



Mid- to long-term outcomes of contemporary total knee arthroplasty in Charcot neuroarthropathy: a systematic review and meta-analysis

Piti Rattanaprichavej¹
Patapong Towiwat²
Artit Laoruengthana¹
Piyameth Dilokthornsakul^{3,4}
Nathorn Chaiyakunapruk^{5,6}

- Total knee arthroplasty (TKA) is an effective procedure to treat many patients with end-stage knee arthropathy. However, the extension of TKA for patients with Charcot neuroarthropathy (CNA) is controversial, with relatively limited evidence defining optimal reconstruction techniques.
- This systematic review of relevant studies that were published from January 2000 to June 2020 aimed to define survivorship, complications, reoperation, and component revision rates of contemporary TKA performed for CNA.
- We identified 127 TKA performed for CNA in five studies that comprised ≥ 7 knees with ≥ 5 years of follow-up.
- Overall implant survivorship was 85.4%. The overall complication rate was 26.4%, with the most common complications including instability (24.0%), periprosthetic fracture (17.4%), infection (13.0%), ligament injury (10.9%) and aseptic loosening (10.9%).
- The aetiology of CNA and prosthesis type had no influence on clinical outcomes, whereas the effect of staging of disease and ataxia status was still inconclusive.
- Understanding the potential determinants, survivorship and risk of complications related to TKA performed in CNA may help surgeons to deal with patient expectations.

Keywords: Charcot; neuroarthropathy; neuro-syphilis; total knee arthroplasty

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Introduction

Total knee arthroplasty (TKA) is an effective procedure of this century to alleviate pain and improve function for end-stage knee arthropathy patients. Nevertheless, performing

TKA for some conditions remains controversial, including TKA performed for patients with neuropathic arthropathy. Jean Martin Charcot first described the relation between neuro-syphilis and neuroarthropathy in 1868, and the association between this neuroarthropathy and diabetes mellitus was proposed by Jordan in 1936.¹ With an improvement of antibiotics, neuroarthropathy caused by syphilis is declining, whereas diabetes has taken over as a major cause of the Charcot joint in this century.² Furthermore, other diseases resulting in neuropathic arthropathy have been identified such as leprosy, alcoholism, lacunar infarct, syringomyelia, spinal cord injury, tabes dorsalis, Charcot–Marie–Tooth disease, Guillain-Barré syndrome.^{2,3} Two hypotheses, neurotraumatic and neurotrophic, have been proposed to explain the pathophysiology of Charcot neuroarthropathy (CNA), and three phases of disease including fragmentation, coalescence, and reconstruction phase have been described.⁴ However, several investigators believe that CNA is an end result of motor, sensory and autonomic neuropathy, subsequently resulting in loss of protective reflex and nociceptive receptor response to undetected microtrauma.²

In fact, the presentation of CNA is often misleading and it is difficult to make such a diagnosis. Despite that, CNA should be suspected when the severity of pain does not correlate with the degree of joint destruction and inflammation, classically known as a painless arthropathy.^{2,5-7} Vopat et al⁸ suggested that CNA should also be suspected if a patient presents with unilateral localized inflammatory symptoms, and particularly with chronic diabetes and peripheral neuropathy. Moreover, a 2°C difference of skin temperature from the contralateral side monitored by infrared cutaneous temperature may be one of the most accurate tools for diagnosis of acute CNA. Recently, various studies have assessed inflammatory factors and bone

remodelling markers, such as TNF α , interleukin 1 β , interleukin 6, RANK-RANK ligand-osteoprotegerin pathway, because significant inflammatory response has been demonstrated in patients with CNA.^{5,9} However, there are no specifically haematological markers or laboratory tests available to date for the diagnosis of CNA.⁵

The ideal treatment for destructive knee arthropathy is controversial. Destructive neuropathic arthropathy was historically considered to contraindicate TKA because of a high incidence of failure and other complications.^{10,11} Therefore, arthrodesis became a preferred treatment.¹² However, arthrodesis still provides low functional and unsatisfactory outcomes, thus leading to less popularity.^{13,14} Currently, TKA remains a possible option for CNA, and some investigators have reported a successful and satisfactory outcome in treating Charcot knee neuroarthropathy with TKA.^{1,15}

Because CNA is uncommonly experienced in contemporary orthopaedic practice, the literature on TKA for these patients mostly consists of small case series with variable outcome reporting.^{13,16,17} This limits the ability for these individual studies to define overall survivorship, complication, reoperation and component revision rates. It is also unclear whether the outcome of TKA is affected by clinical factors including aetiology (neuro-syphilis (NS) and non neuro-syphilis (non-NS)), staging of the disease, ataxia status, and prosthesis use. Hence, the objectives of this systematic review aimed (1) to assess the outcomes of TKA performed for CNA in contemporary studies and (2) to explore the effect of these variable clinical factors on the outcomes.

