RESEARCH ARTICLE

A Systematic Review and Meta-Analysis of Ilizarov Methods in the Treatment of Infected Nonunion of Tibia and Femur

Peng Yin¹,²☯, Qiunan Ji³☯, Tongtong Li¹,²☯, Jiantao Li¹, Zhirui Li¹, Jianheng Liu¹, Guoqi Wang¹, Song Wang¹,², Lihai Zhang¹*, Zhi Mao¹*, Peifu Tang¹*

¹ Department of Orthopaedics, Chinese PLA General Hospital, No. 28 Fuxin Road, Beijing, 100853, P.R. China, 2 School of Medicine, Nankai University, No. 94 Weijin Road, Tianjin, 300071, P.R. China, 3 School of Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong, China

☯ These authors contributed equally to this work.
* pftang301@sina.cn (PFT); maozhiys@sina.com (ZM); zhanglihai74@126.com (LHZ)

Abstract

Background
Infected nonunion of tibia and femur are common in clinical practice, however, the treatment of these diseases has still been a challenge for orthopaedic surgeons. Ilizarov methods can eradicate infection, compensate bone defects and promote the bone union through progressive bone histogenesis. The objective of this systematic review was to review current available studies reporting on Ilizarov methods in the treatment of infected nonunion of tibia and femur, and to perform meta-analysis of bone and functional results and complications to evaluate the efficacy of Ilizarov methods.

Methods
A comprehensive literature search was performed from the SCI, PubMed, Cochrane Library; and Embase between January 1995 and August 2015. Some major data were statistically analyzed using weighted means based on the sample size in each study by SPSS 13.0, including number of patients, mean age, mean previous surgical procedures, mean bone defects, mean length of follow-up, bone union, complications per patient, external fixation time, and external fixation index (EFI). Bone results (excellent, good, fair and poor rate), functional results (excellent, good, fair and poor rate) and complications were analyzed by Stata 9.0.

Findings
A total of 590 patients from 24 studies were included in this systematic review. The average of bone union rate was 97.26% in all included studies. The poor rate in bone results and functional results was 8% (95%CI, 0.04–0.12; I² = 44.1%, P = 0.065) and 10% (95%CI, 0.05–0.14; I² = 34.7%, P = 0.121) in patients with infected nonunion of tibia and femur treated by Ilizarov methods. The rate of refracture, malunion, infectious recurrence, knee
stiffness, amputation, limb edema and peroneal nerve palsy was respectively 4%, 7%, 5%, 12%, 4%, 13% and 13%.

Conclusions
Our systematic review showed that the patients with infected nonunion of tibia and femur treated by Ilizarov methods had a low rate of poor bone and functional results. Therefore, Ilizarov methods may be a good choice for the treatment of infected nonunion of tibia and femur.

Introduction
Infected nonunion of tibia and femur are common in clinical practice [1], however, the treatment of these diseases has still been a challenge for orthopaedic surgeons [2–5]. Some associated factors usually complicate the infected nonunion including bone and soft tissue loss, several sinuses, deformities, limb-length inequalities and polybacterial infection [6]. Several methods have been applied successfully in the treatment of infected nonunion of tibia and femur, including bone grafting, free tissue transfer and antibiotic cement, but these treatments have obvious limitations, such as donor site morbidity, stress fracture, and restriction of the size of bone defects[1]. Moreover, none of these treatments can afford surgeon the ability to treat infected nonunion associated with the mentioned factors simultaneously. The ability is possible with the application of Ilizarov methods. Ilizarov methods can eradicate infection, compensate bone defects and promote the bone union through progressive bone histogenesis [7], at the same time, it can correct the deformities and limb-length discrepancy during the course of bone transport[8].

Ilizarov methods base on the principles of distraction osteogenesis. It entails a segmental bone transport in which corticotomy is performed in the metaphysis and the bone is gradually distracted. Application of Ilizarov methods in the treatment of an infected nonunion depends on the extent of infection, the type of infected nonunion and the condition of the soft tissues [9]. In order to eliminate infection, it is critical to perform radical resection of the necrotic bone and infected segments [1]. Then internal bone transport is used to reconstruct the residual segmental defect [10,11].

Up to now, there are numerous reports on the treatment of infected nonunion of tibia and femur by Ilizarov methods, and it has gradually been a main treatment for infected nonunion. Although infected nonunion treated by Ilizarov methods acquired a satisfactory outcome in most studies, there were still some relative dissatisfactory results in several studies [7,12]. In addition, a relative high rate of complication by Ilizarov methods has been reported in some clinical researches [13–15]. However, no systematic review has been done to evaluate the effect of the treatment of infected nonunion of tibia and femur by Ilizarov methods. Therefore, we did a systematic review and meta-analysis of the scientific literature to evaluate and quantitate this effect, and try our best to give a valuable conclusion

Materials and Methods
Search Strategy
We did serial literature searches for relevant studies according to the guidelines from the Cochrane Collaboration. The following databases were searched: SCI (January 1995 to August
Keywords used to identify relevant articles were ‘infected’ or ‘infection’, ‘nonunion’, ‘non-union’, ‘tibia’, ‘femur’, ‘Ilizarov method’ or ‘Ilizarov methods’, and ‘Ilizarov technique’ or ‘Ilizarov techniques’. We used MeSH terms including ‘infection’, ‘tibia’, ‘femur’, and ‘Ilizarov technique’.

