

BACKGROUND

Periprosthetic joint infection (PJI) is among the most consequential complications of hip and knee arthroplasty. The incidence of PJI is rising and it is now the leading indication for revision TKA and third for revision THA.¹

Culture-negative PJI (CN-PJI) is a clinical syndrome consistent with infection in which cultures fail to isolate an organism. Reported rates range from 5% to 45%, reflecting sampling strategy, incubation duration, prior antibiotics and biofilm.²

CN-PJI has previously been regarded as higher-risk for failed two-stage revision because organism-specific therapy is not possible and negative cultures may signal diagnostic ambiguity.³ However, more recent two-stage cohorts report similar outcomes.⁴

AIM & HYPOTHESIS

Primary aim was to review our 20-year national tertiary referral centre experience and compare the outcomes of CN-PJI with culture-positive PJI (CP-PJI) after two-stage revision in terms of re-infection, re-operation, mortality and patient-reported outcomes. Secondly, we compared the hip and knee revision cohorts and identified factors associated with each adverse outcome.

Null hypothesis: Outcomes would be equivalent in both cohorts.

METHODS

Design — Single-centre retrospective cohort study, January 2001 to December 2021, at a national tertiary referral centre.

Sample — Adults ≥18 years undergoing planned two-stage revision for hip or knee PJI. Excluded: single-stage revision; prior revision for PJI of the index joint; previous revisions for non-infective indications; megaprotheses.

Microbiology — Intraoperative synovial fluid and periprosthetic tissue; standard aerobic and anaerobic technique; 5-day culture protocol. CP-PJI: a pathogenic organism isolated. CN-PJI: no organism isolated from blood cultures, synovial fluid or periprosthetic tissue, with diagnosis supported by Berbari et al. (2007) criteria.⁵

First stage variations — No spacer (resection arthroplasty / Girdlestone); static antibiotic-loaded cement spacer; pre-made articulating spacer; custom-made articulating spacer (CUMARS).

Statistical Analysis — T-test, Mann-Whitney U and χ^2 for baseline cohort comparison; Kaplan-Meier with log-rank testing for time to each outcome; Cox regression adjusted for age, sex and BMI to identify predictive factors. STATA v19.0.

COHORT

236 two-stage revisions · hip and knee PJI · January 2001 – December 2021 · mean follow-up 9.0 years.

Culture-negative 65 (27.5%) · Culture-positive 171 (72.5%)

Re-infection analysed in 233 patients (CN-PJI n = 63; CP-PJI n = 170). Baseline characteristics were comparable.

RESULTS

Outcome	CN-PJI (n=63)	CP-PJI (n=170)	<i>p</i>
Re-infection	6.4%	15.3%	.070
Mean time to re-infection	5.6 years	2.1 years	.029
Re-operation	20.6%	20.6%	.994
Mortality	34.9%	31.2%	.587