Materials and methods

This systematic review was conducted according to the Methodological Expectations of Cochrane Intervention Reviews (MECIR),¹⁸ and was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.¹⁹ The review protocol was registered with PROSPERO.

Search strategies and study selection

The following databases were used to search for original research articles from inception to June 2020: PubMed, EMBASE and Cochrane library. Studies that were published during the period from January 2000 to June 2020 were considered as contemporary literature,³ while studies published prior to January 2000 were considered as historical studies. Strategic search terms used were “neurogenic arthropathy” or “neuropathic joint” or “Charcot joint” or “neuroarthropathy” AND “total knee arthroplasty” or “total knee replacement” or “TKA”. For other sources, online and offline sources such as libraries and references of articles derived for full-text review were scanned to

identify potential studies not indexed in the above databases. Experts were also contacted for additional trials.

We included all studies that reported the outcomes of TKA in patients with Charcot neuroarthropathy and were published in English language. One reviewer scanned all the titles and abstracts to determine whether the studies assessed the survivorship and the complication of TKA in Charcot knee neuroarthropathy. Individual case reports and case series with less than seven knees or less than five years of follow-up were excluded.^{20,21} Full-text articles of the potential studies were subsequently assessed by two reviewers. Disagreements and uncertainties regarding eligibility were resolved by discussions between the reviewers, when necessary.

Data extraction and quality assessment

The data extracted included number of knees, mean age of the patients, average follow-up period, cause of Charcot joint (NS vs. non-NS), staging of disease, ataxia status, prosthesis type (primary or ordinary implant, varus-valgus constraint prosthesis (VVC) and rotating hinge prosthesis (RH)), complications, reoperation, and revision TKA. Studies included in this review were assessed by two reviewers for methodological quality and synthesis of case series and case reports according to Murad et al.²⁰ The methodological quality and synthesis of case series and case reports of each included study were considered in terms of four domains: selection, ascertainment, causality and reporting. Gradings of ‘unsatisfied/fair/satisfy’ were given for each item. Low risk of bias was considered when every item was achieved with a ‘satisfy’ grading. Inter-mediated risk of bias was then justified if one fair grading was recorded. Meanwhile, high risk of bias was defined when one unsatisfied or > one fair grading was identified. Accordingly, all included studies showed low risk of bias. Disagreements between the reviewers were settled through discussion and consensus.

Outcome measure and statistical analyses

The outcomes of interest were knee survival, reoperation, revision, and any complications. Survivorship is determined as revision TKA as an endpoint. Reoperation is defined as additional surgery that did not involve any prosthesis changing. Descriptive statistics were used to explain the outcomes. Mean, standard deviation, median, and inter-quartile range were used to explain continuous data, while numbers and percentages were used to explain categorical data. Meta-analyses of proportion (metaprop) were performed under a random-effects model using the DerSimonian and Laird method to estimate the pooled proportions and their corresponding 95% confidence interval of outcomes of interest across the included studies. The Cochrane I² was used to quantify heterogeneity for the pooled proportion of each outcome.

The Freeman–Tukey double arcsine transformation was used to stabilize the variance of binomial data. In addition, meta-regressions were also performed to explore the effects of clinical factors on the proportion of the outcomes. The clinical factors included prosthesis use (primary, VVC, RH), causes (NS vs. Non-NS), staging (stage I vs. stage II-III), and ataxia status. All analyses were performed using STATA version 15.0 (StataCorp). Statistical significance was defined as $p < 0.05$.

