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Systematic Review and Meta-analysis

What Is the Best Evidence to Guide Management of Acute Achilles Tendon Ruptures? A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials

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Abstract

Background Uncertainty exists regarding the best treatment for acute Achilles tendon ruptures. Simultaneous comparison of the multiple treatment options using traditional study designs is problematic; multiarm clinical trials often are logistically constrained to small sample sizes, and traditional meta-analyses are limited to comparisons of only two treatments that have been compared in head-to-head trials. Network meta-analyses allow for simultaneous comparison of all existing treatments utilizing both direct (head-to-head comparison) and indirect (not previously compared head-to-head) evidence.

Questions/purposes We performed a network meta-analysis of randomized controlled trials (RCTs) to answer the following questions: Considering open repair, minimally invasive surgery (MIS) repair, functional rehabilitation, or primary immobilization for acute Achilles tendon ruptures, (1) which intervention is associated with the lowest risk of rerupture? (2) Which intervention is associated with the lowest risk of complications resulting in surgery?

Methods This study was conducted with methods guided by the Cochrane Handbook for Systematic Reviews of Interventions and is reported in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for incorporating network meta-analysis. Five databases and grey literature sources (such as major orthopaedic meeting presentation lists) were searched from inception to September 30, 2019. Included studies were RCTs comparing treatment of acute Achilles tendon ruptures using two or more of the following interventions: primary immobilization, functional rehabilitation, open surgical repair, or MIS repair. We excluded studies enrolling patients with chronic ruptures, reruptures, and preexisting Achilles tendinopathy as well as studies with more than 20% loss to follow-up or less than 6 months of follow-up. Nineteen RCTs (1316 patients)

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Ethical approval was not sought for the present study.
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were included in the final analysis. The mean number of patients per study treatment arm was 35 ± 16, mean age was 41 ± 5 years, mean sex composition was 80% ± 10% males, and mean follow-up was 22 ± 12 months. The four treatment groups were compared for the main outcomes of rerupture and complications resulting in operation. The analysis was conducted using random-effects Bayesian network meta-analysis with vague priors. Evidence quality was evaluated using Grades of Recommendation, Assessment, Development, and Evaluation methodology. We found risk of selection, attrition, and reporting bias to be low across treatments, and we found the risk of performance and detection bias to be high. Overall risk of bias between treatments appeared similar.

Results We found that treatment with primary immobilization had a greater risk of rerupture than open surgery (odds ratio 4.06 [95% credible interval {CrI} 1.47 to 11.88]; $p < 0.05$). There were no other differences between treatments for risk of rerupture. Minimally invasive surgery was ranked first for fewest complications resulting in surgery and was associated with a lower risk of complications resulting in surgery than functional rehabilitation (OR 0.16 [95% CrI 0.02 to 0.90]; $p < 0.05$), open surgery (OR 0.22 [95% CrI 0.04 to 0.93]; $p < 0.05$), and primary immobilization (OR < 0.01 [95% CrI < 0.01 to 0.01]; $p < 0.05$). Risk of complications resulting in surgery was no different between primary immobilization and open surgery (OR 1.46 [95% CrI 0.35 to 5.36]). Data for patient-reported outcome scores and return to activity were inappropriate for pooling secondary to considerable clinical heterogeneity and imprecision associated with small sample sizes.

Conclusion Faced with acute Achilles tendon rupture, patients should be counseled that, based on the best-available evidence, the risk of rerupture likely is no different across contemporary treatments. Considering the possibly lower risk of complications resulting in surgery associated with MIS repair, patients and surgeons must balance any benefit with the potential risks of MIS techniques. As treatments continue to evolve, consistent reporting of validated patient-reported outcome measures is critically important to facilitate analysis with existing RCT evidence. Infrequent but serious complications such as rerupture and deep infection should be further explored to determine whether meaningful differences exist in specific patient populations.

Level of Evidence Level I, therapeutic study.

Introduction

Achilles tendon ruptures are common and debilitating, and they are followed by intensive rehabilitation to regain function of plantarflexion strength [11]. They most commonly occur during activities that require explosive acceleration with movements such as jumping and sprinting. Typically most common in 30- to 40-year-old males, the incidence of these injuries continues to increase [11, 33, 37, 77]. Despite the rising incidence, there remains little consensus on how best to treat acute Achilles tendon ruptures [11, 37]. Further, both operative and nonoperative treatment strategies continue to evolve, increasing uncertainty for both patients and surgeons.

