

Mortality, patient-reported outcome measures, and the health economic burden of prosthetic joint infection

Yangqi Xu¹, Tony B Huang¹, Michael A Schuetz^{2,3,4}, Peter F M Choong^{1,5} and the ICARAU group

¹Department of Surgery, Melbourne Medical School, University of Melbourne, Victoria, Melbourne, Australia

²Jamieson Trauma Institute, Metro North Hospital and Health Service, Queensland Health, Brisbane, Queensland, Australia

³Department of Orthopaedic Surgery, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia

⁴Queensland University of Technology (QUT), Brisbane, Queensland, Australia

⁵Department of Orthopaedics, St. Vincent's Hospital, Fitzroy, Victoria, Australia

Correspondence should be addressed to P F M Choong
Email
pchoong@unimelb.edu.au

- Prosthetic joint infection (PJI) is one of the most devastating complications for a patient following arthroplasty.
- This scoping review aims to evaluate the burden of PJI on individual patients and the healthcare system regarding the mortality rate, patient-reported quality of life, and healthcare resource utilisation.
- Patients with PJI have up to a five-fold higher mortality rate than those who have undergone an uninfected primary arthroplasty. There is an increased use of ambulatory aids and reduced joint function scores in patients with PJI. Global quality of life is poorer, specifically measured by the EQ-5D. Direct hospitalisation costs are two- to five-fold higher, attributed to surgery and prostheses, antibiotics, and a prolonged inpatient stay.
- There is an immense clinical and health economic burden secondary to PJI worldwide. This is expected to rise exponentially due to the increasing number of primary procedures and an ageing population with comorbidities
- Improving preventative and treatment strategies is imperative for patients and the healthcare system.

Keywords

- ▶ prosthetic joint infection
- ▶ arthroplasty
- ▶ patient-reported outcome measure
- ▶ health economic

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Introduction

Prosthetic joint infection (PJI) is one of the most devastating post-surgical complications for a patient undergoing a total joint arthroplasty (TJA). As one of the leading causes of joint replacement failure, PJI causes implant loosening, tissue necrosis, and eventual loss of limb function, often leading to physical and emotional distress in patients (1). Patients with PJI often have prolonged hospital stays and require multiple reoperations (2). PJI can have long-term negative impacts on patients' quality of life (QoL), even following successful clearance of the infection (3, 4, 5). Chronic infections may require multiple revision operations, and failure to control infection can lead to the need for joint fusion and even amputation (6).

Clinical management of PJI is costly. These patients require complex management by a multidisciplinary team with additional surgeries and prolonged antibiotic

therapy. The delivery of this care results in direct costs of approximately US\$46 000 in developed countries (United States and Australia) (7, 8).

The incidence of PJI is expected to increase substantially over the next few decades because of the ageing populations and changing demographic characteristics, including rates of obesity. The absolute number of total knee arthroplasties (TKAs) and total hip arthroplasties (THAs) performed for osteoarthritis annually in Australia is expected to be more than double by 2030 (9). Similarly, Kurtz *et al.* (10, 11) reported a gradually increasing incidence of PJI from 2.09% to 2.18% and predicted the absolute growth in the US to be 673% for TKA and 174% for THA from 2005 to 2030. With the growing demand for elective orthopaedic procedures and an increasing incidence, PJI cannot be ignored due to its significant clinical and economic impact. The aim of this scoping review is to outline the clinical outcomes (morbidity,

mortality, QoL measures) and healthcare-associated costs of prosthetic joint infection globally.

Methods

Protocol and registration

The study protocol for this scoping review was drafted following Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines. The final version was registered on the Open Science Framework (<https://osf.io/aus5f/>).