Results

Study selection

A total of 150 articles were identified through the screening process. After removal of duplicate studies, the remaining

manuscript titles and abstracts were screened. Thirty-seven articles were retrieved for full-text review. Thirty-two of these articles were excluded from the final analysis, including nine studies that were published prior to January 2000, six studies that did not focus on TKA for CNA, four other articles that were reviews, conference abstracts or letters to the editor, and 13 isolated case report/series which had either < 7 knees or < 5 years of follow-up. Finally, five studies were included and summarized as contemporary results (Fig. 1).^{1,3,6,22,23}

Characteristics of included studies

Of five contemporary studies, there were 91 patients with 127 knees. The mean follow-up period of all studies ranged from 5.2 to 12.3 years. Three studies^{3,6,22} reported

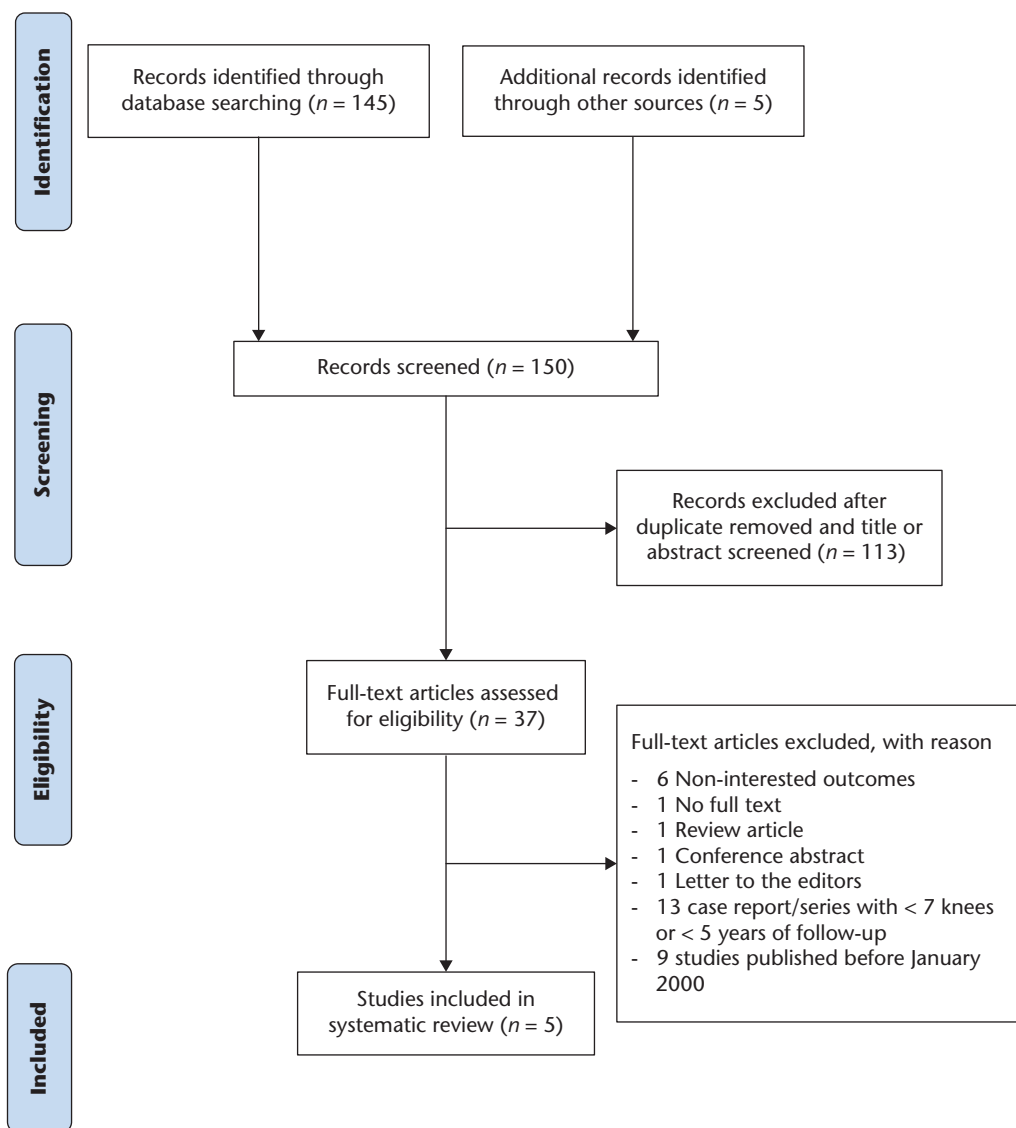


Fig 1. Flow diagram of study selection.