Nonsurgical treatment of Achilles ruptures once consisted of cast immobilization in plantarflexion with prolonged immobilization, allowing for apposition and healing of the ruptured tendon. Because of concerns of rerupture and calf atrophy, open surgical management often has been preferred over nonoperative management for active, healthy patients. However, complications largely unique to surgery such as wound dehiscence, infections, and other soft tissue issues occur in up to 10% to 15% of treated patients [63]. Functional rehabilitation protocols with early weightbearing and ankle mobilization have seen wider use in recent years, with studies reporting similar patient-reported outcome scores, return to sport, and rerupture risk compared with operative treatment but without subjecting patients to the risks of surgery [11, 22, 33, 37, 77]. With increasing evidence supporting functional rehabilitation, practice has shifted rather drastically with an associated reduction in surgical treatment by more than 50% in the past 20 years [3, 56, 57], although this trend has not been seen in the United States [67, 90]. Successful functional rehabilitation programs require substantial patient cooperation and supervision, which may be hindered by patient and system factors, such as lack of physiotherapy access [22, 33, 37, 77]. Despite advances in nonoperative treatment, many surgeons continue to advocate for surgical management because of increased confidence in maintaining tendon apposition, length, and strength [69], as well the traditional belief that rerupture risk is lower [11, 80]. To reduce surgical site complications, minimally invasive and percutaneous repair of the Achilles tendon have been advocated [47, 69]. Although some authors report percutaneous repair is associated with an increased risk of sural nerve complications and rerupture compared with open repair, these findings have been disputed [29, 48, 52].

Numerous meta-analyses have been performed to establish the superiority of one treatment over another [22, 23, 80, 100]. Constrained by design, traditional pairwise meta-analyses can only evaluate two treatments that have been directly compared in trials. Considering the multiple treatments available for Achilles tendon ruptures, the limitations of pairwise analysis have led to pooling of treatments into heterogeneous groups (such as, operative versus nonoperative management) and numerous overlapping meta-analyses [35, 66]. A network meta-analysis addresses this issue by facilitating simultaneous comparison of multiple treatments [6, 9, 53, 63]. Further, a network meta-analysis allows for the comparison of treatments that were not evaluated in a head-to-head manner in the original randomized controlled trials (RCTs). This approach facilitates the estimation of relative treatment effects for interventions that have not been directly compared in head-to-head trials and for treatments that have only been compared in a limited number of trials.

Our goal was to use network meta-analysis to answer the following questions: Considering open repair, minimally invasive surgery (MIS) repair, functional rehabilitation, or primary immobilization for acute Achilles tendon ruptures, (1) which intervention is associated with the lowest risk of rerupture? (2) Which intervention is associated with the lowest risk of complications resulting in surgery?

Materials and Methods

Search Strategy

We conducted a systematic review with network meta-analyses using methods guided by the Cochrane Handbook for Systematic Reviews of Interventions [31]. This review is reported in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for incorporating network meta-analysis [36, 77]. We published a research protocol [66] and registered this study prospectively with PROSPERO (CRD42018093033). Our electronic search of medical and rehabilitation literature related to management of acute Achilles tendon rupture was performed from database inception to the search date (September 30, 2019) using Medline, Embase, CINAHL, PEDro, and Cochrane Central Register of Controlled Trials. The primary author (BM) developed the search strategy in consultation with a senior information specialist (RS). The strategy was then peer reviewed by a second medical librarian in accordance with the Peer Review of Electronic Search Strategies (PRESS) framework [76]. Previously published systematic reviews were cross-referenced for any missed studies. In addition, we manually searched relevant unpublished evidence sources (grey literature), including meeting abstracts from the Orthopaedic Trauma Association, American Academy of Orthopaedic Surgery, and American Orthopaedic Foot and Ankle Society (AOFAS) annual meetings from 2014 to 2019 to identify emerging studies nearing completion. Preprint servers and foreign-language journals not included in the specified databases were not searched. No language limits were used. The search strategy for one database is available with the published study protocol [61].

Inclusion and Exclusion Criteria

Inclusion criteria were RCTs directly comparing two or more interventions for the treatment of first-time, acute (less than 4 weeks since injury) Achilles tendon ruptures with a minimum follow-up of 6 months. This minimum follow-up was chosen to maximize study inclusion while ensuring appropriate demonstration of return to activity and complications [99]. Interventions of interest included conventional cast immobilization with delayed weightbearing for at least 6 weeks (primary immobilization), bracing and/or splinting with ROM earlier than 6 weeks (functional rehabilitation), open surgical repair, and percutaneous or minimally open surgical repair (MIS). For inclusion as a functional rehabilitation protocol, ankle ROM had to be started before 6 weeks postrupture with or without early weightbearing. MIS treatment included all surgical modalities that did not completely open and reflect the paratenon, including limited transverse incisions, suture-shuttling techniques, and device-assisted techniques. Use of primary immobilization has largely decreased in recent years in favor of functional rehabilitation; however, this treatment was included as a comparator for other treatments and therefore any expertise bias resulting from its inclusion was anticipated to have little impact on our key findings. We excluded studies investigating modifications of only one of the above treatments. For example, we did not include RCTs examining early versus late weightbearing after open surgical repair (as both treatment arms would be considered open surgical repair).

