Prevalence and influencing factors of nonunion in patients with tibial fracture: systematic review and meta-analysis

Ruifeng Tian¹, Fang Zheng¹,², Wei Zhao¹,³, Yuhui Zhang⁴, Jinping Yuan⁴, Bowen Zhang¹ and Liangman Li¹*

Abstract

Objective: The aim of this study is to assess the prevalence of nonunion in patients with tibia fracture and the association between influencing factors and tibia fracture nonunion.

Method: A database searches of PubMed, the Cochrane Library, EMBASE, China National Knowledge Infrastructure (CNKI), Weipu database, and Wanfang database from inception until June 2019 was conducted. The pooled prevalence, odds ratio (OR), and 95% confidence intervals (CI) were calculated with Stata software.

Results: In this study, 111 studies involving 41,429 subjects were included. In the study of the relationship between influencing factors and tibia fracture nonunion, 15 factors significantly influenced the fracture union, including > 60 years old, male, tobacco smoker, body mass index > 40, diabetes, nonsteroidal anti-inflammatory drugs (NSAIDs) user, opioids user, fracture of middle and distal tibia, high-energy fracture, open fracture, Gustilo-Anderson grade IIIB or IIIC, Müller AO Classification of Fractures C, open reduction, fixation model, and infection.

Conclusion: The prevalence of nonunion in patients with tibia fracture was 0.068 and 15 potential factors were associated with the prevalence. Closed reduction and minimally invasive percutaneous plate osteosynthesis (MIPPO) have the low risks of nonunion for the treatment of tibial fractures.

Keywords: Tibia fracture, Nonunion, Prevalence, Influencing factors, Systematic review

Introduction

Fracture is a common disease that has a great impact on patients’ lives. Take Canada as an example, fractures and dislocations of the lower limb make up 38% of all injury admissions [1]. It is estimated that the disability from traffic accidents (the major cause of fractures) will rank the top three of all causes of disability by 2020 [2].

Fracture nonunion is one of the most common complications of fracture. The rate of fracture nonunion varies greatly in different anatomical locations of the fracture [3], with an average incidence rate of 4.93% [4]. Fracture nonunion is a chronic condition in terms of pain, and functional and psychosocial disability [5]. Nonunion of some fractures can reduce the quality of life and even increase the risk of death [3]. The cost of treatment for fracture nonunion was much more than that of fracture union [6, 7]. Other economic burdens caused by prolonged disability and downtime of job are more difficult to quantify but must be considered [8].

Good blood supply is an important condition for fracture union [1, 9]. Compared to other long bones with abundant blood vessels and soft tissue, the tibia with a longer subcutaneous boundary normally has a poorer blood supply [10]. Therefore, tibial fracture has a higher risk of nonunion due to its special...
structure and blood supply. The definition of tibia fracture nonunion was no sign of union 9 months after surgical operation or no possibility of union if no further intervention was given assessed by surgeon [11].

Doctors need to know how to predict the risk of fracture nonunion and set up a plan to reduce the rate of fracture nonunion [8, 12]. In 2007, the “diamond concept” was introduced by Giannoudis et al., aiming to define what is required to achieve adequate fracture healing. This concept highlights the importance of three biological factors (osteogenic cells, osteoconductive scaffolds, growth factors) and a fourth factor known as mechanical stabilization. If one or more of these factors are altered, adequate fracture healing will be threatened [9, 13, 14].

Clinical and experimental studies have identified a number of potential factors that may help to predict fracture nonunion [15–18]. These factors include uncontrollable factors (for example, gender, age, underlying diseases, the way of injury) and controllable factors (for example, treatment method) [19, 20]. The uncontrollable factors of tibial nonunion may be similar to those of other anatomic sites. But there are too many influencing factors and even the same influencing factor may lead to different consequences in different anatomical positions [21]. For controllable influencing factors, the treatment of tibial fracture is also controversial [22]. Some doctors believe that intramedullary nailing (IMN) is the gold standard for the treatment of tibial fractures [23, 24]; however, most doctors consider that different treatment options have different advantages [25–28]. The use of non-steroidal anti-inflammatory drugs (NSAIDs) and the fixation of fibular fractures have also been considered as controversial factors for many years [29, 30].

Herein, we conducted a systematic review to explore the prevalence of nonunion in patients with tibia fracture and evaluate the association between influencing factors and tibia fracture nonunion. The study would provide valuable information for future prevention and treatment of tibia fracture nonunion.

**Methods**

**Search strategy**
The PubMed, Cochrane Library, EMBASE, CNKI (China National Knowledge Infrastructure), Wanfang database, and Weipu database were systematically searched, from inception to June 2019. The search keywords were “tibia” AND ”fracture” AND “union OR nonunion OR disunion.” The manual search was performed through checking the reference lists of key studies and review articles to identify additional studies.

**Study selection**
An overall literature search was performed and relevant studies were screened independently by two reviewers (Ruifeng Tian, Fang Zheng). Initially, all the titles and abstracts which were identified based on the keywords were screened. Secondly, full texts of articles which were selected from the first phase were reviewed. Finally, the articles which had contents suitable for data extraction were included in the systematic review. Disagreements between the two reviewers were resolved by a third reviewer (Wei Zhao) via discussion and consensus.

**Exclusion criteria**
Exclusion criteria were as follows: neither English nor Chinese; animal model experiment; patients at the age of <18; the cases of patients being lower than 10; insufficient information; duplicate publication; and obscure definition, such as delay union or mixed-descriptions of delay union and nonunion.