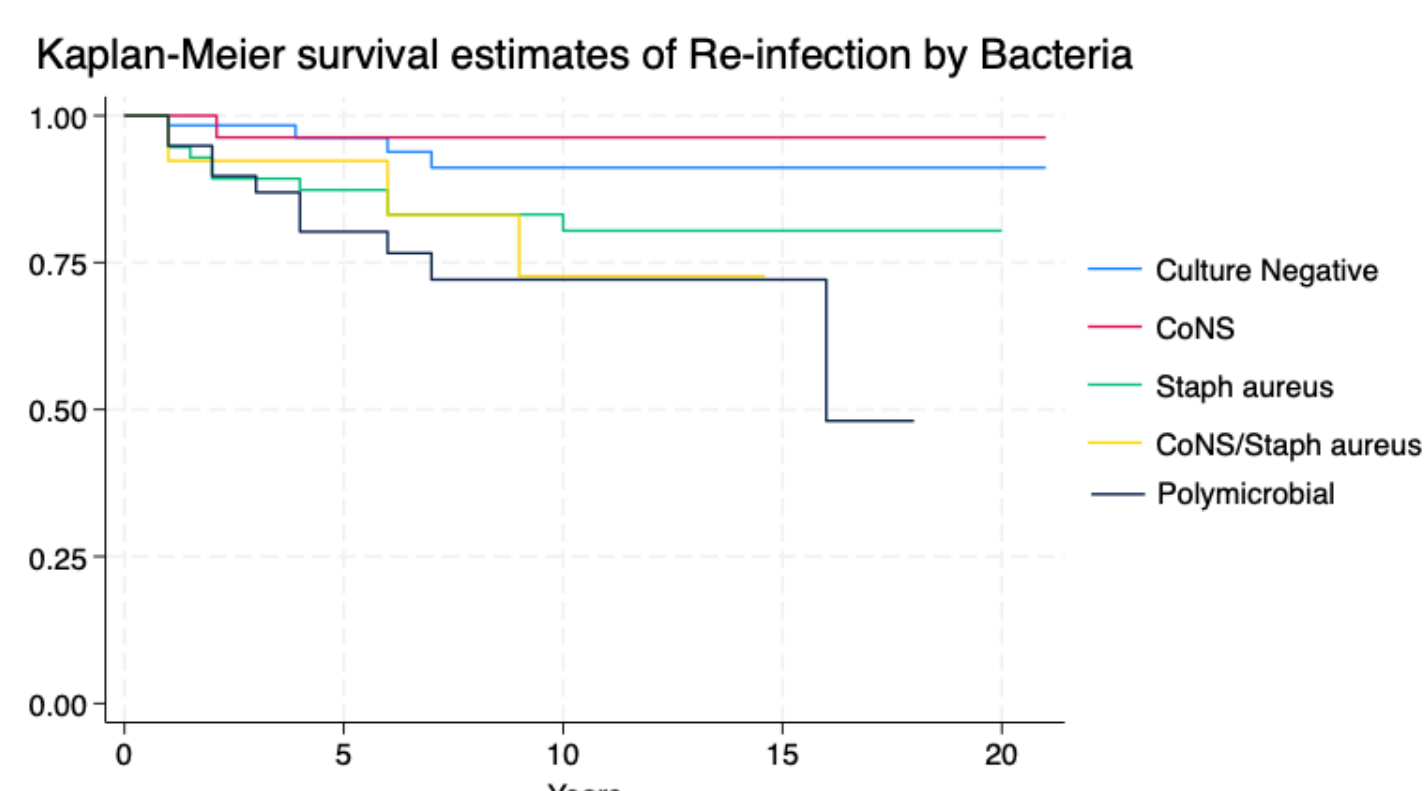
Table 1. Outcomes by culture status after two-stage revision.

Figure 1. Re-infection-free survival by organism.