Table 1. Characteristics and outcomes of included studies

Author (year)	No. of knees	Mean age (yr.)	Average follow-up (yr.)	Cause of CNA		Staging		Ataxia		Prosthetic constraint (knees)			Bone defect Rx	Re-surgery (episodes)		Total complication (episodes) [%]	Complications
				NS	Non-NS	I	II & III	Yes	No	Standard	VVC	RH		Reop	Revis.		
Kim YH (2002) ⁶	19	52.0	5.2	19	0	0	19	0	19	1 (PS)	17	1	11 autograft	4	4	9 [47.4]	1 quadricep rupture, 1 aseptic loosening, 1 PF dislocation, 3 TF dislocation, 3 PPFx
Parvizi J (2003) ²²	40	67.5	7.9	4	36	n/a	n/a	n/a	n/a	8 (CR)	27	5	17 autograft, 2 allograft, 10 metal augment	n/a	6	17 [42.5]	2 MCL avulsion, 1 patellar tendon rupture, 1 tibial tuberosity avulsion, 4 instability, 2 haematoma, 1 DVT, 1 superficial infection, 2 aseptic loosening, 1 PJI, 2 PPFx
Bae DK (2009) ²³	11	60.1	12.3	11	0	n/a	n/a	n/a	n/a	0	0	11	2 autograft, 2 allograft	1	2	3 [27.3]	1 PJI, 2 TF dislocation
Chun KC (2016) ¹	20	56.0	10.7	20	0	0	20	5	15	0	20*	0	20 allograft	0	0	2 [10.0]	1 instability, 1 graft resorption
Tibbo ME (2018) ³	37	60.0	6.0	0	37	n/a	n/a	n/a	n/a	7 (PS)	17	13	3 autograft, 2 allograft, 6 metaphyseal cone	3	6	15 [40.5]	2 aseptic loosening, 4 PJI, 3 PPFx, 1 DVT, 1 patellar clunk, 1 flexion contracture, 1 hematoma, 1 patellar malalignment, 1 superficial wound infection

Note. n/a, data not available; No., number; yr., years; mo., months; CNA, Charcot neuroarthropathy; NS, neuro-syphilis; non-NS, non-neuro-syphilis; Standard, primary implant; VVC, varus-valgus constraint prosthesis; RH, rotating hinge prosthesis; PS, posterior stabilized implant; CR, cruciate retaining implant; bone defect Rx, bone defect management; reop, reoperation; revis., revision TKA; PPFx, periprosthetic fracture; DVT, deep vein thrombosis; PJI, periprosthetic joint infection; TF, tibiofemoral joint; PF, patellofemoral joint; MCL, medial collateral ligament; HO, heterotopic ossification.

*VVC prosthesis and allogeneic femoral head bone graft was used in all knees.

mid-term follow-up (5–10 years) while two studies^{1,23} had more than 10 years of follow-up. Fifty-four TKAs were operated secondary to NS,^{1,6,22,23} 73 knees secondary to non-NS.^{3,22} For the prosthesis implantation, 16 primary implants (eight cruciate retaining (CR), eight posterior stabilized (PS)),^{3,6,22} 81 VVC implants^{1,3,6,23} and 30 RH prostheses were reported^{3,6,22,23} among all studies. Two studies described staging of disease in terms of Eichenholtz classification;⁴ 39 knees being stage II/III at the time of surgery, while none of stage I were operated.^{1,6} Only one study described existing ataxia status, preoperatively.¹ The characteristics and outcomes of each included study are listed in Table 1.

Pooled outcomes of survivorship, complication, reoperation and revision rates

An estimated survivorship from five enrolled studies, with mid- (5–10 years) and long-term (> 10 years) results, was 85.4%, while metaprop analysis demonstrated a cumulative reoperation of 8.8% and revision rate of 12.7% for TKA

in CNA. A summary of results from the five included studies is provided in Fig. 2. Of 127 knees, a 26.4% pooled proportion of complications had occurred. Instability (dislocation and ligament laxity) was the most common complication (24.0%), followed by periprosthetic fracture (PPFx) (17.4%), periprosthetic joint infection (PJI) (13.0%), aseptic loosening (10.9%), and ligament injury (10.9%). Other complications (13.0%) such as flexion contracture, patellar clunk and superficial wound infection could also be found.