We chose exclusion criteria based on factors that may alter the natural history of tendon repair and rehabilitation: (1) patients younger than 16 years of age, (2) chronic tendon ruptures, (3) tendon rerupture, (4) inclusion of patients with preexisting Achilles tendinopathy, and (5) musculotendinous junction tears. If two or more studies reported the same information, we included only the study with most complete data (that is, the complete reporting of outcomes of interest). Studies were excluded if nonrandom loss to follow-up was greater than 20%.

Screening

The search was conducted on September 30, 2019. Studies were screened using Covidence (Veritas Health Information Ltd). Two reviewers (BM, MR) screened all titles, abstracts, and full-text articles independently and in duplicate. Disagreements at the title and abstract stages were resolved by automatic inclusion, and disagreements at the full-text stage were resolved by consensus. Study authors were contacted if eligibility criteria were unclear.

Outcomes

The primary outcomes for quantitative synthesis were (1) rerupture and (2) post-treatment complications resulting in surgery. Secondary outcomes included functional outcome score, strength, and ROM. Both outcomes were evaluated at the longest reported follow-up. Despite inclusion in the published study protocol [61], the outcomes of overall complications and return to activity were not included in the final analysis. During peer-review, it became apparent that analyzing pooled complications, while statistically robust, resulted in an outcome of unclear clinical relevance because it would have involved pooling common but relatively mild complications (such as superficial infection) with rarer but devastating events (like complex regional pain syndrome [CRPS]). Thus, the outcome of pooled complications was excluded from the final analysis. Complications resulting in surgery were chosen partly as surrogates for serious complications as there were an insufficient number of serious complications not resulting in surgery for statistical analysis. Patients with rerupture, if treated surgically, were counted in both rerupture and complications resulting in surgery. Return to function was excluded from the final analysis because of the inconsistent and heterogeneous nature of the available evidence, which precluded appropriate application of network meta-analysis methodology.

Data Extraction

Data were abstracted in duplicate by two reviewers (MR, AG) using a standardized extraction document (Microsoft Excel 16.2), which was developed and piloted a priori. Discrepancies were resolved by consensus and input from a third reviewer (BM or WC). Study authors were contacted in cases of incomplete data. Abstracted data included study author, year, country of publication, outcome data, and participant demographics (mean age, sex, risk factors for complication such as smoking status, fluoroquinolone or steroid use, diabetes, and smoking), surgical repair method including technique and suture, surgeon experience, length of immobilization, and weightbearing status.

Quality Assessment

The Cochrane Risk of Bias version 2 (ROB 2) assessment tool was used to evaluate bias in the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias [83]. Two reviewers (BM, AG) evaluated all studies and assigned risk as high risk, low risk, or unclear, with disagreements resolved by consensus. Risk of bias between studies (such as, small-study effects signaling publication bias) was assessed and presented as funnel plots. The overall quality of the evidence was determined and ranked per the Grades of Recommendation, Assessment, Development, and Evaluation approach for network meta-analyses [25, 71].

Study Characteristics

The search identified 630 citations; 103 studies underwent full-text review, of which 19 RCTs (1316 patients) were included in the final analysis (Fig. 1). Included studies were published between 1981 and 2018 (median = 2008). Unique pairwise comparisons included open surgery versus MIS [1, 2, 21, 41, 46, 52, 73], open surgery versus functional rehabilitation [13, 49, 64, 85, 88, 96], MIS versus functional rehabilitation [60], and open surgery versus primary immobilization [10, 42, 62, 65]. One study had three treatment arms (Supplemental Table 1; Supplemental Digital Content 1, http://links.lww.com/CORR/A584) [54]. The mean number of patients per study treatment arm was 35 ± 16 patients (Table 1). Across studies, the mean age was 41 ± 5 years, and 80% of participants were male. Mean age and sex composition were similar across treatment arms. Mean follow-up across all studies was 22 ± 12 months, which was also similar between treatment groups. Only one study had a follow-up less than 12 months [52].

Study Quality

The cumulative risk of bias was deemed low across domains (Fig. 2). Of the 19 included studies, nine were deemed to be low risk of bias in at least five domains, and 14 studies were deemed low risk in at least four domains (Supplemental Fig. 1; Supplemental Digital Content 2, http://links.lww.com/CORR/A585). Overall, risk of selection, attrition, and reporting bias was low. However, risk of performance bias and detection bias were high, largely because of the difficulty of blinding when performing studies of surgical treatments. Risk of bias was not expected to compromise pooled results, as it appeared similar across treatment arms.