Eligibility criteria

This review considered peer-reviewed studies published in English without time constraints. Included papers cited a validated diagnostic criterion for PJI (Centers for Disease Control and Prevention (CDC), Musculoskeletal Infection Society (MSIS), IDSA, International Classification of Disease (ICD) codes, and the European Bone and Joint Infection Society (EBJIS)) or cited a validated definition published by another author. However, these diagnoses may be impacted by the subjectivity of clinicians, which was infeasible to adjust for in this review. Included studies reported at least one of the following main outcomes: mortality rate, patient-reported QoL, or the economic impact of PJI such as direct and indirect costs.

Search strategy

The search strategy explored health-related outcomes and the economic impact of PJI in comparison to outcomes of uninfected arthroplasty. A search was conducted across the Ovid Medline, and Ovid Embase databases, using expanded keywords and index terms. Citation tracking of included studies was conducted to identify additional eligible studies.

Study selection

Two researchers (YX, TH) independently screened the titles and abstracts and assessed full texts for inclusion against the eligibility criteria on Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia). Disagreements were resolved through discussion between them. Where agreement could not be reached, the senior author (PFMC) was consulted.

Data extraction

The data collection process was performed by two independent researchers (YX, TH). An electronic data extraction sheet (Microsoft Excel; Redmond, WA, USA) was refined during the data extraction process. The key variables collected were author, publication year, country,

sample size, surgery type, infection type, infection prevalence, and further outcomes of interest including mortality rate, cause of mortality, patient-reported outcomes, QoL assessment tools, cost perspective, total cost, and length of stay, all evaluated against an uninfected cohort.

Result synthesis

Studies were grouped according to the outcomes addressed. Health-related QoL and cost of care are largely reported in narrative and tabular forms. Health-related QoL measures include EuroQol Group 5 Dimension (EQ-5D), 12 or 36 Short Form health survey (SF-12, SF-36). Joint pain and function scores include ambulatory outcomes, Oxford Hip Score (OHS), Oxford Knee Score (OKS), Harris Hip Score (HHS), or Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

Results

Search result

A total of 2073 records were identified using the search strategy; of these, 142 full texts were examined, and 30 articles were included in the review (Fig. 1).

Among 30 eligible studies, 27 (90%) were conducted in high-income countries with the United States

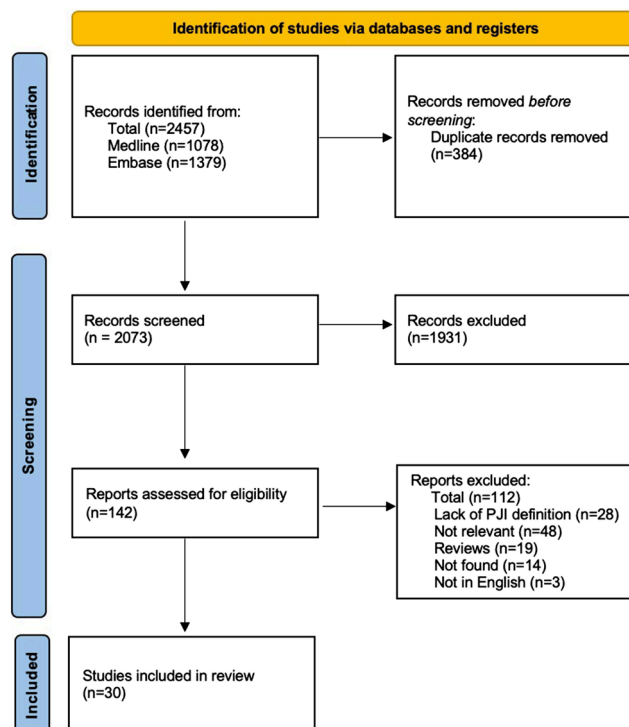


Figure 1 PRISMA flow chart.

predominating ($n=12$, 40%). The knee and hip were the most frequently studied joints with PJI ($n=20$, 67%). Nine of the 30 studies addressed mortality, 8 investigated patient-reported outcomes, while 18 studied the economic impact (Supplementary Table S1 (see section on [supplementary materials](#) given at the end of this article)).