Meta-regressions analysis

To identify an association between variable clinical factors and outcomes, we analysed pooled data with a meta-regressions model (Table 2).

NS vs Non-NS

In a comparison between 50 NS^{1,6,23} and 37 non-NS knees,³ we found an insignificant difference rate of survival ($p = 0.76$), complication ($p = 0.52$), reoperation ($p = 0.86$) and revision TKA ($p = 0.93$).

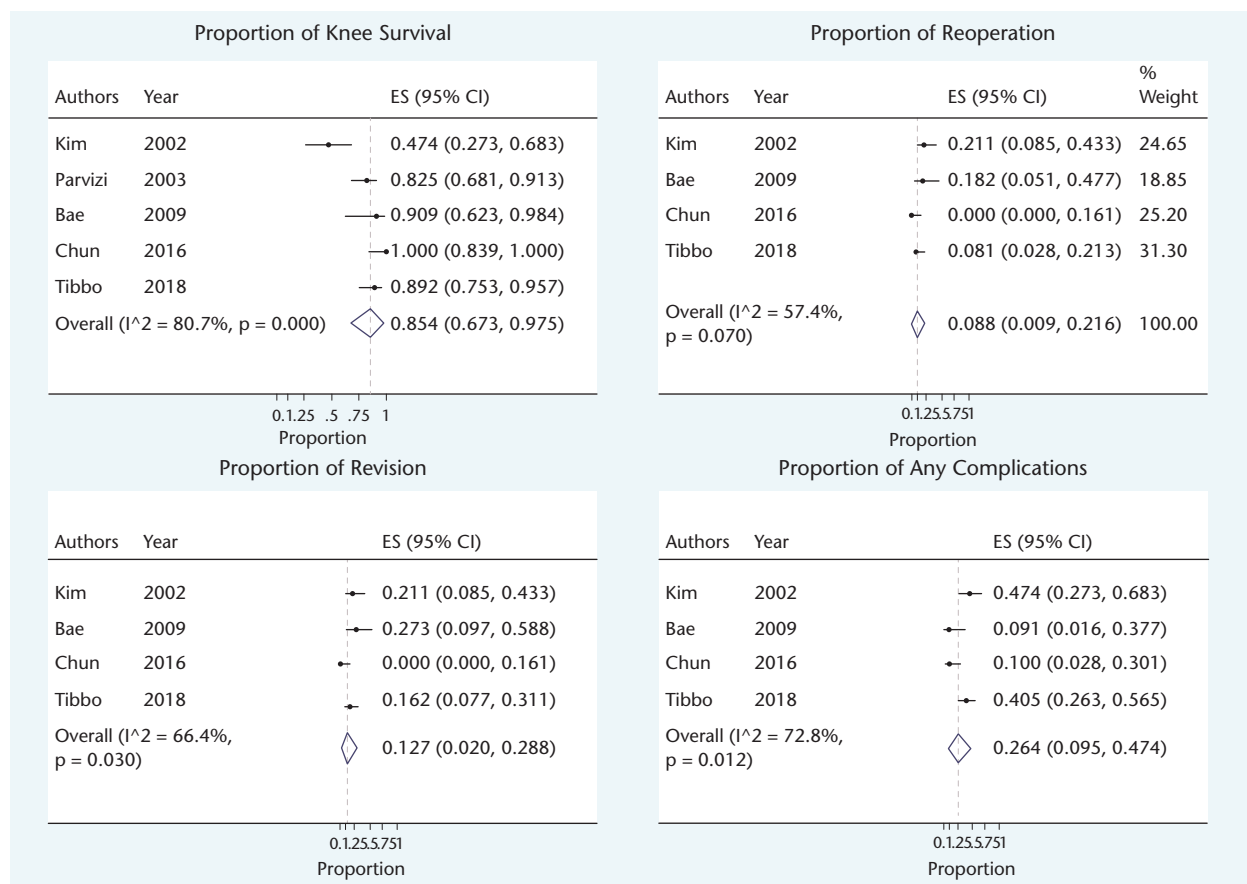


Fig. 2 The pooled proportion of (A) knee survival, (B) reoperation, (C) revision, and (D) any complications.