Ethical Approval

This network meta-analysis did not involve human participants and therefore was not subject to institutional review board approval.

Meta-analysis Methodology

We performed pairwise meta-analysis for all primary outcomes when direct comparisons were available. The Mantel-Haenszel random-effects model was applied to binary outcomes in the presence of sufficient clinical, methodological, and statistical homogeneity (heterogeneity $I^2 < 50\%$) [32]. Pairwise analysis results are expressed

Table 1. Demographic information for included studies

Parameter	Open surgery	MIS	Functional rehabilitation	Primary immobilization
Number of studies	17	9	7	4
Patients per treatment arm	35 ± 16	28 ± 9	33 ± 20	52 ± 9
Age in years	41 ± 5	43 ± 6	39 ±2	39 ± 1
Percent male	81 ± 8	79 ± 11	75 ±13	85 ± 5
Follow-up in months	21 ± 12	22 ± 10	23 ± 11	27 ± 23
Publication year	2009 (1981-2018)	2009 (2008-2018)	2008 (1995-2006)	1997 (1981-2011)

Data presented as mean ± SD or median (range); number of studies represents the number of studies including the specified intervention as a treatment arm and therefore the sum of this row exceeds the total number of studies included in the network meta-analysis; percent male represents the pooled value for the treatment arm calculated using weighted means for each treatment group; MIS = minimally invasive surgery.

as odds ratios for dichotomous outcomes with 95% confidence intervals. Forest plots from pairwise analysis were generated using Review Manager (Version 5.3, The Cochrane Collaboration, Nordic Cochrane Centre).

Network Meta-analysis Methodology

To perform network analyses, we used the OpenBUGS software (Version 3.2.3) and the R2OpenBUGS package (Version 3.2) in R (Version 3.4.2, Open Access Online) [81, 84]. We generated network diagrams for each outcome to ensure well-connected network geometry (at least one closed loop among interventions). We assessed the validity of the transitivity assumption (that is, homogeneity/similarity across studies) by thoroughly reviewing study methods, patient characteristics, and enrollment criteria using established methods [15, 16]. All treatments were assessed to be "jointly randomizable" and could reasonably be applied to any patient in the network [74]. This assumption was supported by relatively strict inclusion criteria and the similar composition of pooled treatment groups [24]. Random-effects Bayesian network meta-analysis with vague priors was performed for each outcome. Prior distributions describe information outside of the included studies used to determine the posterior distribution from which summary measures (such as, mean and SD) are calculated [39]. We used vague priors as there appeared to be sufficient data to estimate variance appropriately without introducing subjectivity into our models, which may occur with truly informative priors [97]. Adequacy of model fit was assessed by comparing the total residual deviance with the number of unconstrained data points (the number of intervention arms across studies in the analysis) and was considered adequate if these quantities were approximately equal. Model selection was based on deviance information criteria, with smaller values being preferred and a difference of five or more points representing an important difference in fit between models. Model convergence was assessed using established methods including the Gelman-Rubin diagnostics and the Potential Scale Reduction Factor [4, 20]. Validity of the consistency

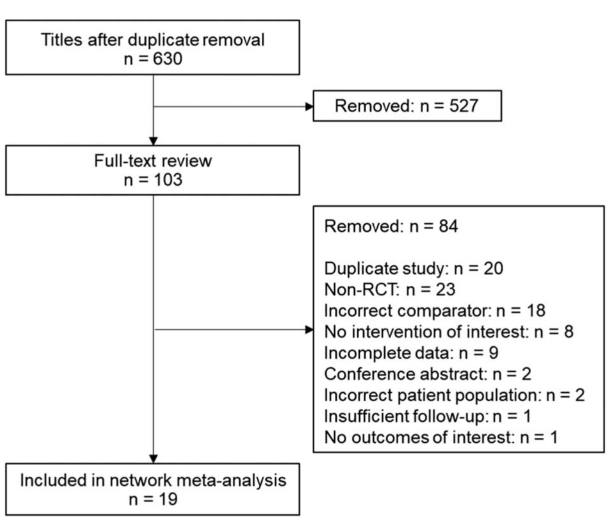

Fig. 1 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for study screening.

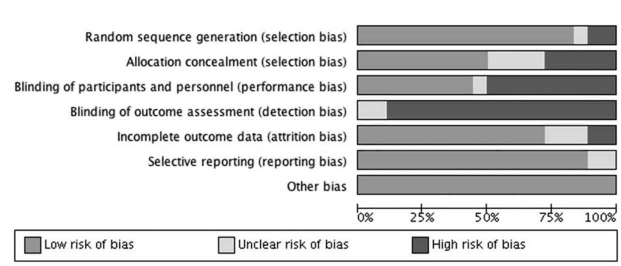

Fig. 2. The pooled risk of bias for all included studies divided by source of bias.