Mortality in septic revision, aseptic revision, and primary arthroplasty

Nine studies compared the mortality rate between patients with PJI, treated either medically or surgically, and an uninfected cohort who either had primary arthroplasty only or with aseptic revision (Supplementary Table S2). Mortality was highest in PJI, followed by aseptic revision, and lowest in primary arthroplasty without infection or revision. Compared with primary arthroplasty, the mortality risk for PJI at 1 year adjusted (for age, sex, and medical comorbidities) was 2.18. Compared with aseptic revision, the adjusted mortality risk for PJI at 1 year was 1.87 (12), whereas in the study by Boddapati *et al.* (13), no difference in mortality was found at 30 days. In the study by Zmistowski *et al.* (14), mortality in the knee and hip PJI was higher than in aseptic revision arthroplasty at any assessed time point, and it remained higher with time from a 90-day mortality of 3.7% (vs0.8%) to a 5-year mortality of 25.9% (vs 12.9%). All-cause 10-year mortality rate was notably higher in PJI patients, with an incidence of 45% compared to 29% in those without infection (3).

However, the direct contribution of PJI to mortality was not provided by these studies.

Patient-reported outcome measures

Intergroup comparison in health-related quality of life

Seven of the eight studies assessed patients' health-related QoL using a validated questionnaire (EQ-5D, SF-12, or SF-36). The most frequently used questionnaire was EQ-5D (4/8) (3, 5, 15, 16), followed by SF-12 (3/8) (17, 18, 19) and SF-36 (1/8) (5) (Supplementary Tables S3 and S4). Patients with PJI scored significantly more poorly on the EQ-5D questionnaire compared to uninfected patients in all studies. However, the three studies that used SF-12 reported no significant differences between the cohorts. Walter *et al.* (5) was the only study that used SF-36, and it reported a lower physical component score in patients with PJI at a median of 5 years following revision surgery. They also reported that 33.3% of PJI patients exceeded the threshold limit for at least one of the five psychiatric syndromes using the International Classification of Disease (ICD)-10-based symptom rating (ISR) (Table 1). The two studies conducted by Aboltins *et al.* (17, 18) noted no significant differences in the rates of improvement in SF-12 scores between the two cohorts.

Intergroup comparison in joint pain and function

Six of the eight studies (3, 15, 16, 17, 19, 20) assessed the patients' post-surgical joint pain and function using

Table 1 Patient-reported QoL outcomes in each study.

Reference	FUD (years)	QoL outcomes							
		Infected cohort				Uninfected cohort			
		EQ-5D	EQ-VAS	SF-12	SF-36	EQ-5D	EQ-VAS	SF-12	SF-36
Wildeman <i>et al.</i> (3)	11*	0.83	65†			0.94	80‡		
Poulsen <i>et al.</i> (15)	8.2*					0.85			
Non-reinfected group		0.71	60.73 (ns)						
Re-infected group		0.6	50.64 (ns)						
Hotchen <i>et al.</i> (16)	1					0.782	77.9		
Uncomplicated PJI		0.730 (ns)	79.4 (ns)						
Complex PJI		0.515	68.4						
Limited options PJI		0.333	60.2						
Romano <i>et al.</i> (19)	4*								
PCS				35.6 (ns)				32.2 (ns)	
MCS				43.1 (ns)				48.7 (ns)	
Aboltins <i>et al.</i> (17)	1								
PCS				+10.9* (ns)				+15.7* (ns)	
MCS				+ ns*				+ ns	
Aboltins <i>et al.</i> (18)	1								
PCS				+11.3* (ns)				+12.8* (ns)	
MCS				+2.9* (ns)				+4.2* (ns)	
Walter <i>et al.</i> (5)	4.9*	0.55	52.14			0.838	68.6		
PCS					24.82				48.36
MCS					46.16 (ns)				50.87 (ns)
Mur <i>et al.</i> (20)	1‡	N/A				N/A			