Staging and ataxia

Three studies (88 knees) did not reveal staging of CNA prior to the operation.^{3,22,23} Moreover, none of the studies operated on knees with a stage I classification, whereas 56 stage II/III knees were operated. Therefore, a meta-regression model could not be analysed.

Two studies that described the preoperative status of concurrent ataxia reported 34 of 39 knees with non-ataxia.^{1,6} However, only a single study described five knees with existing preoperative ataxia.¹ Hence, the effect of ataxia status on rate of complication, reoperation, and revision surgery could not be appropriately interpreted.

Prosthesis type

Among the included studies, there was heterogeneity of data regarding prosthesis type which comprised 16 primary (8 CR, 8 PS), 81 VVC, and 30 RH. Of 81 VVC used in five studies, 27 VVC in one study were assembled with extension stems.²² Tibbo et al³ stated that extension stems applied in 28 cases without specification of the prosthetic constraint, and two studies did not describe the use of stem.^{1,6} Furthermore, two case series^{3,22} revealed the

outcomes of TKA, but did not stratify according to prosthesis type. Nevertheless, our meta-regressions found VVC tended to have lower complication, reoperation and revision rates when compared to primary and RH prostheses ($p = 0.70$, $p = 0.73$ and $p = 0.89$, respectively).

Discussion

CNA is an end result of motor, sensory and autonomic neuropathy that triggers joint damage caused by undetected microtrauma. CNA was thought to be a contraindication for knee replacement by some scholars, due to high failure and complication rates.^{10,11} However, improvement in surgical techniques and development of prosthetic designs with versatile options encourage some surgeons to perform TKA for this complicated pathology. Although the survivorship, complication and reoperation rates of TKA performed for CNA in our systemic review may be inferior to those traditionally reported for TKA in patients with primary osteoarthritis,^{24,25} the results of TKA for CNA appear to be reasonable, understanding the nature of the neuropathic disease process and limited alternate treatment options.

Table 2. Pooled proportion of reoperations, revisions, and any complications in patients with Charcot by clinical variables

Outcomes	Proportion (95% confidence interval)	Number of included studies [Ref.]	p-value for subgroup comparison*
Knee survival			
Overall	0.854 (0.673 – 0.975)	5 ^{1,3,6,22,23}	N/A
Neuro-syphilis	0.849 (0.416 – 1.000)	3 ^{1,6,23}	0.756
Non-neuro-syphilis	0.892 (0.753 – 0.957)	1 ³	
Staging	0.825 (0.684 – 0.934)	2 ^{1,6}	N/A
Reoperations			
Overall	0.088 (0.009 – 0.216)	4 ^{1,3,6,23}	N/A
Primary prosthesis	0.000 (0.000 – 0.793)	1 ⁶	0.730
Varus-valgus constraint prosthesis	0.050 (0.000 – 0.155)	2 ^{1,6}	
Rotating hinge prosthesis	0.073 (0.000 – 0.410)	2 ^{6,23}	
Neuro-syphilis	0.096 (0.000 – 0.318)	3 ^{1,6,23}	0.855
Non-neuro-syphilis	0.081 (0.028 – 0.213)	1 ³	
Staging	0.066 (0.003 – 0.175)	2 ^{1,6}	N/A
Ataxia	0.000 (0.000 – 0.434)	1 ¹	N/A
Non ataxia	0.211 (0.085 – 0.433)	2 ^{1,6}	
Revision			
Overall	0.127 (0.020 – 0.288)	5 ^{1,3,6,22,23}	
Primary prosthesis	1.000 (0.207 – 1.000)	1 ⁶	0.889
Varus-valgus constraint prosthesis	0.033 (0.000 – 0.129)	2 ^{1,6}	
Rotating hinge prosthesis	0.182 (0.000 – 0.558)	2 ^{6,23}	
Neuro-syphilis	0.117 (0.000 – 0.378)	3 ^{1,6,23}	0.929
Non-neuro-syphilis	0.162 (0.077 – 0.311)	1 ³	
Staging	0.066 (0.003 – 0.175)	2 ^{1,6}	N/A
Ataxia	0.000 (0.000 – 0.434)	1 ¹	N/A
Non ataxia	0.211 (0.085 – 0.433)	2 ^{1,6}	
Any complications			
Overall	0.264 (0.095 – 0.474)	5 ^{1,3,6,22,23}	
Primary prosthesis	0.193 (0.000 – 0.654)	2 ^{3,6}	0.699
Varus-valgus constraint prosthesis	0.235 (0.092 – 0.412)	3 ^{1,3,6}	
Rotating hinge prosthesis	0.333 (0.114 – 0.585)	3 ^{3,6,23}	
Neuro-syphilis	0.209 (0.022 – 0.487)	3 ^{1,6,23}	0.520
Non-neuro-syphilis	0.405 (0.263 – 0.565)	1 ³	
Staging	0.262 (0.131 – 0.416)	2 ^{1,6}	N/A
Ataxia	0.400 (0.118 – 0.769)	1 ¹	N/A
Non ataxia	0.474 (0.273 – 0.683)	2 ^{1,6}	