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assumption (the agreement between direct and indirect evidence) was assessed by fitting random effects unrelated means models to the data and comparing deviance information criterion (DIC) values and posterior mean deviance contributions with the DIC values from consistency models. Deviance residuals, the amount of deviance from each observation, were then plotted to identify inconsistency between direct and indirect evidence (Supplemental Fig. 2; Supplemental Digital Content 3, http://links.lww.com/CORR/A586). Total residual deviance values were lower than the number of unconstrained data points due to several studies with zero occurrences of the outcome of interest (Supplemental Table 2; Supplemental Digital Content 4, http://links.lww.com/CORR/A587).

Our results are presented using odds ratios (OR) and 95% credible intervals (CrI), a measure of imprecision derived using the posterior distributions, which are akin to a Bayesian equivalent of confidence intervals. Comparisons were inferred to be significant if the 95% CrI of the OR did not cross one [17]. A Surface Under the Cumulative Ranking (SUCRA) curve, a numeric representation of treatment ranking, was calculated for each intervention. As SUCRA nears one (the maximum possible value), the greater the probability a treatment is in the top ranks of treatments [75]. Values approaching zero indicate a greater probability a treatment is in the bottom ranks. Number needed to treat was calculated using the difference in mean patient-expected event rates [12]. Summary of findings tables are presented using open surgery as the reference treatment as it was most well connected to other interventions by direct evidence. Comparison-adjusted funnel plots were applied to assess for small-study effects as signals of publication bias. We performed a sensitivity analysis for risk of complications by excluding keloid scars as a complication. For the outcome of complications resulting in surgery, we performed a sensitivity analysis by excluding the study with follow-up duration stated to be "at least 6 months" [52].

Results

Rerupture

We found no difference between open surgical repair, MIS repair, and functional rehabilitation for risk of rerupture, and primary immobilization was associated with a greater risk of rerupture than open repair. Specifically, the network analysis for rerupture (19 RCTs, 1316 participants) demonstrated no difference between open surgical repair (reference treatment) and MIS repair (OR 0.96 [95% CrI 0.22 to 4.15]; $p > 0.05$) or functional rehabilitation (OR 2.18 [95% CrI 0.80 to 6.20]; $p > 0.05$) (Fig. 3). We also found no difference between functional rehabilitation and MIS (OR 0.45 [95% CrI 0.10 to 1.82]; $p > 0.05$) (Supplemental Fig. 3; Supplemental Digital Content 5, http://links.lww.com/CORR/A588). Compared with open surgery, primary immobilization was associated with a greater risk of rerupture (OR 4.06 [95% CrI 1.47 to 11.88]; $p < 0.05$) (Table 2). Open surgical repair and MIS were ranked most favorably for risk of rerupture (SUCRA 0.80 and 0.79, respectively) (Supplemental Table 3; Supplemental Digital Content 6, http://links.lww.com/CORR/A589). There were no differences between pairwise and network-derived estimates (Supplemental Fig. 4; Supplemental Digital Content 7, http://links.lww.com/CORR/A590).

Complications Resulting in Surgery

We found a lower risk of complications resulting in surgery with MIS repair relative to both open surgery and functional rehabilitation, and we found no difference in risk between functional rehabilitation and open surgery. The network analysis (15 RCTs, 949 patients) demonstrated that MIS repair was associated with a lower risk of complications resulting in surgery than open surgical repair (OR 0.22 [95% CrI 0.04 to 0.93]; $p < 0.05$) and functional rehabilitation (OR 0.16 [95% CrI 0.02 to 0.90]; $p < 0.05$). We found no difference in complications resulting in surgery between functional rehabilitation and open surgery (OR 1.46 [95% CrI 0.35 to 5.36]; $p > 0.05$). Immobilization was associated with a greater risk of complications resulting in surgery than any other treatment. Minimally invasive surgery was ranked most highly for complications resulting in surgery (SUCRA 0.99) (Table 3). Consistency was present between pairwise and network comparisons (Supplemental Fig. 5; Supplemental Digital Content 8, http://links.lww.com/CORR/A591).