*Mean values. †Median value. ‡Minimum. FUD, follow-up duration; MCS, mental component scores; PCS, physical component scores.

an appropriate joint function tool (ambulatory outcomes, OHS, OKS, HHS, or WOMAC). Wildeman *et al.* (3) and Mur *et al.* (20) reported a greater proportion of PJI patients requiring ambulatory aids and assisted living relative to uninfected patients (Table 2). Wildeman *et al.* (3) identified a worse OHS score in PJI patients. Aboltins *et al.* (17) noted lower HHS improvements in PJI patients at 1-year follow-up, but there were no significant differences in HHS between the two patient cohorts at 4 years. Romano *et al.* (19) were unable to identify any significant differences in the WOMAC score between the two cohorts.

Length of stay

Lengths of hospitalisation were reported in 12 studies (Table 3). With the exception of Kapadia *et al.* (21), all studies reported a two-fold or longer hospitalisation period for PJI patients compared to uninfected patients. Two studies (22, 23) from Canada reported five- to ten-fold longer periods of hospitalisation for patients with PJI. Studies (11, 24, 25, 26) from the United States reported shorter lengths of hospitalisation for both patient cohorts relative to studies from other countries.

Hospital resource use of PJI

Fourteen studies reported the hospital resource use cost of PJI as compared to the total cost for the uninfected cohort (7, 8, 11, 19, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31) (Supplementary Table S5). All focused on the direct cost incurred during in-hospital management. Total

hospital charges commonly comprised operating room services (prosthesis, procedure cost, surgical supplies, etc.), hospital bed charge, medications, diagnostic tests, ICU stay, and physiotherapy. In general, the total cost for patients with hip PJI was remarkably higher, incurring a total cost 2–5.6 times the total cost for the uninfected cohort, regardless of whether they underwent primary or revision arthroplasties. Similarly, treating knee PJI caused a 1.6- to 4-fold increase. Shoulder PJI treatment was more costly than primary shoulder arthroplasty and hemiarthroplasty, but less costly than reverse shoulder arthroplasty (26). Indirect societal costs, including productivity loss and wage loss, were not reported in any of the reviewed studies.

Projected cost

Four studies estimated the future economic burden of PJI on the healthcare system. Chang *et al.* (32) estimated the hospital costs for PJI in Taiwan based on the average cost between 2006 and 2013. PJI costs were predicted to increase from NT\$117M in 2014 to NT\$569M in 2035 (US\$3.8 to US\$18.6 based on the current conversion rate). The number of PJIs was projected to be 5944 in Korea in 2030, leading to an increase in the total annual cost from US\$18.0 million in 2018 to exceed US\$57.0 million by 2030 (33). In the United States, the total annual number of hip and knee PJIs was estimated to be 25 928 and 40 096, respectively, in 2030, resulting in a combined annual cost of US\$1.85 billion (34). All these estimates confirm the enormous magnitude of the challenge faced worldwide.

Table 2 Patient-reported pain and function outcomes in the included studies.

Reference	Pain and function outcomes								
	Infected cohort				Uninfected cohort				
	AO	OHS	OKS	HHS	WOMAC	AO	OHS	HHS	WOMAC
Wildeman <i>et al.</i> (3)		36					44		
Assisted Living	21%					12%			
Ambulatory aid	65%					42%			
Poulsen <i>et al.</i> (15)									
Non-reinfected group		31.15 (ns)							
Re-infected group		23.22 (ns)							
Hotchen <i>et al.</i> (16)									
Uncomplicated PJI		40.2	33.0						
Complex PJI		32.3	22.9						
Limited options PJI		19.5	23.7						
Romano <i>et al.</i> (19)				71.2 (ns)				74 (ns)	
Function					76.6 (ns)				66.2 (ns)
Pain					77.4 (ns)				75.8 (ns)
Stiffness					71.4 (ns)				70.1 (ns)
Aboltins <i>et al.</i> (17)				+35.9*				+44.6*	
Mur <i>et al.</i> (20)									
Requires 1 or 2 crutches									
TKA	42.1%					22.4%			
THA	63.4%					25.6%			

*Mean values.
AO, ambulatory outcomes; ns, non-significant.