Eligibility Criteria
The following eligibility criteria were performed in articles selection: (1) target population: patients with infected nonunion of tibia and femur; (2) intervention: Ilizarov methods, including bone transport, acute compression and lengthening, and compression osteosynthesis; (3) outcomes: bone union, bone results evaluated by ASAMI (rated as excellent, good, fair and poor), functional results evaluated by ASAMI (rated as excellent, good, fair and poor), complications, external fixation time and external fixation index. The eligible study included two above-mentioned outcomes at least; (4) article types: any type of the articles, excluding case report and review; (5) language restriction: articles written in the English language. We did the language restriction in order to avoid translation costs. Duplicate or multiple publications of the same study were excluded. We also excluded studies involving animal models, children, basic research, and when it was impossible to extract or calculate the data of infected nonunion from the studies.

Data Extraction
All relevant data that met the eligibility criteria were independently and separately extracted by two authors. Discrepancies were resolved by discussion with each other. The following data were extracted from each included study: first author, publication year, study design, technique, site of infected nonunion, number of patients, mean age, mean previous surgical procedures, mean bone defects, mean length of follow-up, bone union, bone results evaluated by ASAMI, functional results evaluated by ASAMI, complications per patient, external fixation time, and external fixation index (EFI), complications (pin-track infection, axial deviation, bone grafting, loosening of wires, breakage of wires, malunion, refracture, knee stiffness, ankle stiffness, amputation, limb edema and peroneal nerve palsy).

Data Analysis
Bone results (excellent, good, fair and poor rate), functional results (excellent, good, fair and poor rate) and complications were analyzed by using STATA 9.0. Differences were expressed as effect size (ES) with 95% CIs for the rate meta-analysis. Heterogeneity among studies was tested by using the standard chi-square test (with significance defined as P < 0.1), and the I-squared test (with a value greater than 50% representing substantial heterogeneity) [16]. A random effect model was chosen regardless of heterogeneity. Because the sites of infected nonunion were inconsistent among studies, we further conducted subgroup analyses to explore possible explanations for heterogeneity and examine the influence of various overall pooled estimate. We also tested the influence of a single study on the overall pooled estimate by omitting one study in each turn, if the study reported bone results and/or functional results. Other major data extracted in this study were recorded and statistically analyzed using weighted means based on the sample size in each study by SPSS 13.0, including number of patients, mean age, mean previous surgical procedures, mean bone defects, mean length of follow-up, bone union, complications per patient, external fixation time, and external fixation index (EFI). The remaining data was analyzed by description from original studies.


Results

Literature Search

The initial literature search identified 243 relevant records published from January 1995 to August 2015. 30 studies remained after screening by reading titles and abstracts. Ultimately, 24 studies met the inclusion and exclusion criteria in the systematic review by reviewing the full-text articles (Fig 1) [1,7,8,10–15,17–31]. Of the included studies, 22 were retrospective case series [1,8,10–15,17–21,23–31], 1 was retrospective comparative study [22], and 1 was prospective comparative study [7].

Patient Information

The systematic review included a total of 590 patients with infected nonunion of tibia and femur treated by Ilizarov methods. The mean age of all patients was 33.79 years; the mean age was 34.11 years in patients with infected tibia nonunion and 32.68 years in patients with infected femur nonunion. The patients had an average of 3.64 previous surgical procedures before receiving the treatment of Ilizarov method [1,7,8,10–15,17–21,23,24,27,29–31]; the mean previous surgical procedures was 3.84 in patients with infected tibia nonunion and 3.81 in patients with infected femur nonunion. The mean bone defects was 6.70 cm in the patients [1,7,8,10–15,17–25,27–31], and 6.54 cm in patients with infected tibia nonunion and 8.05 cm in patients with infected femur nonunion. The mean length of follow-up was 39.79 months in the patients [1,7,8,10–14,17–24,26–31], and 32.49 months in patients with infected tibia nonunion and 64.47 months in patients with infected femur nonunion. Further details were listed in Table 1.

Interventions and Outcomes

The interventions mainly included three parts: radical debridement, antibiotic treatment, and Ilizarov methods. Ilizarov methods included three techniques: bone transport, acute compression and lengthening, and compression osteosynthesis. Flap transfer was reported in 2 included studies [11,28]. Bone grafting as a routine treatment was recommended in 1 included study [22].

The average of bone union rate was 97.26% in all included studies, and 97.50% in the studies of infected tibia nonunion and 97.59% in the studies of infected femur nonunion. The mean complications of every patient were 1.36 in all patients, and 1.23 in patients with infected tibia nonunion and 2.24 in patients with infected femur nonunion. The mean external fixation time was 10.69 months in the patients [1,7,8,10–14,17–28,30,31], and 9.41 months in patients with infected tibia nonunion and 18.26 months in patients with infected femur nonunion. The mean external fixation index was 1.70 months/cm in the patients [1,7,8,10,13,14,17–24,26–28,31], and 1.64 months/cm in patients with infected tibia nonunion and 2.19 months/cm in patients with infected femur nonunion. Further details were listed in Table 2.