**Data extraction**
Relevant data were extracted independently by two reviewers (Ruifeng Tian and Yuhui Zhang). Each of the following information was entered into a pre-designed form: first author’s name, publication year, basic information of patients (including history of medication, unhealthy habits and basic diseases), fracture type, operative information, the number of all tibia fracture patients, and the number of tibia fracture nonunion patients. The information of 19 potentially influencing factors were also exacted for comparison analyses, including age, gender, tobacco smoke, drink, body mass index (BMI), diabetes, non-steroidal anti-inflammatory drugs (NSAIDs) user, opioids user, osteofascial compartment syndrome, fracture site, injury energy (low or high energy that causes tibia fracture), open fracture, Gustilo-Anderson grade, Müller AO Classification of Fractures (AO), debride time (the time from injury to debride), open reduction, fibula fixation, infection, and fixation models. Disagreements between the two reviewers were resolved by a third reviewer (Jinping Yuan) via discussion and consensus.

**Data analysis**
Stata software (v12.0, Stata Corp, College Station, TX, USA) was used to assess all statistical analyses and a $p < 0.05$ was considered statistically significant. First, for exploring the prevalence of nonunion in patients with tibia fracture, the pooled prevalence and its 95% confidence intervals (CI) were calculated by using a random-effect model ($p < 0.05, I^2 > 50$%), otherwise, or a fixed-effect model was selected ($p > 0.05, I^2 < 50$%). When the
prevalence rate in the included study was zero, double arcsine was used to deal with the data in case of data exclusion. Second, in the study of the association between potentially influencing factors and nonunion, the odds ratio (OR) and its 95% CI were calculated. To assess sources of heterogeneity, subgroup analyses were conducted, stratified by above 19 potentially influencing factors. Sensitivity analysis was performed by eliminating individual studies one by one. Publication biases were assessed by using the Begg’s test and Egger’s test.

Results
Characteristics of included studies
A total of 3846 studies (2195 English and 1651 Chinese) were searched. Following selection process (Fig. 1), 111 studies were included in this systematic review and meta-analysis [6, 15, 16, 19, 31–136].

These studies were published between 1997 and 2019 from USA, China, Australia, Belarus, Canada, Egypt, France, India, Iran, Italy, Japan, Malaysia, Singapore, Turkey, and UK. There were 46 studies written in

![Fig. 1 Flow diagram of the study selection process](image-url)
English and 65 studies in Chinese. The number of patients with tibia fracture ranged from 30 to 14638, and the prevalence of tibia fracture nonunion ranged from 0 to 42.7%. The basic information in all included studies were listed in Table 1.

Pooled results, sensitive analysis, publication bias of the prevalence of tibia fracture nonunion
Based on the results of random-effects method ($p < 0.05$, $I^2 > 50\%$), the prevalence of nonunion from tibia fracture patient was 0.068 (95% CI 0.060–0.077) (Fig. 2, Table 2). The sensitive analysis demonstrated that there was no individual studies significantly affected the pooled results. The publication bias were found in pooled results ($t = 3.19$, $p = 0.002$) (Fig. 3).

Subgroup analysis of prevalence of tibia fracture nonunion and comparison results
The prevalence of tibia fracture nonunion in different countries were of various (Tables 2, 3, and 4), for example, USA was 0.094 (95% CI 0.075–0.114), China was 0.047 (95% CI 0.039–0.057), etc.

In the following comparisons of influencing factors (Table 3), each of the former prevalence of tibia fracture nonunion was significantly higher than the latter one ($p < 0.05$), i.e., >60 years old (0.204) vs. <60 years old (0.125), male (0.131) vs. female (0.118), tobacco smoker (0.173) vs. non-smoking (0.111), BMI > 40 (0.160) vs. BMI < 40 (0.091), diabetes (0.221) vs. no diabetes (0.102), NSAIDs user (0.153) vs. none NSAIDs user (0.117), opioids user (0.140) vs. none opioids user (0.097), fracture of middle segment (0.146) vs. proximal segment (0.043), fracture of distal segment (0.139) vs. proximal segment (0.043), high-energy injury (0.149) vs. low-energy injury (0.065), open fracture (0.197) vs. close fracture (0.062), Gustilo-Anderson grade I or II (0.070) vs. IIIA (0.130) vs. IIIB and IIIC (0.382), AO Classification A (0.059) vs. B (0.140) vs. C (0.158), open reduction (0.075) vs. close reduction (0.043), infection (0.510) vs. without infection (0.076). No significant difference was found between other comparisons ($p > 0.05$).

There were 5 fixation models of tibial fractures available, including open reduction and internal fixation (ORIF), intramedullary nailing (IMN), minimally invasive percutaneous plate osteosynthesis (MIPPO), external fixation, and conservative treatment. Significant difference was found between each other comparison of the following 3 fixation models, ORIF (0.081) vs. IMN (0.054) vs. MIPPO (0.023) ($p < 0.05$) (Fig. 4). No significant difference was found between external and ORIF, conservative and ORIF, or external and IMN ($p > 0.05$).

Discussion
To our knowledge, this is the first systematic review and meta-analysis to estimate the prevalence of nonunion in patients with tibia fracture and the relationship between different influence factors and tibia fracture nonunion. The pooled prevalence of tibial fracture nonunion was 0.068. Different countries were in variety of prevalence, indicating a heredity disparity. The lowest prevalence was seen in Turkey (0.014) and next was Egypt (0.033); however, the numbers of included studies were so small that the conclusions were not so robust. There were 68 studies that were conducted in China involving 7550 tibia fracture patients and the prevalence of nonunion was 0.047. However, one study in Singapore, a country that has lots of Chinese population, presented a very high prevalence of tibia fracture nonunion 0.427, indicating other influencing factors other than heredity. In calendar year 2011, an inception cohort study in a large payer database of patients with fracture in the USA was conducted using patient-level health claims for medical and drug expenses compiled for approximately 12,808 patients, and the prevalence of tibial fracture nonunion was reported to be 0.074 [137]. In contrast, the present systematic review involved 30,167 patients in a total of 19 studies conducted in the USA and the prevalence was 0.094. The pooled results enabled a larger sample size and accessed more to the real conclusion.