Discussion

Treatment of acute Achilles tendon ruptures remains an area of uncertainty, despite an abundance of RCTs and resultant meta-analyses. Our goal was to use a network meta-analysis to compare treatments for acute Achilles tendon ruptures, including treatments infrequently compared in head-to-head RCTs, in a simultaneous and comprehensive manner not otherwise possible with simple meta-analysis. We found no difference in the rerupture risk between open surgical repair, MIS repair, and functional rehabilitation; immobilization was associated with a greater risk of rerupture than open surgical

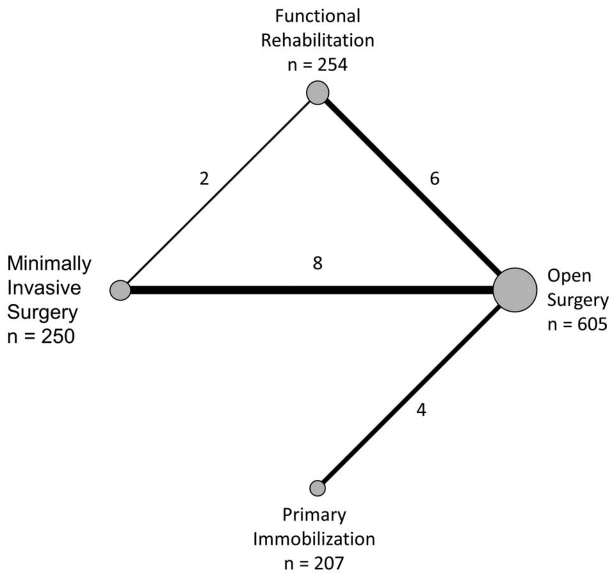

Fig. 3. The network geometry for risk of rerupture. Node size is proportionate to the number of participants in the specified treatment arm and is indicated by n = below the treatment name. Edge (connecting line) thickness is proportionate to the number of studies informing an indicated comparison and is specified with the number adjacent the edge.

repair. We found a lower risk of complications resulting in surgery after MIS repair relative to both open surgery and functional rehabilitation.

Limitations

Network meta-analysis can be a powerful tool for comparing nearly all randomized evidence for treatment of a given pathology. However, this study has several key limitations, two of which resulted from the choice of complications resulting in surgery as a primary outcome. First, rerupture was the most common complication resulting in surgery, and most reported reruptures were treated surgically. Therefore, readers must be aware that treatments with an increased risk of rerupture will be overrepresented in our study (because rerupture was counted in both study endpoints), and any conclusions should be balanced with information gathered from existing studies on complications other than rerupture [44, 66]. Specifically, following functional rehabilitation, more than 80% of complications resulting in operation were from rerupture, a greater proportion than MIS and open surgery. Second, we settled on the outcome of complications resulting in surgery for pragmatic reasons—to facilitate robust, pooled analysis of serious complications with tangible implications for both patients and surgeons. Unfortunately, specific complications resulting in surgery other than rerupture (such as deep infection) were reported with insufficient frequency for independent network analysis [95]. Complications associated with serious morbidity not resulting in further surgery such as deep vein thrombosis

Table 2. Summary of findings table for rerupture

Studies: 19[a] Participants: 1316	**Minimally invasive surgery (9 RCTs[b]; 250 participants)**	**Functional rehabilitation (7 RCTs[b]; 254 participants)**	**Primary immobilization (4 RCTs[b]; 207 participants)**	**Open surgery (17 RCTs[b]; 605 participants)**
Relative effect (95% CrI)	0.96 (0.22-4.15)[c]	2.18 (0.80-6.20)[c]	4.06 (1.47-11.88)[d]	Reference
NNT	173.9	18.9[e] (Harm)	12.9[e] (Harm)	Reference
GRADE evaluation	Low[f,g]	Moderate[g]	Low[f,g]	Reference
Mean ranking (95% CrI)	1.65 (1-4)	3.00 (2-4)	3.76 (2-4)	1.59 (1-3)
Interpretation of findings	Possibly superior	Possibly inferior	Probably inferior	Reference

Relative effect values are odds ratios relative to open surgery; mean rank was calculated based on surface under the cumulative ranking curve (SUCRA) values; small sample sizes were considered in the evaluation of imprecision.
[a]Total number of studies across all treatments.
[b]Number of RCTs including the treatment of interest.
[c]95% CrI for odds ratio crosses one, indicating no difference relative to reference treatment; $p > 0.05$.
[d]Inferred to be statistically significant with a 95% CI for odds ratio not crossing one; $p < 0.05$
[e]Treatment associated with a relative effect indicating harm. Therefore, associated value is number needed to harm.
[f]Downgraded for risk of bias.
[g]Downgraded for imprecision; NNT = number needed to treat; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; CrI = credible interval.