Bone Results and Functional Results

The criteria recommended by ASAMI were adopted to evaluate bone results and functional results in the studies [1,7,8,10,12,14,15,17–24,27,29,31]. Bone results were evaluated by 4 criteria: union, infection, deformity and limb-length discrepancy. Functional results were evaluated by 5 criteria: active, limp, minimum stiffness (knee or ankle joint), reflex sympathetic dystrophy and pain.
Bone results were evaluated in 16 studies by ASAMI [1,7,10,12,14,15,17–24,29,31]. Random effects meta-analysis showed that the weighted frequency of excellent rate, good rate, fair rate and poor rate in bone results were listed in Table 3.

Functional results were reported in 16 studies [1,7,8,10,12,14,15,17,20–24,27,29,31]. Random effects meta-analysis showed that the weighted frequency of excellent rate, good rate, fair rate and poor rate in functional results were listed in Table 3.

Table 4 showed subgroup analysis of bone results and functional results evaluated by ASAMI based on the sites of infected nonunion.

Complications

Complications were summarized in Table 5. Subgroup analysis of complications based on the sites of infected nonunion was performed and the outcomes were listed in Table 6.

Discussion

This is the first systematic review of infected nonunion of tibia and femur treated by Ilizarov methods. The systematic review included 24 studies, and we conducted a meta-analysis of 16 studies to evaluate the efficacy of Ilizarov methods in the treatment of infected nonunion of tibia and femur. The poor rate in bone results and functional results was 8% (95%CI, 0.04–0.12; I² = 44.1%, P = 0.065) and 10% (95%CI, 0.05–0.14; I² = 34.7%, P = 0.121). The data were not statistically heterogeneous. Therefore, our results showed that the patients with infected nonunion...
nonunion of tibia and femur treated by Ilizarov methods had a low rate of poor bone and functional results.

We did a meta-analysis of complication in patients with infected nonunion of tibia and femur treated by Ilizarov method. Statistically homogeneity was found in most of the complications (Table 4). The rate of refracture and amputation was 4% and 4% in our study, which is similar with the 5% and 2.9% reported by Papakostidis et al[32]. The rate of peroneal nerve palsy was 13% in our study, which is higher than the 2.2% neurovascular complications reported by Papakostidis et al[32]. We considered that the reason was the different characteristics of included patients. The rate of malunion, infectious recurrence, limb edema, and knee stiffness was respectively 7%, 5%, 13% and 12%. The rate of infectious recurrence is lower than the rate in the study by Strujs using other treatments[33]. Pin-track infection is the most common complication by using Ilizarov methods, and significant statistically heterogeneity was found in the complication. The heterogeneity was still found after performing the subgroup analysis. The rate of pin-track infection was 10%-100% among included studies in our

Table 1. Characteristics of included studies.

| Author  | Study No. | Year | Study design | Number of patients | Mean age (years) | MPSP (per patient) | Mean bone defects(cm) | Follow-up (months) |
|---------|-----------|------|--------------|--------------------|------------------|---------------------|----------------------|-------------------|
| Yin     | 1         | 2015 | RS           | 72                 | 38.45            | 2.55                | 6.46                 | 24.13             |
| Khan    | 2         | 2015 | RS           | 24                 | 38               | 2                   | 3.3                  | 11                |
| Peng    | 3         | 2015 | RS           | 58                 | 29.4             | 6.3                 | 9.2                  | 31.6              |
| Xu      | 4         | 2014 | RS           | 30                 | 34.1             | 6                   | 6.43                 | 29                |
| Feng    | 5         | 2013 | RS           | 21                 | 34.6             | 6                   | 6.6                  | 31                |
| Blum    | 6         | 2010 | RS           | 50                 | 29.9             | 3.8                 | 8.8                  | 70.8              |
| Megas   | 7         | 2010 | RS           | 9                  | 39.7             | 4.8                 | 5                    | 26.6              |
| Bumbasirevic | 8     | 2010 | RS           | 30                 | 30.4             | 1.3                 | 6.9                  | 99                |
| Emara   | 9         | 2008 | RC           | 33                 | 29               | 9                   | 6                    | 36                |
| Madhusudhan | 10   | 2008 | PC           | 22                 | 37.2             | 3                   | 4/5.4*               | 13                |
| Rose    | 11        | 2007 | RS           | 6                  | 31.83            | 3.83                | 4.33                 | 7.6               |
| Magadum | 12        | 2006 | RS           | 27                 | 39               | 2                   | 10                   | 27                |
| Krishnan | 13      | 2006 | RS           | 20                 | 38.4             | 4.4                 | 6                    | 63                |
| Saridis | 14        | 2006 | RS           | 13                 | 34.6             | 3                   | 8.3                  | 42.4              |
| Abdel-Aal | 15     | 2006 | RS           | 9                  | 30.66            | 9                   | 10.7                 | 36                |
| McHale  | 16        | 2004 | RS           | 10                 | 31               | 9                   | ___                  | 36                |
| Arora   | 17        | 2003 | RS           | 46                 | 35               | 2.1                 | 6                    | 67                |
| Atesalp | 18        | 2002 | RS           | 14                 | 25               | ___                 | 4.4                  | 33.2              |
| Barbarossa | 19    | 2001 | RS           | 23                 | 40.7             | 4.2                 | 6.2                  | ___               |
| Maini   | 20        | 2000 | RS           | 15                 | 27.4             | 2.5                 | 7                    | 31.2              |
| Laursen | 21        | 2000 | RS           | 9                  | 25.78            | 6.9                 | 4.89                 | 39.4              |
| Ring    | 22        | 1999 | RS           | 10                 | 34               | ___                 | 4.3                  | 7.2               |
| Hosny   | 23        | 1998 | RS           | 11                 | 27               | 2                   | 3.7                  | 13                |
| Dendrinos | 24     | 1995 | RS           | 28                 | 37               | 9                   | 6                    | 39                |