Some influencing factors contributed to the non-union of tibial fractures. In 2016, O’Halloran K et al. created a Nonunion Risk Determination Score (NURDS) to predict nonunion risk, based on 7 influencing factors ($p < 0.05$, OR > 2), including flaps, compartment syndrome, chronic condition(s), open fractures, male gender, grade of American Society of Anesthesiologists Physical Status, and percent cortical contact. While another 2 factors including spiral fractures and low-energy injuries can be predictive of union [19]. In our study, we found more influencing factors, including age >60 years old, diabetes, opioids user, middle and distal fracture, high-energy injury, open fracture, Gustilo-Anderson grade IIIB and IIIC, and AO Classification C met above criteria ($p < 0.05$, OR > 2) and can be regarded as predictive indicators. Still, there were some other influencing factors, including male, tobacco smoker, BMI >40, and NSAIDs user, partially predicated the risks ($p < 0.05$, OR < 2).

The present study showed that BMI >40 and diabetes were the influencing factors of nonunion of tibia fractures. With the improvement of quality of life, the negative impact of obesity has gradually become a hot issue of concern. Obesity can lead to...
Table 1: The basic information and prevalence of tibia fracture nonunion in each included study

| Author         | Year | Country | Age  | Male | Female | Number of tibia fracture | Number of nonunion | Prevalence |
|----------------|------|---------|------|------|--------|--------------------------|-------------------|------------|
| Su CA          | 2018 | USA     | 40.4 | 225  | 102    | 284                      | 19                | 0.067      |
| Mehta D        | 2018 | USA     | 35.2 | 29   | 11     | 40                       | 4                 | 0.100      |
| Milenkovic S   | 2018 | USA     | 43.5 | 20   | 12     | 32                       | 6                 | 0.188      |
| Chang BS       | 2018 | China   | 23-57| 38   | 26     | 60                       | 7                 | 0.117      |
| Liu BQ         | 2018 | China   | 36.1 | 46   | 5      | 51                       | 3                 | 0.059      |
| Zhang JS       | 2018 | China   | 49.4 | 60   | 34     | 94                       | 5                 | 0.053      |
| Zhang QL       | 2018 | China   | 35   | 50   | 36     | 86                       | 0                 | 0.000      |
| Yu JQ          | 2018 | China   | 42.4 | 65   | 39     | 94                       | 5                 | 0.053      |
| Jin PF         | 2018 | China   | 57.6 | 90   | 107    | 197                      | 26                | 0.132      |
| Ge Y           | 2018 | China   | 39.3 | 50   | 42     | 92                       | 2                 | 0.022      |
| Fang YS        | 2018 | China   | 45.2 | 49   | 13     | 62                       | 1                 | 0.016      |
| Li J           | 2018 | China   | 35.5 | 46   | 39     | 70                       | 2                 | 0.029      |
| Xu DY          | 2018 | China   | 40.9 | 38   | 26     | 64                       | 3                 | 0.047      |
| Li ZT          | 2018 | China   | 52.4 | 48   | 42     | 90                       | 1                 | 0.011      |
| Dalley HL      | 2018 | UK      | 739  | 264  | 1003   | 121                      | 0.121             |
| Singh A        | 2018 | Singapore | 38.2 | 101  | 2      | 103                      | 44                | 0.427      |
| Galal S        | 2018 | Egypt   | 37.2 | 52   | 8      | 60                       | 2                 | 0.033      |
| Javdan M       | 2017 | USA     | 36.1 | 46   | 5      | 51                       | 3                 | 0.061      |
| Auston DA      | 2017 | USA     | 42   | 184  | 131    | 315                      | 17                | 0.054      |
| Zura R         | 2017 | USA     | 18-63| 6273 | 6535   | 12808                    | 944               | 0.074      |
| Thakore RV     | 2017 | USA     | 36   | 364  | 102    | 486                      | 56                | 0.115      |
| Chan DS        | 2017 | USA     | 44   | 82   | 32     | 114                      | 24                | 0.211      |
| Xiong SR       | 2017 | China   | 42.5 | 82   | 66     | 148                      | 8                 | 0.054      |
| Javdan M       | 2017 | Iran    | 35.9 | 45   | 4      | 49                       | 3                 | 0.061      |
| Beytemürô      | 2017 | Turkey  | 40.6 | 52   | 21     | 73                       | 1                 | 0.014      |
| Daolagupu AK   | 2017 | India   | 37.14| 32   | 10     | 42                       | 3                 | 0.071      |
| Garg S         | 2017 | India   | 38.9 | 5    | 31     | 36                       | 4                 | 0.111      |
| Mukherjee S    | 2017 | India   | 40.3 | 26   | 14     | 40                       | 3                 | 0.075      |
| Blair JA       | 2016 | USA     | 42.2 | 156  | 28     | 184                      | 16                | 0.087      |
| Burrus MT      | 2016 | USA     | 8132 | 6506 | 14,638 | 1758                     | 0.120             |
| Avilucea FR    | 2016 | USA     | 40.6 | 162  | 54     | 216                      | 29                | 0.134      |
| O'Halloran K   | 2016 | USA     | 39.3 | 93   | 289    | 382                      | 56                | 0.147      |
| Barcakê        | 2016 | USA     | 64   | 5    | 5      | 0                        | 0.078             |
| Shen J         | 2016 | China   | 45   | 54   | 71     | 125                      | 0                 | 0.000      |
| Fang JH        | 2016 | China   | 36.8 | 40   | 16     | 56                       | 2                 | 0.036      |
| Hao LS         | 2016 | China   | 19-67| 67   | 15     | 82                       | 2                 | 0.024      |
| Hu H           | 2016 | China   | 36.7 | 30   | 22     | 52                       | 1                 | 0.019      |
| Liu JQ         | 2016 | China   | 43.2 | 44   | 16     | 60                       | 1                 | 0.017      |
| Rao HR         | 2016 | China   | 35.7 | 35   | 15     | 50                       | 2                 | 0.040      |
| Bai T          | 2016 | China   | 36.8 | 43   | 17     | 60                       | 4                 | 0.067      |
| Zhao KP        | 2016 | China   | 35.6 | 41   | 17     | 58                       | 1                 | 0.017      |
| Uchiyama Y     | 2016 | Japan   | 41.9 | 77   | 8      | 85                       | 3                 | 0.035      |