Table 3. Summary of findings table for complications resulting in surgery

Studies: 15[a] Participants: 949	Minimally invasive surgery (9 RCTs[b]; 250 participants)	Functional rehabilitation (6 RCTs[b]; 182 participants)	Primary immobilization (2 RCTs[b]; 99 participants)	Open surgery (14 RCTs[b]; 418 participants)
Relative effect (95% CrI)	0.22 (0.04-0.93)[c]	1.46 (0.35-5.36)[d]	> 100 (22.1 to > 100)[c]	Reference
NNT	40.5	32.5[e] (Harm)	101.7[e] (Harm)	Reference
GRADE evaluation	Moderate[f]	Low[f,g]	Very low[f,h]	Reference
Mean ranking (95% CrI)	1.04 (1-2)	2.71 (2-3)	4.00 (4-4)	2.25 (2-3)
Interpretation of findings	Probably superior	Possibly inferior	Definitely inferior	Reference

Relative effect values are odds ratios relative to open surgery; mean rank was calculated based on surface under the cumulative ranking curve (SUCRA) values; small sample sizes were considered in the evaluation of imprecision.
[a]Total number of studies across all treatments.
[b]Number of RCTs including the treatment of interest.
[c]Inferred to be statistically significant with a 95% CI for mean difference not crossing one; $p < 0.05$.
[d]95% CrI for odds ratio crosses one, indicating no difference relative to reference treatment; $p > 0.05$.
[e]Treatment associated with a relative effect indicating harm. Therefore, associated value is number needed to harm.
[f]Downgraded for risk of bias.
[g]Downgraded for imprecision.
[h]Downgraded two levels for imprecision; NNT = number needed to treat; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; CrI = credible interval.

and pulmonary embolism (both of which are more common after operative management) were inconsistently reported in the included studies and were therefore excluded from our analysis [70]. Readers should interpret the risk of complications resulting in surgery within the context of existing evidence that has explored serious complications not resulting in further surgery, complications that may still lead to substantial patient morbidity [59].

Another limitation of our study is that we were unable to analyze both minor, more frequent complications, such as keloid scars, skin adhesions, and superficial infection, as well as other complications such as sural nerve injury (24% of all complications after MIS) and complex regional pain syndrome (CRPS). At the outset of this study, it was our goal to analyze these complications [61]; however, during the review process it became clear that pooling in this manner would have resulted in a study endpoint that grouped relatively inconsequential complications with very serious ones, which can be misleading. For example, it would not be appropriate to pool superficial skin infection resolving with a short course of oral antibiotics—the most common complication of surgical management (31% of all complications)—with permanent sural nerve dysfunction or CRPS, which are associated with substantial morbidity [43, 60]. Although independent analysis of these complications is undoubtedly important, it was not possible to do that in the context of this network meta-analysis. For example, other than very rare instances, wound complications and infection occur only after MIS and open surgical repair, and therefore, a pairwise meta-analysis may be more appropriate [19]. Further, with a complication such as sural nerve injury (24% of all MIS-associated complications), analyzing a variety of MIS techniques together may be inappropriate secondary to a vastly different risk of sural nerve injury across the techniques [55]. Considering the above, our conclusions are based on only two facets of morbidity after treatment and should therefore be viewed in light of past analyses on specific complications. In addition to rerupture and complications resulting in surgery, patients should be counseled about the risks of other complications such as wound complications, infection, nerve injury, and deep vein thrombosis [44, 57, 70]

Patient-reported outcomes are increasingly important in Achilles tendon rupture literature; focus has shifted at least partly from rerupture risk to validated measures of patient function. Although described in our protocol, we were unable to perform an appropriate network meta-analysis for this outcome because of small sample sizes and heterogeneity of outcome measures, even after considering the use of standardized mean differences [14, 31, 45, 51]. Inferences would have been driven by limited direct comparisons and frequent third-order comparisons (two intermediary comparators are needed to form a network), resulting in very low confidence in network estimates [95]. Differences in treatment specifics within groups may have further limited the validity of pooling studies to perform this analysis. Recent evidence has found that distinct surgical variations and variations in postoperative protocols result in different degrees of tendon elongation [8, 18, 27, 30, 40, 72, 86]. Further, post-treatment tendon elongation has been associated with lower patient-reported outcomes scores and reduced plantarflexion strength [28, 79, 91]. For these reasons, surgeons must largely rely on direct RCT evidence of patient-reported outcomes rather than pooled comparisons when putting the findings of our study into context. For reference, most included studies (6 of 7) reported no difference between MIS and open surgery, and one study reported MIS was superior to open surgery. One study reported that open surgery outperformed functional rehabilitation (Supplemental Table 4; Supplemental Digital Content 9, http://links.lww.com/CORR/A592). Only the minority of studies found differences in strength parameters (Supplemental Table 5; Supplemental Digital Content 10, http://links.lww.com/CORR/A593).