Total number of patients: 590

MPSP mean previous surgical procedures
RS retrospective case series
RC retrospective comparative study
PC prospective comparative study

* The study included two groups, the mean bone defects is 4cm in one group, and 5.4cm in another group.

doi:10.1371/journal.pone.0141973.t001
Table 2. Interventions and Outcomes of included studies.

| Study No. | Technique | Site | Bone union No. (%) | Bone results (ASAMI) (excellent/good/fair/poor) | Functional results (ASAMI) (excellent/good/fair/poor) | Complications (per patient) | EFT (months) | EFI (Ms/cm) |
|-----------|-----------|------|-------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|--------------|--------------|
| 1         | RD,AT,BT (IEF) | 72T  | 72/72 (100%)      | 46/17/7/2                                    | 25/27/13/0*                                   | 1.10 (79/72)                                  | 9.56         | 1.48         |
| 2         | RD,AT,BT or CO (IEF) | 24T  | 22/23 (95.7%)##   | 6/14/1/2                                     | 8/12/2/0 (1 failure)                          | 0.5 (12/24)                                   | 8            | 4.2          |
| 3         | RD,AT,BT (IEF) | 58T  | 58/58 (100%)      | 30/23/5/0                                    | 28/18/12/0                                   | 0.67 (39/58)                                  | 10.6         | 1.2          |
| 4         | RD,AT,BT (IEF) | 30 T | 30/30 (100%)      | 28/2/0/0                                     | __                                          | 0.27 (8/30)                                   | 10           | 1.37         |
| 5         | RD,AT,BT (IEF) | 21 T | 21/21 (100%)      | 19/2/0/0                                     | __                                          | 0.4 (8/21)                                    | 9.8          | 1.48         |
| 6         | RD,AT,BT (IEF) | 50 F | 49/50 (98%)       | __                                          | __                                          | 2.1 (105/50)                                  | 24.5         | 2.8          |
| 7         | RD,AT,CO or ACL (IEF) | 9 T  | 9/9 (100%)       | 5/4/0/0                                     | 3/4/2/0                                     | 1.89 (17/9)                                   | 7.83         | 1.07         |
| 8         | RD,AT,BT (IEF) | 30 T | 29/30 (97%)       | 19/10/0/1                                    | 13/14/2/1                                   | 1.4 (42/30)                                   | 9.7          | 1.48         |
| 9         | RD,AT,BT (IEF), BG | 16 T | 16/16 (100%)     | 15/1/0/0                                     | 12/1/3/0                                    | 0.4 (6/16)                                    | 8.5          | 1.5          |
| 10        | RD,AT,ACL (IEF) | 17 T | 17/17 (100%)     | 17/0/0/1                                     | 13/2/2/0                                    | 0.12 (2/17)                                   | 3.1          | 0.55         |
| 11        | RD,AT,CO or BT (IEF) | 5 T/F | 5/6 (83.3%) | 1/3/1/1                                     | 1/3/0/2                                     | 1.33 (8/6)                                   | 10           | __           |
| 12        | RD,ACL (IEF) | 27 T | 24/25 (96%)      | 19/5/0/1                                     | 15/8/1/1                                    | 1.16 (29/25)                                  | 10.2         | 1.02         |
| 13        | RD,AT,BT or ACL (IEF) | 20 F | 19/20 (95%)      | 13/4/1/1 (1AMP)                              | 3/9/3/4 (1AMP)                              | 3.55 (71/20)                                  | 7.8          | 1.28         |
| 14        | RD,AT,ACL or BT (IEF) | 13 F | 13/13 (100%)     | 8/4/1/0                                     | 3/4/4/2                                     | 0.76 (10/13)                                  | 10.33        | 1.24         |
| 15        | RD,BT (IEF) | 9 T  | 9/9 (100%)       | __                                          | __                                          | 1.11 (10/9)                                   | 12.78        | 1.22         |
| 16        | RD,AT,BT or ACL or CO (IEF) | 10 T | 10/10 (100%)    | __                                          | __                                          | 0.4 (4/10)                                    | 9.0          | __           |
| 17        | RD,BT or CO (IEF) | 38 T/8 F | 44/46 (95.4%)  | __                                          | 15/16/13/2                                  | 0.74 (34/46)                                  | 8.7          | 1.33         |
| 18        | RD,AT,3 flaps, BT (IEF) | 14 T | 13/14 (92.9%) | __                                          | __                                          | 1.21 (17/14)                                  | 6.8          | 1.55         |
| 19        | RD,AT,BT (IEF) | 23 T | 20/23 (87%)      | 8/8/2/4 (1AMP)                               | 2/10/6/4 (1AMP)                             | 3.39 (78/23)                                  | __           | __           |
| 20        | RD,AT,BT (IEF) | 3 F/12 T | 15/15 (100%) | 7/3/0/5                                     | 4/7/1/3                                    | 2.27 (34/15)                                  | __           | __           |
| 21        | RD,AT,CO or BT (IEF) | 9 T  | 9/9 (100%)       | __                                          | __                                          | 1.56 (14/9)                                   | 6.7          | __           |
| 22        | RD,3flaps, BT or ACL or CO (IEF) | 10 T | 9/10 (90%)      | __                                          | __                                          | 2.5 (25/10)                                   | 6.9          | __           |
| 23        | RD,3AT, BT or CO (IEF) | 11 T | 11/11 (100%)    | 5/3/2/1                                     | __                                          | 1.27 (14/11)                                  | 8.5          | 2.3          |