| Gupta P        | 2016 | India   | 42.7 | 22   | 8      | 30                       | 1                 | 0.033      |
| Piątkowski K   | 2015 | USA     | 49.5 | 24   | 17     | 45                       | 12                | 0.267      |
| Author            | Year | Country | Age       | Male | Female | Number of tibia fracture | Number of nonunion | Prevalence |
|-------------------|------|---------|-----------|------|--------|--------------------------|-------------------|------------|
| Sun KF [71]       | 2015 | China   | 43.1      | 32   | 20     | 115                      | 7                 | 0.061      |
| Sun JQ [72]       | 2015 | China   | 48        | 35   | 21     | 56                       | 7                 | 0.125      |
| Ma N [73]         | 2015 | China   | 45.4      | 334  | 246    | 580                      | 82                | 0.141      |
| Huang H [74]      | 2015 | China   | 17-65     | 52   | 44     | 96                       | 5                 | 0.052      |
| Huang PZ [75]     | 2015 | China   | 32        | 43   | 13     | 56                       | 1                 | 0.018      |
| Zhang YH [76]     | 2015 | China   | 36.5      | 49   | 21     | 70                       | 2                 | 0.029      |
| Luo BX [77]       | 2015 | China   | 38.5      | 47   | 31     | 78                       | 1                 | 0.013      |
| Wang B [78]       | 2015 | China   | 41.2      | 39   | 33     | 72                       | 2                 | 0.028      |
| Cui LH [79]       | 2015 | China   | 37.5      | 53   | 21     | 74                       | 2                 | 0.027      |
| Meng YH [80]      | 2015 | China   | 31.6      | 19   | 35     | 54                       | 1                 | 0.019      |
| Gong Y [81]       | 2015 | China   | 16-39     | 38   | 32     | 70                       | 11                | 0.157      |
| Lian HK [82]      | 2015 | China   | 35.1      | 51   | 43     | 94                       | 4                 | 0.043      |
| Meena RC [83]     | 2015 | India   | 37.5      | 32   | 12     | 44                       | 2                 | 0.045      |
| Sathiyakumar V [84]| 2014 | USA     | 37.5      | 63   | 30     | 93                       | 17                | 0.183      |
| Li Y [85]         | 2014 | China   | 43.3      | 116  | 5      | 121                      | 2                 | 0.017      |
| Dai QH [86]       | 2014 | China   | 34.5      | 23   | 19     | 42                       | 0                 | 0.000      |
| Wu ZH [87]        | 2014 | China   | 48.5      | 32   | 18     | 50                       | 1                 | 0.020      |
| Li ZZ [88]        | 2014 | China   | 43.8      | 76   | 44     | 60                       | 5                 | 0.083      |
| Ren Y [89]        | 2014 | China   | 34.7      | 49   | 21     | 70                       | 4                 | 0.057      |
| Luan HX [90]      | 2014 | China   | 37.1      | 78   | 20     | 98                       | 6                 | 0.061      |
| Zhang WJ [91]     | 2014 | China   | 44        | 43   | 25     | 68                       | 3                 | 0.044      |
| Heng WX [92]      | 2014 | China   | 18-79     | 45   | 23     | 68                       | 4                 | 0.059      |
| Yavuz U [93]      | 2014 | Turkey  | 42        | 32   | 23     | 55                       | 3                 | 0.055      |
| Lack WD [94]      | 2014 | USA     | 45        | 92   | 71     | 163                      | 13                | 0.080      |
| Berlusconi M [95] | 2014 | Italy   | 45        | 42   | 18     | 60                       | 5                 | 0.083      |
| Antonovaë [6]     | 2013 | USA     | 52.5      | 378  | 475    | 853                      | 99                | 0.116      |
| Huang Q [96]      | 2013 | China   | 36.9      | 80   | 40     | 120                      | 3                 | 0.025      |
| Gong M [97]       | 2013 | China   | 40.3      | 41   | 11     | 52                       | 2                 | 0.038      |
| Lv YM [98]        | 2013 | China   | 39.1      | 77   | 34     | 111                      | 6                 | 0.054      |
| Xu YD [99]        | 2013 | China   | 39        | 105  | 58     | 163                      | 2                 | 0.012      |
| Clement ND [100]  | 2013 | UK      | 77.9      | 63   | 170    | 233                      | 23                | 0.099      |
| Sitnik AA [101]   | 2013 | Belarus | 43        | 54   | 26     | 80                       | 7                 | 0.088      |
| Yusof NM [102]    | 2013 | Malaysia| 24.5      | 52   | 6      | 58                       | 10                | 0.172      |
| Bishop JA [103]   | 2012 | USA     | 36.6      | 222  | 194    | 416                      | 33                | 0.031      |
| Lin ZF [104]      | 2012 | China   | 39.6      | 58   | 38     | 96                       | 1                 | 0.010      |
| Zhang H [105]     | 2012 | China   | 39.6      | 58   | 38     | 96                       | 1                 | 0.010      |
| Jia QT [106]      | 2012 | China   | 36        | 61   | 27     | 88                       | 4                 | 0.045      |
| Zhou JL [107]     | 2012 | China   | 53        | 43   | 9      | 52                       | 10                | 0.192      |
| Rouhani A [108]   | 2012 | Iran    | 26.4      | 45   | 8      | 54                       | 3                 | 0.056      |
| Vallier HA [109]  | 2011 | USA     | 38.3      | 85   | 19     | 114                      | 6                 | 0.053      |
| Zhu DK [110]      | 2011 | China   | 18-76     | 53   | 31     | 84                       | 3                 | 0.036      |
| Zhao DL [111]     | 2011 | China   | 37.8      | 54   | 26     | 80                       | 1                 | 0.013      |
| Liu F [112]       | 2011 | China   | 32.6      | 32   | 14     | 46                       | 4                 | 0.087      |
| Enninghorst N [113]| 2011 | Australia| 42.4     | 66   | 23     | 89                       | 26                | 0.292      |
vitamin D deficiency, and whether there is a causal relationship between fracture nonunion and vitamin D deficiency is the focus of discussion [138, 139]. But we cannot ignore the fact that diabetes mellitus is closely related to obesity. In our study, the use of NSAIDs was also associated with fracture nonunion. Some experiments have proved that NSAIDs can temporarily inhibit the process of fracture union [140, 141]; however, other studies considered that the pain caused by fracture nonunion of patients led to their resorting to NSAIDs [142].

