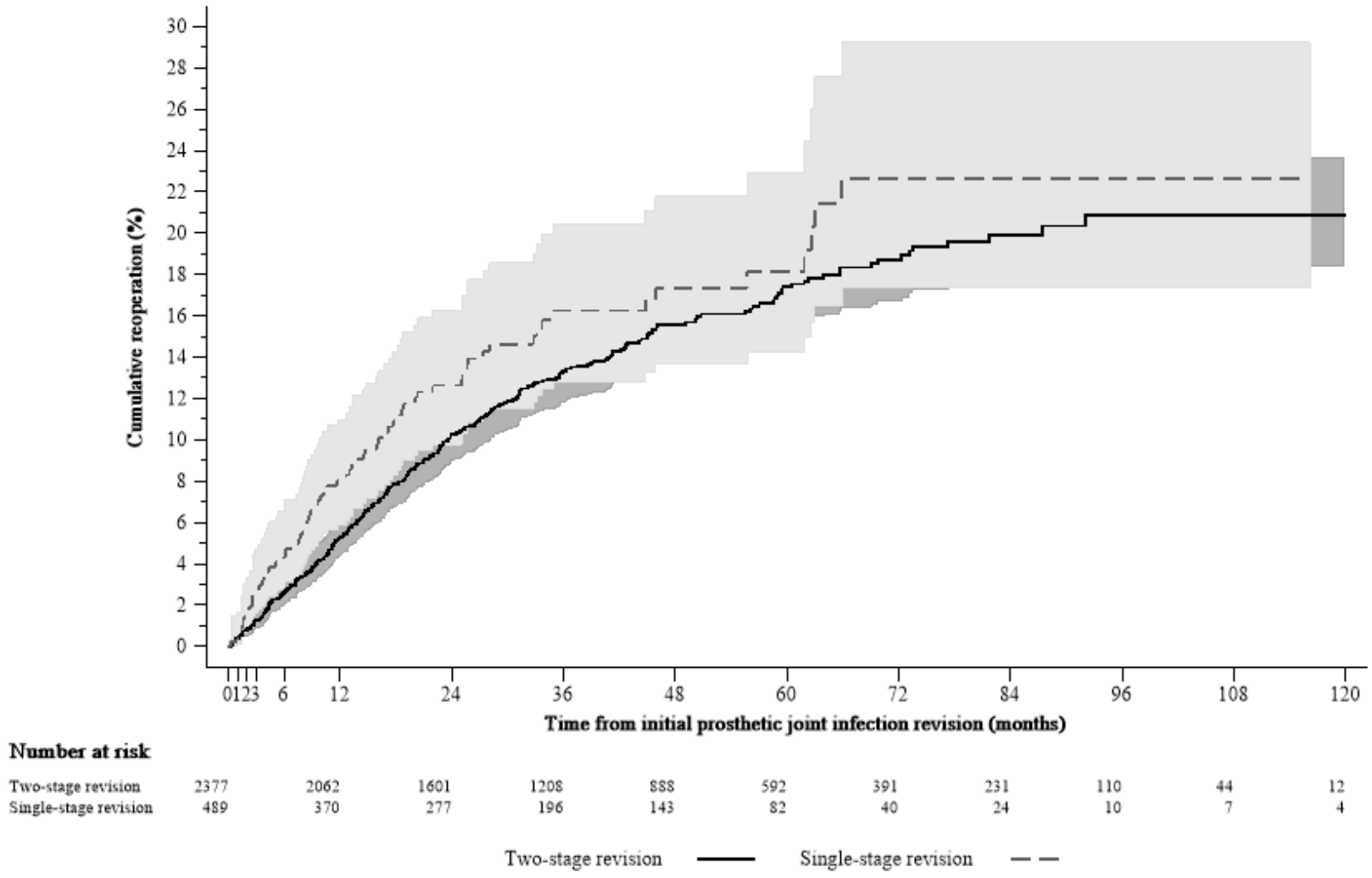


Fig b. Kaplan–Meier cumulative hazard function of all-cause re-revision by single-stage or two-stage revision procedure for infected primary knee arthroplasty.