Table 3 Overview of reported length of hospitalisation.

Study	Country	Sample size (n)		Length of hospitalisation (days)	
		IFC	UIFC	IFC	UIFC
Morcos <i>et al.</i> (23)	Canada	73	73	22.7	3.8
Akindolire <i>et al.</i> (22)	Canada	50	50	26.5	2.0
Kasch <i>et al.</i> (30)	Germany	35	71	34.0	15.0
Puhto <i>et al.</i> (31)	Finland	42		16.0	
Primary arthroplasty			1708		4.0
Aseptic revision			18		14.0
Peel <i>et al.</i> (7)	Australia	21	42	31.6	7.9
Alp <i>et al.</i> (27)	Turkey	16	654	49.0	7.0
Iqbal <i>et al.</i> (28)	Pakistan	27	27	11.0	5.0
Kapadia <i>et al.</i> (24)	USA	21	21	5.3	3.0
Brochin <i>et al.</i> (25)	USA	70 011*	395 198*	6.0	3.0
Kapadia <i>et al.</i> (29)	USA	16	32	7.6	3.3
Kurtz <i>et al.</i> (11)	USA	NIS data*	NIS data*		
Hip					
1990				27.5	10.3
2004				9.2	4.3
Knee					
1990				23.5	9.7
2004				8.8	3.9
Padegimas <i>et al.</i> (26)	USA	808*	81690*	4.0	2.0

*Data derived from the United States National Inpatient Sample (NIS) database.
IFC, infected cohort; UIFC, uninfected cohort.

Discussion

The key findings of this review were that patients with PJI scored significantly lower compared to uninfected patients on the EQ-5D and SF-36 questionnaires following recovery and generally required greater ambulatory assistance. PJI incurred a greater hospital expenditure, and the patients with PJI experienced longer lengths of hospitalisation across all studies.

Mortality

Suffering a PJI seems to be associated with a higher mortality rate compared to the uninfected cohort. Polymicrobial infection was a significant independent predictor of mortality in PJI (12, 13, 35, 36). Other studies found Gram-negative organisms and enterococci resulted in a two- or three-fold increase, respectively, in the 1-year mortality risk (18). As causative pathogens of PJI were not the focus of this review, no conclusion can be drawn concerning the association between certain organisms and mortality risks.

Quality of life outcomes

Individual studies revealed that PJI tended to inflict negative impacts on QoL outcomes, but it was difficult to compare between studies given the heterogeneity of study populations, surgery types (one-stage revision,

two-stage revision, debridement, antibiotics and implant retention (DAIR)), and surgery numbers. Participants between studies varied in age, co-morbidities, and reasons for surgery. The contribution of each surgery type to the clinical outcomes also remained uncertain in this review, although it was previously argued that DAIR could be a successful alternative to two-stage revision for knee PJI within 2 weeks of onset (37). Additionally, some studies did not properly match the infected and uninfected cohorts. For example, Walter *et al.* (5) matched only age between the two cohorts. Other important confounding factors such as sex, comorbidities, and BMI were not considered. Comorbidities were also overlooked in the study by Mur *et al.* (20). This reduces the quality of their findings. Propensity score matching can be a suitable approach in retrospective studies to minimise these confounding effects, as performed by Wildeman *et al.* (3, 38). An increase in properly powered, prospective multi-centre studies is required to produce more generalisable and accurate results.