Our comparison showed that open reduction had a higher rate of fracture nonunion than closed reduction. In surgery, although open reduction can bring good fracture repair, but closed reduction can better protect blood supply and soft tissue. In addition, our study did not find a relationship between fibular fixation and nonunion rates of tibial fractures. However, Strauss EJ and Kumar A’ experiments on cadavers showed that fibular fixation can increase the stability of tibial fractures after surgery [143–145]. So whether it is necessary to fix the fibula for the treatment of tibial fracture accompanied by fibular fracture should be further determined.

Table 1 The basic information and prevalence of tibia fracture nonunion in each included study (Continued)

| Author         | Year | Country | Age (Mean) | Male | Female | Number of tibia fracture | Number of nonunion | Prevalence |
|----------------|------|---------|------------|------|--------|--------------------------|-------------------|------------|
| Xu JQ [114]    | 2009 | China   | 36.3       | 121  | 49     | 170                      | 8                 | 0.047      |
| Li ZG [115]    | 2009 | China   | 35.8       | 71   | 56     | 127                      | 3                 | 0.024      |
| Mahmudi N [116]| 2009 | China   | 37         | 34   | 10     | 44                       | 3                 | 0.068      |
| Deng HP [117]  | 2009 | China   | 40.3       | 51   | 34     | 85                       | 4                 | 0.047      |
| Dong JH [118]  | 2009 | China   | 18-74      | 77   | 51     | 128                      | 2                 | 0.016      |
| Fu KL [119]    | 2009 | China   |            |      |        | 112                      | 11                | 0.098      |
| Zhou L [120]   | 2009 | China   | 37.9       | 52   | 41     | 93                       | 5                 | 0.054      |
| Lang ZY [121]  | 2009 | China   | 33.6       | 51   | 16     | 67                       | 2                 | 0.030      |
| Wu C [122]     | 2009 | China   | 19-71      | 25   | 12     | 37                       | 2                 | 0.054      |
| Li QM [123]    | 2009 | China   | 37.6       | 168  | 51     | 219                      | 6                 | 0.027      |
| Yokoyama K [124]| 2008 | Japan   | 34.6       | 70   | 14     | 84                       | 17                | 0.202      |
| Aderinto J [125]| 2008 | UK      |            |      |        | 54                       | 3                 | 0.056      |
| Lu HY [126]    | 2007 | China   | 34.5       | 158  | 98     | 256                      | 9                 | 0.035      |
| Hu GZ [127]    | 2007 | China   | 33.4       | 301  | 116    | 396                      | 11                | 0.028      |
| Zeng CJ [128]  | 2006 | China   | 30.7       | 390  | 264    | 541                      | 14                | 0.026      |
| Zhang YL [129]| 2006 | China   | 35         | 73   | 25     | 98                       | 9                 | 0.092      |
| Zhao XZ [130]  | 2006 | China   | 43.8       | 52   | 26     | 78                       | 5                 | 0.064      |
| Zhu GH [131]   | 2005 | China   | 34         | 55   | 23     | 78                       | 5                 | 0.064      |
| Harris I [132] | 2005 | Australia | 34       | 124  | 39     | 163                      | 13                | 0.080      |
| Cole PA [133]  | 2004 | USA     |            |      |        | 89                       | 2                 | 0.022      |
| Bonnevialle P [134]| 2003 | France | 40.8       | 34   | 15     | 49                       | 8                 | 0.163      |
| Harvey EJ [135]| 2002 | Canada  |            |      |        | 110                      | 13                | 0.118      |
| Keating J [136]| 1997 | USA     |            |      |        | 112                      | 9                 | 0.080      |

The choice of fixation mode is a way to control the nonunion rate of tibial fracture artificially [146, 147]. We compared 5 fixation modes available. The nonunion rate of conservative treatment was the highest one compared with that of surgical treatment. This is obviously different from the lowest rate reported by Li H et al. [148]. This may be related to the insufficient number of articles in conservative treatment. Compared with traditional ORIF, IMN and MIPPO have lower fracture nonunion rate. No significant difference was found between external fixation and ORIF. Ebraheim NA et al. reported that IMN can achieve better healing effect in the treatment of tibial fractures, comparing to ORIF and external fixation [149]. MIPPO had the lowest nonunion rate of all fixation modes. It was proved that MIPPO can maximize the protection of soft tissue and bone marrow around the fracture site [150]. The above 5 fixation modes destroy the necessary conditions of fracture healing to varying degrees. However, it is worth mentioning that different options have different advantages in the treatment of tibial fractures [151, 152]. For example, in distal tibial fractures, more comminuted fractures would rather require open...
Fig. 2 The forest plot of prevalence of tibia fracture nonunion
Table 2 The pooled results and subgroup analysis of prevalence of nonunion from tibia fracture patient