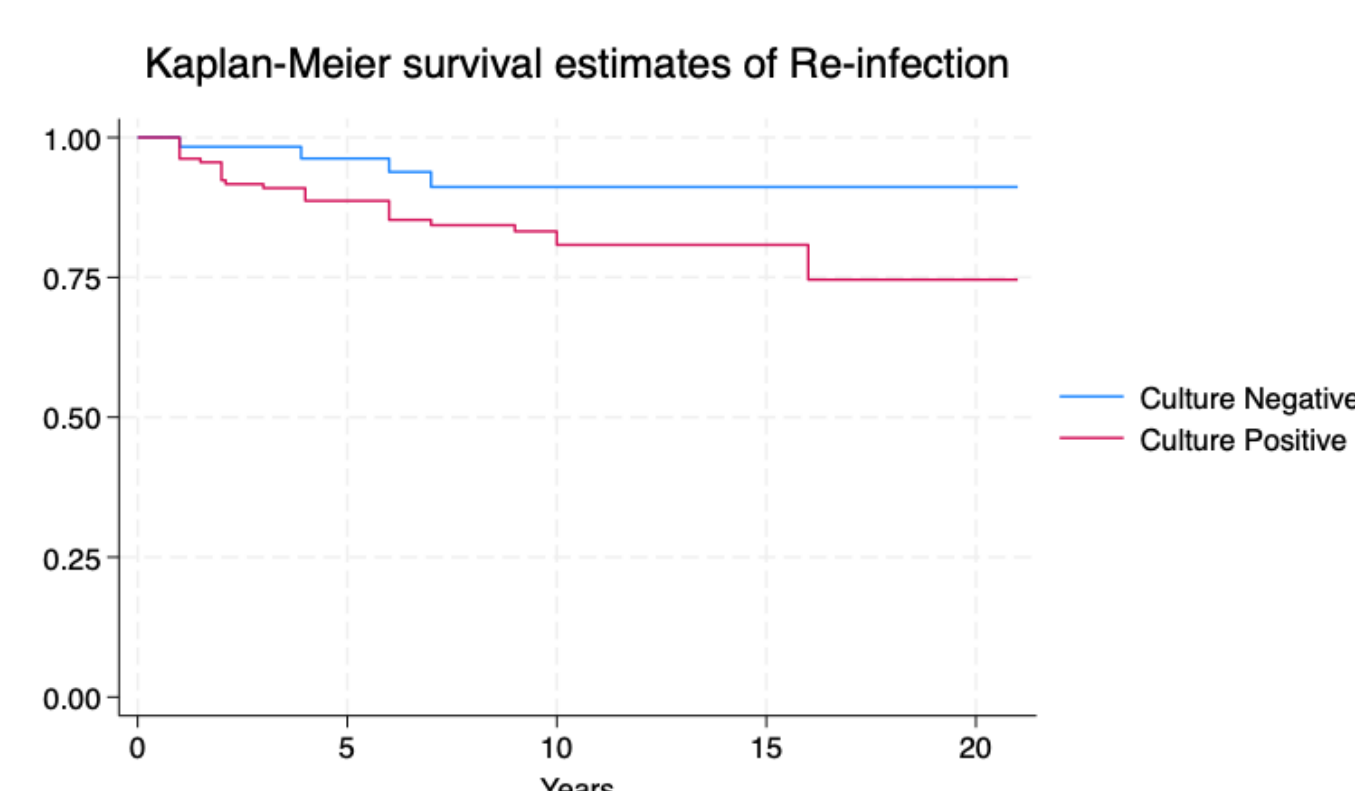


Figure 2. Re-operation rates by culture status.

Timepoint	Culture-negative	Culture-positive	<i>p</i>
Pre-operative	65.1 ± 19.1	68.4 ± 16.2	.331
2 years	37.3 ± 19.4	35.1 ± 20.0	.415
5 years	43.8 ± 20.4	38.0 ± 21.0	.145
10 years	41.0 ± 18.8	36.6 ± 17.3	.365

Table 2. WOMAC by culture status (mean $\pm$ SD).