(Continued)
systematic review. Hence, we considered that meticulous pin care was the key to decreasing the complication.

In our systematic review, most studies involved infected tibia nonunion, and we performed subgroup analysis based on the sites of infected nonunion. The data of infected tibia nonunion could be found in Tables 4 and 6. The poor rate in bone results and functional results was 7% (95%CI, 0.02 – 0.11; I² = 40.8%, P = 0.119) and 9% (95%CI, 0.03 – 0.15; I² = 40.0%, P = 0.139). The rate of bone grafting, knee stiffness, malunion, refracture, infectious recurrence, limb edema, amputation and Peroneal nerve palsy was respectively 14%, 13%, 7%, 4%, 6%, 13%, 4% and 13%. These data were not statistically heterogeneous.

To our best knowledge, this is the first systematic review of infected nonunion of tibia and femur treated by Ilizarov methods. We were able to provide a large number of data on characteristics of patients and treatment results through 24 included studies. We also conducted meta-analyses of bone and functional results in our systematic review. High heterogeneity existed in several pooling data in our study, and we thought the heterogeneity was probably resulted from different research quality, various surgeons’ experience and diversity of rehabilitation nursing. Failure to include the non-English language studies in our article could have resulted in missing data and our estimates of effect size might have been biased, nevertheless, 24 studies were included in our article and they were not unduly affected by significant heterogeneity.

| Study No. | Technique | Site | Bone union No. (%) | Bone results (ASAMI) (excellent/good/fair/poor) | Functional results (ASAMI) (excellent/good/fair/poor) | Complications (per patient) | EFT (months) | EFI (Ms/cm) |
|-----------|-----------|------|-------------------|-----------------------------------------------|-------------------------------------------------|----------------------------|-------------|-------------|
| 24        | RD,BT(IEF)| 28 T | 25/28(89%)        | 14/8/1/5                                      | 7/11/4/5(1AMP)                                 | 2.5(71/28)                 | 10          | 1.67        |

* 1 patient die for advanced liver disease  
* 7 patient lost for follow up  
**3 patients were unable to evaluate  
***Complications did not be recorded separately by groups  
****2 patients lost for follow up  
_The data did not be reported in studies.

ACL acute compression and lengthening AMP amputation ASAMI Association for the Study of the Method of Ilizarov AT antibiotics treatment BG bone graft BT bone transport CO compression osteosynthesis EFI external fixation index EFT external fixation time F femur IEF Ilizarov external fixator IMN intramedullary nailing Ms/cm months/cm RD radical debridement T tibia

doi:10.1371/journal.pone.0141973.t002

Table 3. Meta-analysis of bone results and functional results evaluated by ASAMI.

| Results                  | Relevant studies (n) | Heterogeneity(I²,%; P) | ES(95% CI) | Range of incidence (%) |
|--------------------------|----------------------|------------------------|------------|------------------------|
| Bone results             |                      |                        |            |                        |
| Rate of excellent results| 16 [1,7,10,12,14,15,17–24,29,31] | I² = 93.1; P = 0.000 | 0.58 (0.44,0.72) | 17–97                  |
| Rate of good results     | 16 [1,7,10,12,14,15,17–24,29,31] | I² = 80.8; P = 0.000 | 0.26 (0.18,0.34) | 3–61                   |
| Rate of fair results     | 9 [1,7,10,12,14,15,17,23,31] | I² = 26.9; P = 0.205 | 0.08 (0.04,0.12) | 4–36                   |
| Rate of poor results     | 10 [1,7,10,12,14,15,21,24,29,31] | I² = 44.1; P = 0.065 | 0.08 (0.04,0.12) | 3–33                   |
| Functional results       |                      |                        |            |                        |
| Rate of excellent results| 16 [1,7,8,10,12,14,15,17–20–24,27,29,31] | I² = 84.8; P = 0.000 | 0.33 (0.23,0.44) | 6–76                   |
| Rate of good results     | 16 [1,7,8,10,12,14,15,17–20–24,27,29,31] | I² = 59.3; P = 0.001 | 0.36 (0.28,0.43) | 9–52                   |
| Rate of fair results     | 15 [1,7,8,10,14,15,17–20–24,27,29,31] | I² = 56.4; P = 0.004 | 0.17 (0.11,0.22) | 4–50                   |
| Rate of poor results     | 11 [1,7,8,10,14,15,21,23,24,27,29,31] | I² = 34.7; P = 0.121 | 0.10 (0.05,0.14) | 3–33                   |

doi:10.1371/journal.pone.0141973.t003
statistical heterogeneity. The data of the present review were extracted from observational studies, which are prone to cause both systematic and random error [34–37]. Therefore, more prospective randomized controlled trials are needed to overcome the limitation of our study.