| Number of study | N  | n    | Prevalence rate | Heterogeneity | Model |
|-----------------|----|------|-----------------|---------------|-------|
|                 |    |      | effect size     | lower limit   | upper limit | $I^2$ | $p$   |
| Total           | 111| 4142 | 3817            | 0.068         | 0.060       | 0.077 | 86.60% < 0.01 Random |
| 1. Age (year)   |    |      |                 |               |             |       |       |
| < 60            | 3  | 545  | 60              | 0.125         | 0.060       | 0.189 | 77.50% < 0.01 Random |
| > 60            | 3  | 316  | 65              | 0.204         | 0.160       | 0.249 | 0.000 0.689 Fixed   |
| 2. Gender       |    |      |                 |               |             |       |       |
| Male            | 11 | 8186 | 790             | 0.131         | 0.104       | 0.159 | 77.80% < 0.01 Random |
| Female          | 11 | 8123 | 618             | 0.118         | 0.085       | 0.150 | 84.50% < 0.01 Random |
| 3. Tobacco smoker |   |      |                 |               |             |       |       |
| Yes             | 8  | 1226 | 299             | 0.173         | 0.119       | 0.226 | 91.80% < 0.01 Random |
| No              | 8  | 1217 | 888             | 0.111         | 0.072       | 0.150 | 87.30% < 0.01 Random |
| 4. Drink        |    |      |                 |               |             |       |       |
| Yes             | 2  | 348  | 42              | 0.136         | 0.036       | 0.235 | 82.50% 0.017 Random |
| No              | 2  | 1284 | 958             | 0.098         | 0.043       | 0.152 | 86.90% 0.006 Random |
| 5. Body mass index |     |      |                 |               |             |       |       |
| < 30            | 2  | 24466| 2257            | 0.091         | 0.049       | 0.133 | 93.30% < 0.01 Random |
| > 30            | 2  | 3790 | 451             | 0.119         | 0.109       | 0.129 | 0.000 0.557 Fixed   |
| 30–40           | 2  | 2507 | 236             | 0.094         | 0.083       | 0.105 | 0.000 0.441 Fixed   |
| < 40            | 2  | 2697 | 2493            | 0.091         | 0.053       | 0.128 | 99.20% < 0.01 Random |
| > 40            | 2  | 1283 | 215             | 0.160         | 0.020       | 0.218 | 87.80% 0.004 Random |
| 6. Diabetes     |    |      |                 |               |             |       |       |
| Yes             | 4  | 347  | 73              | 0.221         | 0.178       | 0.267 | 85.00% 0.335 Fixed   |
| No              | 4  | 984  | 103             | 0.102         | 0.065       | 0.139 | 67.50% 0.046 Random |
| 8. Opioids user |    |      |                 |               |             |       |       |
| Yes             | 3  | 371  | 58              | 0.153         | 0.116       | 0.189 | 0.000 0.420 Fixed   |
| No              | 3  | 1197 | 144             | 0.117         | 0.099       | 0.135 | 59.90% 0.083 Random |
| 9. Fracture site|    |      |                 |               |             |       |       |
| Proximal        | 7  | 586  | 30              | 0.043         | 0.027       | 0.06  | 26.50% 0.254 Fixed   |
| Middle          | 7  | 724  | 115             | 0.146         | 0.080       | 0.211 | 84.60% < 0.01 Random |
| Distal          | 7  | 614  | 88              | 0.139         | 0.104       | 0.178 | 24.10% 0.253 Fixed   |
| 10. Injury energy |   |      |                 |               |             |       |       |
| High            | 4  | 710  | 105             | 0.149         | 0.083       | 0.241 | 83.60% < 0.01 Random |
| Low             | 4  | 298  | 22              | 0.065         | 0.007       | 0.175 | 87.30% < 0.01 Random |
| 11. Open fracture |   |      |                 |               |             |       |       |
| Yes             | 10 | 1403 | 916             | 0.062         | 0.049       | 0.074 | 56.20% 0.015 Random |
| No              | 10 | 1985 | 390             | 0.197         | 0.145       | 0.294 | 84.80% < 0.01 Random |
| 12. Gustilo-Anderson gradea |   |      |                 |               |             |       |       |
| I or II         | 9  | 680  | 57              | 0.070         | 0.051       | 0.089 | 31.30% 0.168 Fixed   |
| IIIA            | 9  | 394  | 55              | 0.130         | 0.097       | 0.163 | 0.000 0.686 Fixed   |
| III B or IIIC   | 9  | 220  | 89              | 0.382         | 0.198       | 0.566 | 88.90% < 0.01 random |
| 13. Müller AO Classification of Fractures (AO) classificationb | |      |                 |               |             |       |       |
| A               | 7  | 1039 | 69              | 0.059         | 0.027       | 0.090 | 68.90% 0.004 Random |
| B               | 7  | 600  | 103             | 0.140         | 0.086       | 0.204 | 65.90% 0.007 Random |
| C               | 7  | 285  | 54              | 0.158         | 0.078       | 0.260 | 74.50% 0.001 Random |
| 14. Debride time |   |      |                 |               |             |       |       |
| < 6 h           | 2  | 138  | 41              | 0.302         | 0.074       | 0.530 | 89.10% 0.002 Random |
| > 6 h           | 2  | 49   | 20              | 0.405         | 0.268       | 0.541 | 0.000 0.411 Fixed   |
| 15. Open reduction |   |      |                 |               |             |       |       |
| Yes             | 9  | 573  | 48              | 0.075         | 0.043       | 0.107 | 52.40% 0.032 Random |
| No              | 9  | 606  | 26              | 0.043         | 0.028       | 0.060 | 42.10% 0.086 Fixed   |
| 16. Fixation modec | |      |                 |               |             |       |       |
| ORIF            | 41 | 6216 | 703             | 0.081         | 0.058       | 0.107 | 82.10% < 0.01 Random |
| IMN             | 51 | 1264 | 1326            | 0.054         | 0.040       | 0.070 | 77.30% < 0.01 Random |
| MIPPO           | 25 | 988  | 18              | 0.023         | 0.015       | 0.032 | 0.000 0.835 Fixed   |
| External fixation |    |      |                 |               |             |       |       |
| Conservative treatment | 4  | 116  | 22              | 0.134         | 0.003       | 0.409 | 92.10% < 0.01 Random |
Table 2  The pooled results and subgroup analysis of prevalence of nonunion from tibia fracture patient (Continued)