Note. Ref., references; N/A, not available.

*Analyzed by random-effects meta-regression

Our systematic review of contemporary literatures found 85.4% of survivorship among studies reporting mid- and long-term follow-up of TKA in CNA. Based on the two largest case series, Parvizi et al²² and Tibbo et al³ reported an 85–90% survival of 77 CNA knees that were treated with modern design TKA (15 primary prosthesis, 44 VVC and 18 RH). Kim et al⁶ revealed an 84.2% of survival rate when performing one ordinary, 17 VVC, and one RH implant in 19 CNA knees secondary to NS. Indeed, a satisfactory survivorship of TKA was also demonstrated in two studies reporting long-term follow-up. Bae et al²³ found an 81.8% survival rate of RH design in 11 CNA knees with 10–22 years of follow-up. Chun et al,¹ the largest series with long-term follow-up, revealed 100% survival of 20 VVC prostheses in CNA knees, with two complications that did not require reoperation or revision surgery after a mean follow-up of 10.7 years. However, the small number of patients in this study (31 of 127 TKAs) may limit the ability to confirm whether these long-term outcomes would be reproduced by the other surgeons.

Overall, a 26.4% complication rate was identified, with instability as the most common followed by PPFx, PJI, aseptic loosening and ligament injury, respectively. Additionally, most of these complications occurred during 5–10 years of follow-up. Therefore, pattern and frequency of complications following TKA in CNA seemed to be different from those seen in osteoarthritic knees. Instability is a common complication that may be associated with preoperative status. Parvizi et al²² reported that 80% of their CNA knees had evidence of bony defect or ligament laxity resulting in instability detected clinically or intraoperatively. Kim et al⁶ found that three NS knees with preoperative tibiofemoral joint dislocation had recurrent dislocation following TKA, even if they were successfully managed with cylindrical brace applied for six months. According to PPFx, Tibbo et al³ reported PPFx seen in their cohort were all intraoperative during removal or insertion of trial implants. Improper gait balance, osteopenia and osteoporosis of disuse from prior pathology may also be factors increasing the risk of PPFx.^{6,15,22} Four of five ligamentous injuries were identified intraoperatively,²² while

the other was found 1.5 years after the index surgery.⁶ These intraoperative complications reflect the complexity that was encountered during the operations of these severe deformed and distorted joints. Thus, patients should be counselled on the risks and benefits of the procedure.

In 1966, Eichenholtz⁴ classified the natural history of CNA into three phases consisting of fragmentation, coalescence, and reconstruction phase. The first phase, or fragmentation phase, may be characterized by joint inflammation and radiological findings of periarticular fragmentation. Recently, Baumhauer et al found that inflammatory cytokine may be responsible for bony resorption in CNA.²⁶ In this stage, osteopenia, bony fragmentation and joint subluxation or dislocation may compromise the intrinsic stability of the prosthesis, and lead to implant failure.²⁷ In addition, patients with improper gait balance due to loss of neurological coordination or ataxia had also been reported with a higher incidence of complication and revision surgery.^{28–30} Accordingly, several authors proposed that early surgery in fragmentation stage (Eichenholtz stage I)^{1,13,15,31} and ataxia^{13,28,30} are poor prognostic factors for arthroplasty in Charcot patients. Hence, this may be an explanation why our systematic review found no contemporary TKA performed during fragmentation stage, and it might not allow us to make a definitive statement about this consideration. Also, a limited number of patients with ataxia had been described by a single contemporary study, which would impair the ability to interpret with respect to this issue.¹