In conclusion, our systematic review showed that the patients with infected nonunion of tibia and femur treated by Ilizarov methods had a low rate of poor bone and functional results.

### Table 4. Subgroup analysis of bone results and functional results evaluated by ASAMI based on the sites of infected nonunion.

| Results | Relevant studies (n) | Heterogeneity(I²,%; P) | ES(95% CI) | Range of incidence (%) |
|---------|---------------------|------------------------|------------|------------------------|
| **Tibia** | | | | |
| **Bone results** | | | | |
| Rate of excellent results | 12 | I² = 94.4; P = 0.000 | 0.61 (0.45,0.77) | 18–97 |
| Rate of good results | 12 | I² = 85.2; P = 0.000 | 0.26 (0.16,0.36) | 3–61 |
| Rate of fair results | 6 | I² = 51.5; P = 0.067 | 0.09 (0.03,0.14) | 4–36 |
| Rate of poor results | 7 | I² = 40.8; P = 0.119 | 0.07 (0.02,0.11) | 3–18 |
| **Functional results** | | | | |
| Rate of excellent results | 11 | I² = 89.2; P = 0.000 | 0.38 (0.23,0.52) | 6–76 |
| Rate of good results | 11 | I² = 69.7; P = 0.000 | 0.34 (0.25, 0.44) | 9–52 |
| Rate of fair results | 6 | I² = 59.1; P = 0.007 | 0.16 (0.10,0.22) | 4–50 |
| Rate of poor results | 7 | I² = 40.0; P = 0.139 | 0.09 (0.03,0.15) | 3–22 |
| **Femur** | | | | |
| **Bone results** | | | | |
| Rate of excellent results | 2 | I² = 0; P = 0.839 | 0.64 (0.47,0.80) | 61–65 |
| Rate of good results | 2 | I² = 0; P = 0.489 | 0.24 (0.09,0.38) | 20–31 |
| Rate of fair results | 2 | I² = 0; P = 0.760 | 0.06 (-0.02,0.14) | 5–8 |
| Rate of poor results | 1 | _ | 0.05 (-0.05,0.15) | 5 |
| **Functional results** | | | | |
| Rate of excellent results | 2 | I² = 0; P = 0.567 | 0.18 (0.05,0.30) | 15–23 |
| Rate of good results | 2 | I² = 0; P = 0.402 | 0.39 (0.22,0.55) | 31–45 |
| Rate of fair results | 2 | I² = 0; P = 0.295 | 0.20 (0.06,0.34) | 15–31 |
| Rate of poor results | 2 | I² = 0; P = 0.732 | 0.18 (0.05,0.31) | 15–20 |

doi:10.1371/journal.pone.0141973.t004

### Table 5. Meta-analysis of complications of infected nonunion of tibia and femur treated by Ilizarov methods.

| Complications | Relevant studies (n) | Heterogeneity(I²,%; P) | ES(95% CI) | Range of incidence (%) |
|---------------|---------------------|------------------------|------------|------------------------|
| Pin-track infection | 23 | I² = 97.6; P = 0.000 | 0.56 (0.43,0.69) | 10–100 |
| Axial deviation | 6 | I² = 76.5; P = 0.001 | 0.40 (0.25,0.56) | 22–70 |
| Bone grafting | 5 | I² = 56.4; P = 0.057 | 0.20 (0.09,0.31) | 10–30 |
| Loosening of wires | 9 | I² = 64.7; P = 0.004 | 0.15 (0.08,0.22) | 6–48 |
| Breakage of wires | 5 | I² = 57.1; P = 0.054 | 0.05 (0.00,0.09) | 2–32 |
| Knee stiffness | 4 | I² = 1.6; P = 0.384 | 0.12 (0.05,0.19) | 9–30 |
| Ankle stiffness | 4 | I² = 64.9; P = 0.036 | 0.31 (0.11,0.52) | 13–56 |
| Malunion | 8 | I² = 0; P = 0.570 | 0.07 (0.03,0.11) | 4–22 |
| Refracture | 9 | I² = 0; P = 0.931 | 0.04 (0.02,0.07) | 3–13 |
| Infectious recurrence | 7 | I² = 24.2; P = 0.245 | 0.05 (0.01,0.10) | 2–30 |
| Limb edema | 3 | I² = 0; P = 0.890 | 0.13 (0.04,0.21) | 9–14 |
| Amputation | 4 | I² = 0; P = 0.936 | 0.04 (0.00,0.09) | 4–10 |
| Peroneal nerve palsy | 2 | I² = 0; P = 0.585 | 0.13 (-0.01,0.28) | 10–18 |

doi:10.1371/journal.pone.0141973.t005
Therefore, Ilizarov methods may be a good choice for the treatment of infected nonunion of tibia and femur.

Author Contributions
Conceived and designed the experiments: PY QNJ ZM PFT. Performed the experiments: PY QNJ ZM PFT TTL LHZ. Analyzed the data: PY QNJ ZM PFT TTL LHZ JTL ZRL. Contributed reagents/materials/analysis tools: PY QNJ ZM TTL LHZ JTL JHL GQW SW. Wrote the paper: PY QNJ ZM PFT. Revised the manuscript: PY QNJ TTL PFT LHZ JTL ZRL JHL SW.