| Number of study | Number of study | Nn   | n   | Prevalence rate | Heterogeneity | Model |
|-----------------|-----------------|------|-----|-----------------|---------------|-------|
|                 |                 |      |     |                 | I²            |       |
| 17. Fibula fixed| Yes             | 7    | 166 | 11              | 0.073         | 53.20% | Random |
|                 | No              | 7    | 538 | 69              | 0.122         | < 0.01 | Fixed  |
| 18. Osteofascial compartment syndrome | Yes | 3 | 210 | 31 | 0.134 | 61.90% | Fixed |
|                 | No              | 3    | 1359| 162             | 0.105         | 85.40% | Random |
| 19. Infection   | Yes             | 2    | 217 | 84              | 0.510         | 93.80% | Random |
|                 | No              | 2    | 1366| 119             | 0.076         | 92.80% | Random |

*Gustilo-Anderson classification: grade I: clean wound < 1 cm in length; grade II: wound 1–10 cm in length without extensive soft-tissue damage, flaps or avulsions; grade III: extensive soft-tissue laceration (>10 cm) or tissue loss/damage or an open segmental fracture; grade IIIa: adequate periosteal coverage of the fracture bone despite the extensive soft-tissue laceration or damage; grade IIIb: extensive soft-tissue loss, periosteal stripping and bone damage, usually associated with massive contamination; grade IIIc: associated with an arterial injury requiring repair, irrespective of degree of soft-tissue injury

AO classification of tibia fractures with designations of A: simple, B: wedge, C: complex

ORIF open reduction and internal fixation, IMN intramedullary nailing, MIPPO minimally invasive plate osteosynthesis

Fig. 3  The publication bias of prevalence of tibia fracture nonunion
reduction than “simple” type A fractures. So it is unreasonable to only consider the nonunion rate of fracture of operation [148]. The systematic review and meta-analysis had made strict inclusion and exclusion criteria, but still had some limitations and bias which may be unavoidable.

Table 3 The comparison results stratified by 19 influencing factors

| Study | Comparison results | Heterogeneity | Model |
|-------|--------------------|---------------|-------|
| 1. Age (year) | > 60 vs. < 60 | < 0.05 | 2.602 1.686 4.016 | 48.70% 0.142 Fixed |
| 2. Gender | Male vs. Female | < 0.05 | 1.256 1.122 1.407 | 14.00% 0.311 Fixed |
| 3. Tobacco smoker | Yes vs. No | < 0.05 | 1.692 1.458 1.964 | 49.30% 0.055 Fixed |
| 4. Drink | Yes vs. No | 0.083 1.367 0.960 1.947 | 0.00% 0.518 Fixed |
| 5. Body mass index (BMI) | 30 < BMI < 40 vs. BMI < 30 | 0.081 1.085 0.575 2.050 | 93.70% < 0.05 Random |
| | BMI > 40 vs. BMI < 30 | < 0.05 | 1.874 1.607 2.185 | 0.00% 0.660 Fixed |
| | BMI > 30 vs. BMI < 30 | 0.189 1.351 0.862 2.119 | 93.00% < 0.05 Random |
| | BMI > 40 vs. 30 < BMI < 40 | 0.045 1.773 1.014 3.102 | 84.30% 0.012 Random |
| 6. Diabetes | Yes vs. No | < 0.05 | 2.731 1.857 4.014 | 32.20% 0.029 Fixed |
| 7. Nonsteroidal anti-inflammatory drugs user | Yes vs. No | 0.018 | 1.536 1.076 2.194 | 0.00% 0.384 Fixed |
| 8. Opioids user | Yes vs. No | 0.012 | 2.010 1.166 3.468 | 0.00% 0.370 Fixed |
| 9. Fracture site | Middle vs. Proximal | < 0.05 | 3.152 2.019 4.922 | 0.00% 0.788 Fixed |
| | Distal vs. Proximal | < 0.05 | 2.877 1.822 4.543 | 0.00% 0.911 Fixed |
| | Distal vs. Middle | 0.670 0.932 0.673 1.290 | 0.00% 0.650 Fixed |
| 10. Injury energy | High vs. Low | 0.001 | 2.602 1.484 4.562 | 35.90% 0.182 Fixed |
| 11. Open fracture | Yes vs. No | < 0.05 | 2.846 1.700 4.202 | 15.00% 0.206 Fixed |
| 12. Gustilo-Anderson gradea | IIIA vs. I or II | 0.005 | 1.831 1.204 2.784 | 0.00% 0.847 Fixed |
| | IIIB or IIIC vs. I or II | < 0.05 | 7.202 4.781 10.848 | 46.00% 0.394 Fixed |
| | IIIB or IIIC vs. IIIA | < 0.05 | 3.695 2.422 5.639 | 32.60% 0.168 Fixed |
| 13. Müller AO Classification of Fractures (AO) classificationb | B vs. A | 0.010 | 2.522 1.249 5.930 | 54.20% 0.041 Random |
| | C vs. A | < 0.05 | 3.685 2.405 5.648 | 37.00% 0.160 Fixed |
| | C vs. B | < 0.05 | 3.569 2.428 5.325 | 39.60% 0.142 Fixed |
| 14. Debride time | < 6 h vs. > 6 h | 0.631 | 1.190 0.585 2.419 | 0.00% 0.520 Fixed |
| 15. Open reduction | Yes vs. No | < 0.05 | 2.887 1.715 4.861 | 26.20% 0.220 Fixed |
| 16. Fixation modec | IMN vs. ORIF | 0.003 | 2.681 1.397 5.146 | 0.00% 0.980 Fixed |
| | ORIF vs. MIPPO | 0.020 | 1.127 1.019 1.247 | 54.10% < 0.05 Random |
| | External vs. ORIF | < 0.05 | 3.495 1.351 9.045 | 0.00% 0.859 Fixed |
| | Conservative vs. ORIF | 0.264 | 1.496 0.737 3.035 | 64.10% 0.062 Fixed |
| | External vs. IMN | 0.093 | 1.006 0.266 3.806 | 55.40% 0.022 Random |
| 17. Fibula fixed | Yes vs. No | 0.435 | 1.317 0.659 2.634 | 47.60% 0.075 Random |
| 18. Osteofascial compartment syndrome | Yes vs. No | 0.106 | 1.420 0.968 2.173 | 80.30% 0.006 Fixed |
| 19. Infection | Yes vs. No | < 0.05 | 11.877 7.461 18.906 | 52.10% 0.149 Fixed |