The ideal prosthesis for CNA, in terms of level of constraint, is still debated. Poor bone quality and gross instability due to severe bone loss are quite typical characteristics of Charcot knee. This pathology may hinder secure fixation of ordinary prosthesis³² as Yoshino et al¹³ reported two PPFx and one aseptic loosening with CNA knee treated with ordinary implant. For VVC prosthesis, Chun et al¹ reported 10.7 years of follow-up of 20 Charcot knees implanted with VVC, and they reported only two complications (10%) without reoperation or revision surgery throughout the study period. Our investigation demonstrated that VVC prostheses tended to have lower rates of complication, reoperation and revision surgery compared to either ordinary or RH implants, but this difference could not trigger the statistically significant threshold. RH implants have also been frequently used in the included studies because of their intrinsic stability. While VVC implants might be chosen for CNA knees with a milder degree of deformity, selection of an RH prosthesis when encountering severe bony destruction and gross instability might be a reason for having higher complication and failure rates.² Constraint of RH prostheses may

increase stress at the interface of implant and sclerotic bone, and lead to a higher risk of failure. The transitional area at the tip of RH may also increase risk of PPFx due to stress riser.^{16,33} It is not certain that these findings are related to the implant design or related to the conditions under which the higher constraint devices are required. The conflicting outcomes of previous studies and the limitation of current data suggest that it is not possible to define a single best approach to treat CNA.

Generally, TKA in Charcot joint caused by NS is likely to have poorer outcomes than in non-NS,^{6,13} because NS patients have the risk of deteriorating and developing ataxia that may have a detrimental effect on the outcome of joint arthroplasty due to uneven and abnormal stress impacted on the prosthesis.^{2,22,27} Nevertheless, when a larger cohort was assessed, we found that Charcot joint secondary to non-NS had a non-significant difference in terms of complications, reoperation and revision surgery compared to NS. Bae et al²³ concluded from their long-term study that the result of TKA in patients with CNA secondary to NS was not significantly different to the outcomes of TKA in other patients. Thus, NS may not be a predictor of unsatisfactory outcome for TKA.

This study had some limitations that should be noted. The first and main limitation is that our assessment was based on the results from several case series, thus heterogeneity of available data and risk of bias could not be avoided. To the best of our knowledge, there was no study that directly makes comparisons between different surgical treatments in patients with Charcot knee. Second, meta-analysis could not be conducted for every variable clinical factor because information from included studies was limited and the inferences might not be accurate. Some interesting information including knee score, functional score, radiographic evaluation, results of revision surgery and treatment for complications also could not be evaluated. Despite these limitations, our review may provide additional evidence and clues to those unclear questions regarding TKA in CNA.

Conclusion

Total knee arthroplasty may be considered as a viable option for patients with CNA, even if the overall outcomes seem to be inferior to those for TKA performed in primary knee osteoarthritis. The aetiology of CNA and prosthesis type had no influence on clinical outcomes, while the effect of staging of disease and ataxia status was still inconclusive. Understanding the potential determinants, survivorship and risk of complications related to TKA performed in CNA may help surgeons in dealing with patient expectations.

AUTHOR INFORMATION

¹Department of Orthopaedics, Faculty of Medicine, Naresuan University, Phitsanulok, Thailand.

²Department of Internal Medicine, Faculty of Medicine, Naresuan University, Phitsanulok, Thailand.

³Center of Pharmaceutical Outcomes Research, Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Naresuan University, Phitsanulok, Thailand.

⁴Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Naresuan University, Phitsanulok, Thailand.

⁵Department of Pharmacotherapy, College of Pharmacy, University of Utah, Salt Lake City, Utah, USA.

⁶School of Pharmacy, University of Wisconsin, Madison, Wisconsin, USA.

Correspondence should be sent to: Artit Laoruegthana, Department of Orthopaedics, Faculty of Medicine, Naresuan University, Phitsanulok, Thailand. Email: artitlao@gmail.com

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