References
1. Yin P, Zhang L, Li T, Zhang L, Wang G, Li J, et al. Infected nonunion of tibia and femur treated by bone transport. J Orthop Surg Res. 2015; 10:49. Epub 2015/04/19. doi:10.1186/s13018-015-0189-5 PMID: 25889513; PubMed Central PMCID: PMCPmc4415215.
2. Wu CC. Single-stage surgical treatment of infected nonunion of the distal tibia. Journal of Orthopaedic Trauma. 2011; 25(3):156–61. doi: 10.1097/BOT.0b013e3181eaaa35 PMID: 21278604
3. Selhi HS, Mahindra P, Yamin M, Jain D, De Long WG, Singh J. Outcome in Patients With an Infected Nonunion of the Long Bones Treated With a Reinforced Antibiotic Bone Cement Rod. Journal of orthopaedic trauma. 2012; 26(3):184–8. doi: 10.1097/BOT.0b013e318225f77c IS1:000300605400012. PMID: 22089916
4. Bumbasirevic M, Tomic S, Lesic A, Milosevic I, Atkinson HDE. War-related infected tibial nonunion with bone and soft-tissue loss treated with bone transport using the Ilizarov method. Archives of Orthopaedic and Trauma Surgery. 2010; 130(6):739–49. doi: 10.1007/s00402-009-1014-6 WOS:000277626500005. PMID: 19946693
5. Dhar SA, Mir MR, Ahmed MS, Afzal S, Butt MF, Badoo AR, et al. Acute peg in hole docking in the management of infected non-union of long bones. International Orthopaedics. 2008; 32(4):559–66. PMID: 17387474
6. Jain AK, Sinha S. Infected Nonunion of the Long Bones. Clinical Orthopaedics and Related Research. 2005; &NA;(431):57–65. PMID: 15685056

7. Madhusudhan TR, Ramesh B, Manjunath K, Shah HM, Sundaresh DC, Krishnappa N. Outcomes of Ilizarov ring fixation in recalcitrant infected tibial non-unions—a prospective study. Journal of trauma management & outcomes. 2008; 2(1):6. Epub 2008/07/25. doi: 10.1186/1752-2897-2-6 PMID: 18651977; PubMed Central PMCID: PMCPMC2515289.

8. Hosny G, Shawky MS. The treatment of infected non-union of the tibia by compression-distraction techniques using the Ilizarov external fixator. International Orthopaedics. 1998; 22(6):298–302. PMID: 9914932

9. Cattanoo R, Catagni M, Johnson EE. The treatment of infected nonunions and segmental defects of the tibia by the methods of Ilizarov. Clinical Orthopaedics and Related Research. 1992; (280):143–52. PMID: 1611734

10. Khan MS, Rashid H, Umer M, Qadir I, Hafeez K, Iqbal A. Salvage of infected non-union of the tibia with an Ilizarov ring fixator. J Orthop Surg (Hong Kong). 2015; 23(1):52–5. Epub 2015/04/30. PMID: 25920644.

11. Ring D, Jupiter JB, Gan BS, Israel I, Yaremchuk MJ. Infected nonunion of the tibia. Clinical Orthopaedics and Related Research. 1999; (369):302–11. PMID: 10611886

12. Rose RE, Palmer WS. The Ilizarov method in infected non-union of long bones. The West Indian medical journal. 2007; 56(3):246–51. Epub 2007/12/13. PMID: 18072406.

13. Blum AL, Bongiovanni JC, Morgan SJ, Flierl MA, dos Reis FB. Complications associated with distraction osteogenesis for infected nonunion of the femoral shaft in the presence of a bone defect: a retrospective series. The Journal of bone and joint surgery British volume. 2010; 92(4):565–70. Epub 2010/04/02. doi: 10.1302/0301-620x.92b4.23475 PMID: 20357336.

14. Krishnan A, Pamecha C, Patwa JJ. Modified Ilizarov technique for infected nonunion of the femur: the principle of distraction-compression osteogenesis. Journal of orthopaedic surgery (Hong Kong). 2006; 14(3):265–72.

15. Barbarossa V, Matkovic BR, Vucic N, Bielen M, Gluhinic M. Treatment of osteomyelitis and infected non-union of the femur by a modified Ilizarov technique: Follow-up study. Croatian Medical Journal. 2001; 42(6):634–41. PMID: 11740846

16. Wei DH, Poolman RW, Bhandari M, Wolfe VM, Rosenwasser MP. External fixation versus internal fixation for unstable distal radius fractures: a systematic review and meta-analysis of comparative clinical trials. J Orthop Trauma. 2012; 26(7):386–94. Epub 2011/11/24. doi: 10.1097/BOT.0b013e318225963c PMID: 22108259.

17. Peng J, Min L, Xiang Z, Huang F, Tu C, Zhang H. Ilizarov bone transport combined with antibiotic cement spacer for infected tibial nonunion. International journal of clinical and experimental medicine. 2015; 8(6):10058–65. Epub 2015/08/27. PMID: 26309700; PubMed Central PMCID: PMC4537994.