*aGustilo-Anderson classification: grade I: clean wound < 1 cm in length; grade II: wound 1–10 cm in length without extensive soft-tissue damage, flaps or avulsions; grade III: extensive soft-tissue laceration (> 10 cm) or tissue loss/damage or an open segmental fracture; grade IIia: adequate periosteal coverage of the fracture bone despite the extensive soft-tissue laceration or damage; grade IIib: associated with massive contamination; grade IIic: associated with an arterial injury requiring repair, irrespective of degree of soft-tissue injury

*bAO classification of tibia fractures with designations of A: simple, B: wedge, C: complex

*cORIF open reduction and internal fixation, IMN intramedullary nailing, MIPPO minimally invasive plate osteosynthesis
Table 4 Prevalence of nonunion from tibia fracture in different countries

| Number of study | N     | n    | Prevalence rate | Heterogeneity | Model |
|----------------|-------|------|-----------------|---------------|-------|
| USA            | 19    | 30167| 3083            | 0.094         | 0.075 | 0.114 | 93.40% | < 0.01 | Random |
| China          | 68    | 7550 | 396             | 0.047         | 0.039 | 0.057 | 69.50% | < 0.01 | Random |
| Australia      | 2     | 252  | 39              | 0.182         | 0.026 | 0.389 | 93.90% | < 0.01 | Random |
| Belarus        | 1     | 80   | 7               | 0.088         | –     | –     | –      | –      | –      |
| Canada         | 1     | 110  | 13              | 0.118         | –     | –     | –      | –      | –      |
| Charlotte      | 1     | 163  | 13              | 0.08          | –     | –     | –      | –      | –      |
| Egypt          | 1     | 60   | 2               | 0.033         | –     | –     | –      | –      | –      |
| France         | 1     | 49   | 8               | 0.162         | –     | –     | –      | –      | –      |
| India          | 5     | 150  | 10              | 0.059         | 0.026 | 0.092 | 0      | 0.73   | Fixed  |
| Iran           | 3     | 152  | 9               | 0.059         | 0.022 | 0.097 | 0      | 0.99   | Fixed  |
| Italy          | 1     | 60   | 5               | 0.083         | –     | –     | –      | –      | –      |
| Japan          | 2     | 169  | 20              | 0.114         | 0.049 | 0.278 | 91.70% | 0.001  | Random |
| Malaysia       | 1     | 58   | 10              | 0.172         | –     | –     | –      | –      | –      |
| Singapore      | 1     | 103  | 44              | 0.427         | –     | –     | –      | –      | –      |
| Turkey         | 1     | 73   | 1               | 0.014         | –     | –     | –      | –      | –      |
| UK             | 4     | 1042 | 156             | 0.108         | 0.092 | 0.124 | 47.60% | 0.126  | Fixed  |

Fig. 4 The comparison of MIPO with IMN
Firstly, due to different attentions of individual studies, the influencing factors were only extracted from partial studies with available data and some other influencing factors such as hemoglobin and bone defect were not mentioned. Secondly, different doctors and different hospitals had a variety of surgical technologies and conditions, which may cause unavoidable bias. Thirdly, the number of included studies and the data for meta-analysis were limited which may affect the final results to a certain degree. Fourthly, publication bias was found in the study. Therefore, the data from literature in other languages, more areas, and ongoing studies are required to reflect a more accurate and wide variation. Finally, non-randomized controlled trials (nRCTs) were involved in this systematic review. As a result, subjective factors may affect the result. More rigorous designs and large RCTs are required to make further verification.

In conclusion, the prevalence of nonunion in patients with tibia fracture was 0.068 and 15 potential factors were associated with the prevalence. Closed reduction and MIPPO have low risks of nonunion for the treatment of tibial fractures. A series of factors shed the light which may affect the union rate of tibial fracture for doctors’ reference, and provide the probability of nonunion of tibial fracture under different treatment schemes. The authors hope to help doctors assess the risk of nonunion and propose the most suitable treatment for patients with tibial fractures under different conditions.

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Authors’ contributions
An overall literature search was performed and relevant studies were screened independently by FZ. Disagreements of data were resolved by WZ via discussion and consensus. YZ extracted the relevant data. BJ extracted the relevant data. Disagreements of data extraction were resolved by JY via discussion and consensus. LL: Technical guidance of the writing process. All authors read and approved the final manuscript.

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Availability of data and materials
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This study has obtained ethics approval and consent of the ethics committee in our hospital.

Consent for publication
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Competing interests
The authors declare that they have no competing interests.

Author details
1Department of Orthopaedics, No.1 Hospital of China Medical University, Shenyang, China. 2Department of Orthopaedics, Shenyang Orthopaedic Hospital, Shenyang, China. 3Department of Orthopaedics, No.4 Hospital of China Medical University, Guangzhou, China. 4Department of Dermatology, No.1 Hospital of China Medical University, Guangzhou, China.

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