The use of different QoL assessment tools may also influence the patient-reported outcomes. PJI patients reported significantly lower general QoL in studies that used EQ-5D but not SF-12. This may be because the EQ-5D surveys were generally conducted at much longer follow-ups compared to SF-12 and SF-36 in included studies. The discrepancies between the two questionnaires could also reflect the poor discriminatory validity of both tools in assessing patients with chronic joint pain (39). It is nevertheless tempting to speculate that the EQ-5D may provide superior validity in assessing the general health of PJI patients, as four of its subdomains (self-care, mobility, activities, and anxiety/depression) arguably have cross-over with tools that did report significant differences in the other studies. For example, Wildeman *et al.* (3) and Mur *et al.* (20) both reported increased requirements for ambulatory and living assistance in PJI patients, with clear implications on the self-care, mobility, and activities subdomains of EQ-5D. The subdomains in SF-12 do not appear to have the same level of cross-over potential.

Length of stay

PJI patients had a longer in-patient stay compared to uninfected patients, which is consistent with the higher hospital costs in PJI management. Although longer hospitalisations are known to be correlated with costs, the extent of PJI as the main cause of this increased expenditure was difficult to disentangle from the studies included in this review. Despite studies in the United States reporting slightly shorter hospital stays compared to studies conducted in the other countries, they had the highest PJI management expenditure. This is consistent with the exceptionally high cost of healthcare in the

United States that has been observed and discussed by other authors (40).

Hospital resource use cost

Many of the reviewed studies evaluating the costs associated with PJI have small sample sizes and employ various approaches to estimating costs, which resulted in a wide range of findings presented. Data from the United States National Inpatient Sample (NIS) database did not include other resource use such as the surgeon's and physician's fees or costs of further rehabilitation, and studies that used NIS data or did not consider indirect costs likely underestimated the episode of care costs (26). Studies may also benefit from specifying patient out-of-pocket costs vs government or other payer-funded burden as knowing how PJI management is funded may help explain whether PJI is associated with the greater economic burden on the healthcare system, PJI patients, or both.

Strengths and limitations

Although arthroplasty is considered highly successful and cost-effective (41), uncommon but detrimental complications such as PJI can cause an enormous burden on patients and health systems. These results provide further insight into the major health-related and economic burden of PJI that is rising with the increasing volume of primary arthroplasty. This review demonstrates the tremendous societal burden of PJI and identifies knowledge gaps for future studies, yet it has several limitations. First, it was difficult to directly compare costs between analyses conducted in different countries due to the heterogeneity of currencies used and the different periods of time involved. Second, variations in surgical treatment for PJI between studies could have influenced the outcomes reported here in an unpredictable manner. Mortality rates associated with these procedures vary slightly, and this variability may not be fully attributable to PJI but instead to multiple other factors affecting the surgical outcome, such as the number and duration of procedures. Studies with no appropriately matched cohorts would not have considered pre-existing conditions such as immune deficiency, which have deleterious effects on patients' recovery from infection and subsequently affect their QoL and mortality risk. Given the nature of a scoping review, none of these additional variables were adjusted or analysed. Finally, the findings in this review may not be generalisable to other complications or procedures.

Conclusion

In this scoping review, there were a relatively lower number of identified studies that reported QoL

outcomes and mortality rates, compared to costs of PJI. Nevertheless, the review revealed that PJI is associated with an enormous humanistic burden due to its higher mortality risk and negative impacts on QoL and joint function. With the increasing volume of elective arthroplasty, PJI also inflicted a growing economic burden on healthcare systems via immense hospital resource use including hospital stay charges and operation costs. Future comparison of PJI-related clinical and economic impacts in different arthroplasty procedures would assist in further exploration of new knowledge.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EOR-23-0078>.

ICMJE Conflict of interest statement

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

Y Xu, PFM Choong, and MA Schuetz developed and formulated the research goals. Y Xu and TB Huang developed the research methodology. Y Xu and TB Huang conducted screening, data extraction, and wrote the initial manuscript. The ICARAUS group managed and coordinated the research activity and reviewed and edited the manuscript. PFM Choong and MA Schuetz supervised the research execution.

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