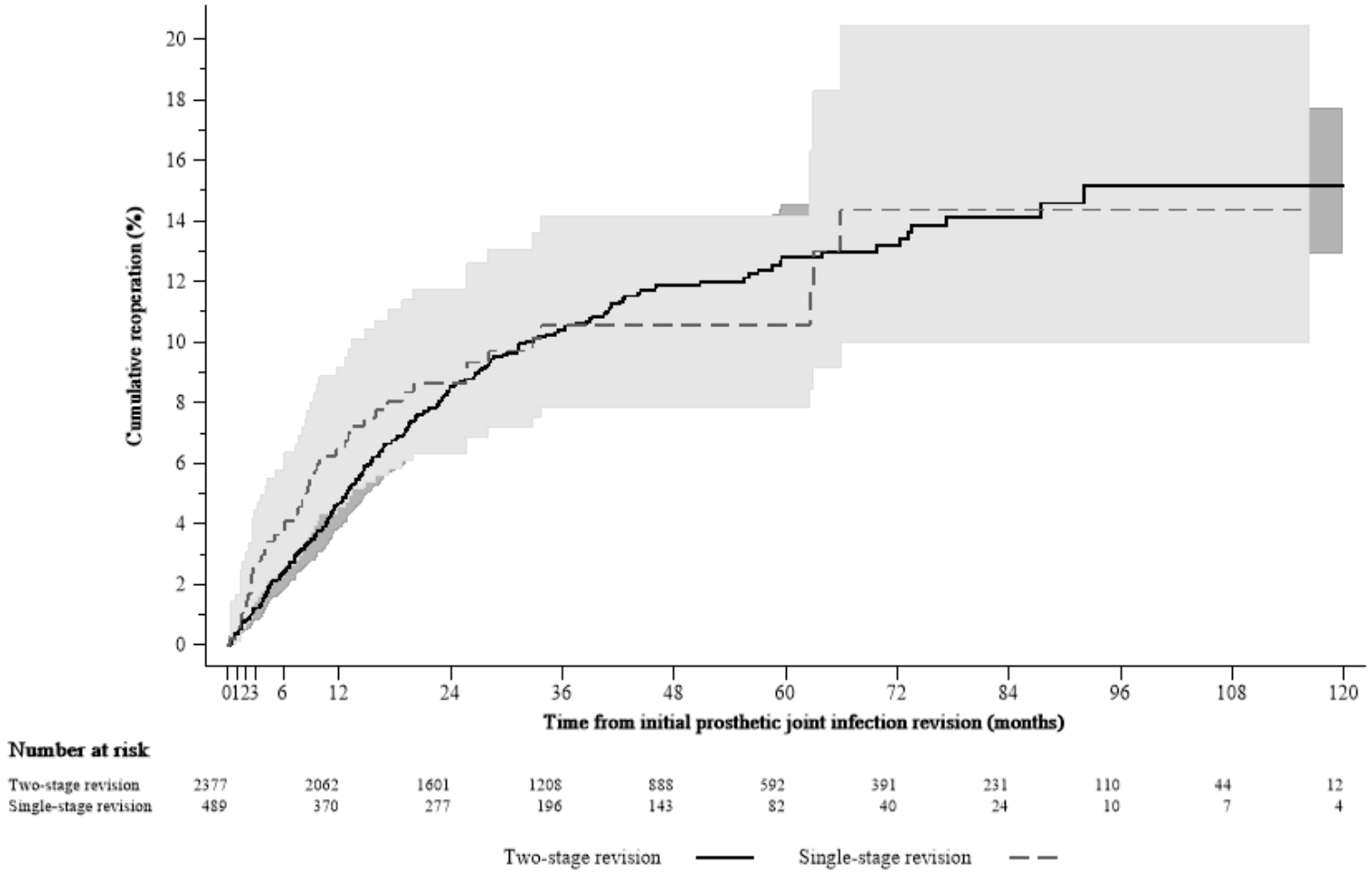
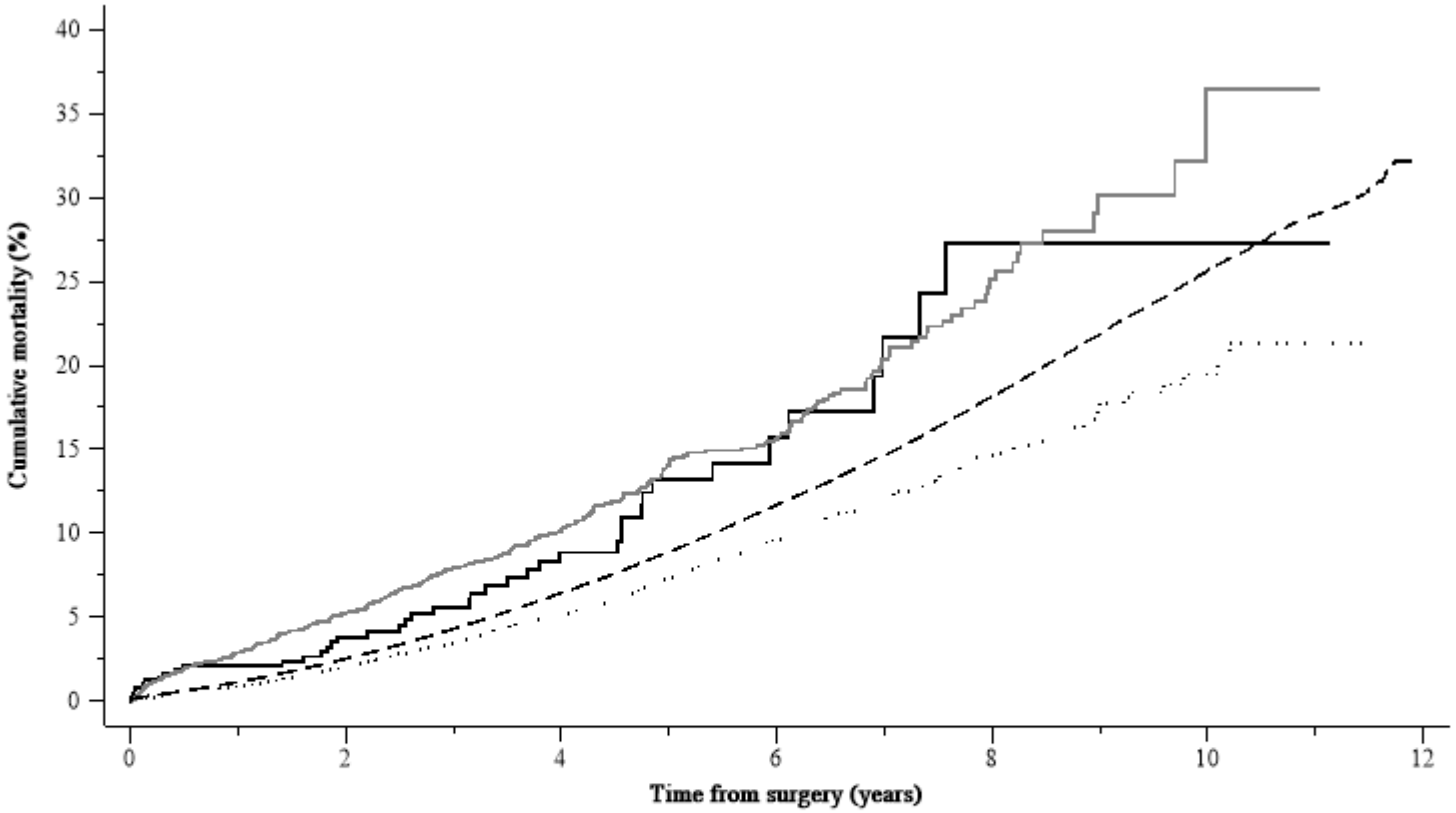


Fig c. Kaplan–Meier cumulative hazard function of re-revision for periprosthetic joint infection by single-stage or two-stage revision procedure for infected primary knee arthroplasty.



Number at risk

Single-stage revision	489	319	102	55	34	6	0
Two-stage revision	2,880	2,030	832	573	329	15	0
Non-septic rev.	16,550	11,521	4,577	2,902	1,628	99	0
Primary	658,453	559,247	302,988	228,396	159,883	28,065	0

Fig d. Kaplan–Meier cumulative hazard function of mortality by revision procedures performed to manage infected primary knee arthroplasty or other arthroplasty procedures.

References

1. **Lenguerrand E, Whitehouse MR, Beswick AD, et al.** Risk factors associated with revision for prosthetic joint infection following knee replacement: an observational cohort study from England and Wales. *Lancet Infect Dis*. 2019;19(6):589–600.