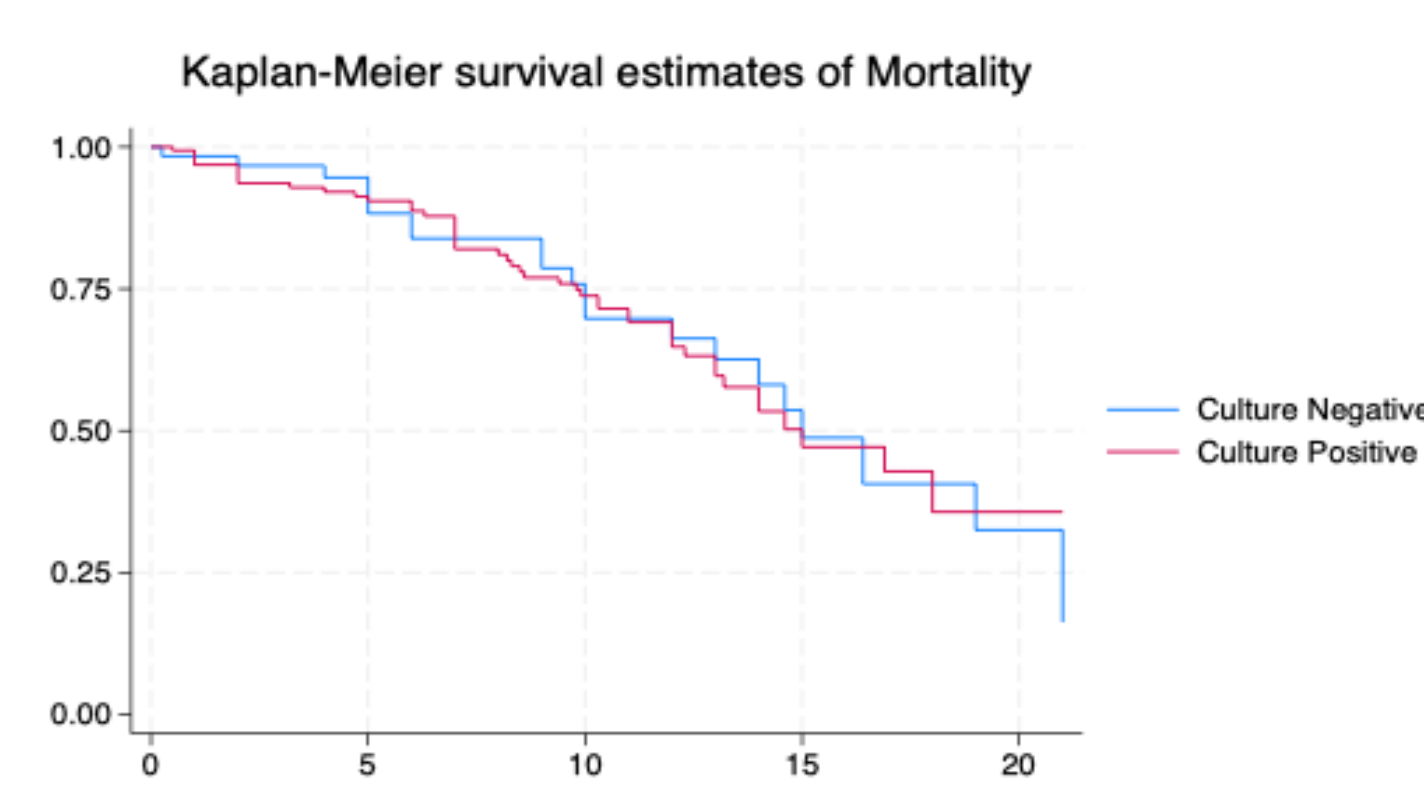


Figure 3. Survival (mortality) by culture status.