Similarly, return to work and sport analyses were not performed because of very low evidence quality and poor assessment of the endpoints in question. Inconsistency in return-to-sport reporting has been previously noted by other researchers [3, 44, 66], although studies have found no difference between open repair, MIS repair, and functional rehabilitation [23, 60, 66]. In our study, most included RCTs found no difference between return to work (Supplemental Table 6; Supplemental Digital Content 11, http://links.lww.com/CORR/A594); some studies also found no difference in return to sport (Supplemental Table 7; Supplemental Digital Content 12, http://links.lww.com/CORR/A595). Of great concern regarding risk of bias, nearly all studies lacked rigorous blinding, and authors largely did not outline return to activity (such as work and sport) criteria in detail. Surgeons must be cautious when considering our findings in the context of existing, high risk-of-bias RCT evidence on inter-treatment differences in return to activity.

Finally, several studies did not report the presence of risk factors for complications such as smoking, diabetes, and fluoroquinolone use [5]. However, the treatment indications and inclusion criteria were very similar or identical between included studies so it is unlikely that there was unequal distribution of effect modifiers between pooled network groups.

Rerupture

We found no difference in the risk of rerupture between open surgical repair, MIS repair, and functional rehabilitation. We also found that immobilization was associated with a greater risk of rerupture than open surgical repair, and although the quality of evidence was low, this finding is in agreement with existing evidence [66]. Although our study did not investigate the effect of early versus late weightbearing after open surgical treatment, previous analyses have demonstrated both postoperative protocols reduce rerupture risk compared with primary immobilization [66, 80]. When a functional rehabilitation protocol is used (that is, early full weightbearing with progressive ROM), our study and others, including recent meta-analyses pooling observational data from thousands of patients, have found no difference in rerupture risk between open surgery, MIS, and nonoperative treatment [60, 66, 78, 80, 89, 99]. Our findings are congruent with and further support the paradigm shift over the past decade: Although previously, operative treatment was considered the gold standard largely because of decreased rerupture risk, nonoperative treatment with functional rehabilitation has been accepted as a viable alternative with a rerupture risk that is no different from operative treatment [44, 66, 77]. However, the question of rerupture risk remains unsettled. To further inform treatment decision-making, future research, both randomized and observational, should examine rerupture risk between treatments in populations that may be at higher risk for poor outcomes and rerupture such as those with increased tendon diastasis or more proximal ruptures [26, 92], and older patients or those with higher BMI [7, 50, 67, 82, 93]. Rerupture risk between treatments should also be investigated in high-demand groups such as younger patients and those engaged in athletics [38].

Complications Resulting in Surgery

Our analysis of reoperation found that MIS was associated with a lower reoperation risk relative to open surgery, functional rehabilitation, and primary immobilization. The comparison between MIS and open surgery was informed by moderate-quality evidence, and the difference between MIS and functional rehabilitation was supported by low-quality evidence. Interestingly, it appears that the risk of complications resulting in operation (or reoperation, in the case of operative management) is rarely, if ever, reported in existing meta-analyses. Our findings contrast with a recent retrospective study comparing 270 patients treated with either percutaneous or open repair that found no difference in risk of complications resulting in surgery [34]. Complications resulting in surgery, most frequently rerupture and deep infection, have been associated with poor patient-reported outcomes, and in many instances, lead to severe long-term functional deficits, particularly if repeat or extensive revision surgery is needed [58, 59, 68]. For this reason, we believe patients and surgeons should consider the moderate-quality evidence that MIS may be associated with a reduced risk of complications resulting in surgery (number needed to treat = 40), particularly when compared with open surgical repair. However, patients and surgeons must balance this benefit with the potential drawbacks of MIS repair [55]. Of note, reruptures may be treated with either nonoperative management or revision surgery, though in the case of revision surgery, more involved techniques such as fascial flaps and allograft are typically used [58, 59, 68, 93]. The difference we found also calls into question the conclusions of existing cost-efficacy analyses that have assumed equal reoperation between treatments [87, 94]. The implications of further surgery on total treatment cost are likely substantial, and therefore, our findings may be of interest to policy-makers. Overall, as our study is the first to demonstrate a difference in complications resulting in surgery, future studies (including meta-analyses) should include this outcome, as it is likely of interest to patients and surgeons alike.

Conclusion

Faced with acute Achilles tendon rupture, patients should be counseled that, based on current evidence, the rerupture risk likely is no different across contemporary treatments. Considering the possibly lower risk of complications resulting in surgery associated with MIS repair, patients and surgeons must balance any benefit with the potential risks of MIS techniques. As treatments continue to evolve, consistent reporting of validated patient-reported outcome measures is critically important to facilitate analysis with existing RCT evidence. Infrequent but serious complications such as rerupture and deep infection should be further explored to determine whether meaningful differences exist in specific patient populations.

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