18. Xu K, Fu X, Li YM, Wang CG, Li ZJ. A treatment for large defects of the tibia caused by infected nonunion: Ilizarov method with bone segment extension. Irish journal of medical science. 2014; 183 (3):423–8. Epub 2013/10/30. doi: 10.1007/s11845-013-1032-9 PMID: 24166049.

19. Feng ZH, Yuan Z, Jun LZ, Tao Z, Fa ZY, Long MX. Ilizarov method with bone segment extension for treating large defects of the tibia caused by infected nonunion. Saudi medical journal. 2013; 34(3):316–8. Epub 2013/03/12. PMID: 23475099.

20. Megas P, Saridis A, Kouzelis A, Kallivokas A, Mylonas S, Tyllianakis M. The treatment of infected nonunion of the tibia following intramedullary nailing by the Ilizarov method. Injury. 2010; 41(3):298–302. Epub 2013/10/30. doi: 10.1016/j.injury.2009.09.013 PMID: 20176169

21. Bumbasirevic M, Tomic S, Lesic A, Milosevic I, Atkinson HD. War-related infected tibial nonunion with bone and soft-tissue loss treated with bone transport using the Ilizarov method. Arch Orthop Trauma Surg. 2010; 130(6):739–49. Epub 2009/12/01. doi: 10.1007/s00402-009-1014-6 PMID: 19946693.

22. Emara KM, Allam MF. Ilizarov external fixation and then nailing in management of infected nonunions of the tibial shaft. Journal of Trauma—Injury, Infection and Critical Care. 2008; 65(3):685–91.

23. Saridis A, Panagiotopoulos E, Tyllianakis M, Matzaroglou C, Vandoros N, Lambris I. The use of the Ilizarov method as a salvage procedure in infected nonunion of the distal femur with bone loss. Journal of Bone and Joint Surgery—Series B. 2006; 88(2):232–7.

24. Magadum MP, Basavaraj Yadav CM, Phaneesha MS, Ramesh LJ. Acute compression and lengthening by the Ilizarov technique for infected nonunion of the tibia with large bone defects. Journal of orthopaedic surgery (Hong Kong). 2006; 14(3):273–9.

25. Abdel-Aal A. Ilizarov bone transport for massive tibial bone defects. Orthopedics. 2006; 29(1):70–4. PMID: 16429937
26. McHale KA, Ross AE. Treatment of infected tibial nonunions with debridement, antibiotic beads, and the Ilizarov method. Military Medicine. 2004; 169(9):728–34. PMID: 15495730

27. Arora RK. Usefulness of Ilizarov's procedure in infected non-union of tibia and femur. JK Science. 2003; 5(1):22–5.

28. Atesalp AS, Komurcu M, Basbozkurt M, Kurktlu M. The treatment of infected tibial nonunion with aggressive debridement and internal bone transport. Mil Med. 2002; 167(12):978–81. Epub 2002/12/28. PMID: 12502170.

29. Maini L, Chadha M, Vishwanath J, Kapoor S, Mehtani A, Dhaon BK. The Ilizarov method in infected nonunion of fractures. Injury. 2000; 31(7):509–17. PMID: 10908744

30. Laursen MB, Lass P, Christensen KS. Ilizarov treatment of tibial nonunions results in 16 cases. Acta Orthopaedica Belgica. 2000; 66(3):279–85. PMID: 11033919

31. Dendrinos GK, Kontos S, Lyritis E. Use of the Ilizarov technique for treatment of non-union of the tibia associated with infection. J Bone Joint Surg Am. 1995; 77(6):835–46. Epub 1995/06/01. PMID: 7782356.

32. Papakostidis C, Bhandari M, Giannoudis PV. Distraction osteogenesis in the treatment of long bone defects of the lower limbs: effectiveness, complications and clinical results; a systematic review and meta-analysis. The bone & joint journal. 2013; 95-b(12):1673–80. Epub 2013/12/03. doi: 10.1302/0301-620x.95b12.32385 PMID: 24293599.

33. Struijs PA, Poolman RW, Bhandari M. Infected nonunion of the long bones. Journal of orthopaedic trauma. 2007; 21(7):507–11. Epub 2007/09/01. doi: 10.1097/BOT.0b013e31812e5578 PMID: 17762489.

34. Bhandari M, Morrow F, Kulkarni AV, Tornetta P, 3rd. Meta-analyses in orthopaedic surgery. A systematic review of their methodologies. J Bone Joint Surg Am. 2001; 83-a(1):15–24. Epub 2001/02/24. PMID: 11205853.

35. Egger M, Schneider M, Davey Smith G. Spurious precision? Meta-analysis of observational studies. BMJ (Clinical research ed). 1998; 316(7125):140–4. Epub 1998/02/14. PMID: 9462324; PubMed Central PMCID: PMCPmc2665367.

36. Montori VM, Swiontkowski MF, Cook DJ. Methodologic issues in systematic reviews and meta-analyses. Clin Orthop Relat Res. 2003;(413):43–54. Epub 2003/08/05. doi: 10.1097/01.blo.0000079322.41006.5b PMID: 12897595.

37. Mulrow CD. Rationale for systematic reviews. BMJ (Clinical research ed). 1994; 309(6954):597–9. Epub 1994/09/03. PMID: 8086953; PubMed Central PMCID: PMCPmc2541393.