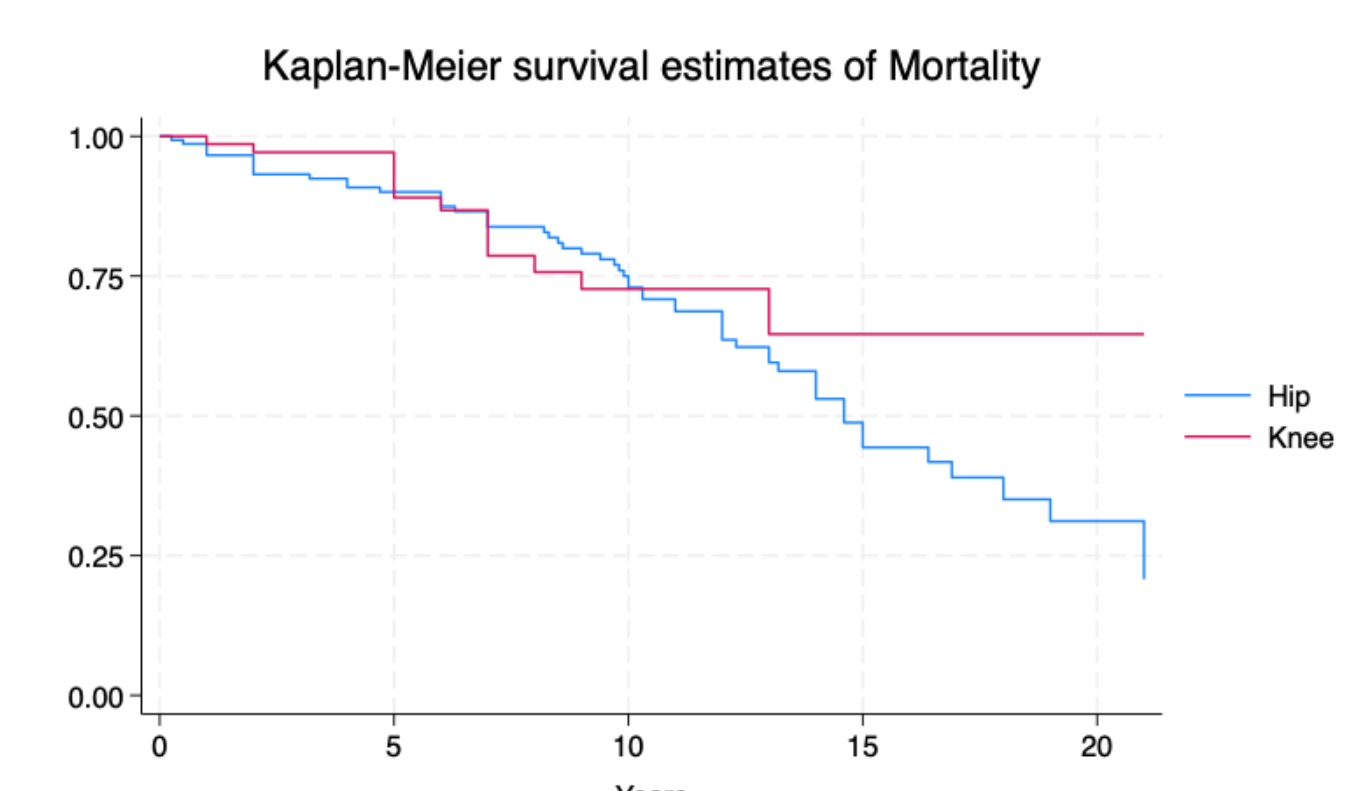


Figure 4. Survival (mortality) by joint involved.

Cox Regression analysis

Culture status was not independently associated with re-infection, re-operation or mortality.

Increasing age (HR 1.09, 95% CI 1.06–1.12; $p<.001$), smoking (HR 2.22, 95% CI 1.16–4.23; $p=.015$) and higher ASA grade (HR 1.75, 95% CI 1.05–2.94; $p=.033$) independently predicted mortality.

Timepoint	Hip	Knee	<i>p</i>
Pre-operative	67.9 ± 16.8	66.8 ± 17.5	.887
2 years	34.2 ± 19.7	38.8 ± 19.8	.168
5 years	37.1 ± 20.6	45.2 ± 20.8	.045
10 years	37.0 ± 18.2	40.1 ± 15.5	.527

Table 3. WOMAC by joint involved (mean $\pm$ SD).

DISCUSSION

CN-PJI did not have an inferior outcome once a structured two-stage protocol with appropriate antimicrobial cover was applied. A longer mean time to re-infection in CN-PJI (5.6 vs 2.1 years, $p = .029$) alongside a numerically lower re-infection rate that did not reach significance ($p = .070$) suggests a more indolent or clinically distinct infection phenotype — but with only four events this is hypothesis-generating. Overall mortality rate of 32.2% at nine years indicates the significance of PJI and frailty of this cohort.

Limitations — Retrospective, single-centre design. Culture technique and antimicrobial practice evolved across the 20-year interval, and a 5-day protocol without sonication or extended incubation means some culture-negative cases may reflect detection failure rather than a distinct entity. With only four re-infections in the CN-PJI group the non-significant difference is underpowered and does not establish equivalence. Confounding by indication and survivorship bias cannot be excluded.

CONCLUSIONS

Two-stage revision produced comparable mid- to long-term outcomes in CN-PJI and CP-PJI. Culture status was not independently associated with re-infection, re-operation or mortality.

Prognosis appeared more strongly influenced by host factors — age, smoking and ASA grade — than by culture status. Absence of an isolate should not itself signal a poorer prognosis.

References — 1. Huotari K, Peltola M, Jämsen E. The incidence of late prosthetic joint infections: a registry-based study of 112,708 primary hip and knee replacements. *Acta Orthop*. 2015;86(3):321-325. 2. Yoon HK, Cho SH, Lee DY, et al. A Review of the Literature on Culture-Negative Periprosthetic Joint Infection: Epidemiology, Diagnosis and Treatment. *Knee Surg Relat Res*. 2017;29(3):155-164. 3. Tan TL, Kheir MM, Shohat N, et al. Culture-Negative Periprosthetic Joint Infection: An Update on What to Expect. *JBJS Open Access*. 2018;3(3):e0060. 4. Wang J, Wang Q, Shen H, Zhang X. Comparable outcome of culture-negative and culture-positive periprosthetic hip joint infection for patients undergoing two-stage revision. *Int Orthop*. 2018;42(3):469-477. 5. Berbari EF, Marculescu C, Sia I, et al. Culture-negative prosthetic joint infection. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2007;45(9):1113-1119.