



## Fragility of statistically significant findings from randomized clinical trials of surgical treatment of humeral shaft fractures: A systematic review

Stephen Craig Morris, Anirudh K Gowd, Avinesh Agarwalla, Wesley P Phipatanakul, Nirav H Amin, Joseph N Liu

**Specialty type:** Orthopedics

**Provenance and peer review:**

Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B, B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Nyamuryekung'e MK, Tanzania; Sabalic S, Croatia

**Received:** October 26, 2021

**Peer-review started:** October 26, 2021

**First decision:** February 15, 2022

**Revised:** February 28, 2022

**Accepted:** August 12, 2022

**Article in press:** August 12, 2022

**Published online:** September 18, 2022



**Stephen Craig Morris, Wesley P Phipatanakul,** Department of Orthopaedic Surgery, Loma Linda University, Loma Linda, CA 92354, United States

**Anirudh K Gowd,** Department of Orthopaedic Surgery, Wake Forest University Baptist Medical Center, Winston-Salem, NC 27157, United States

**Avinesh Agarwalla,** Department of Orthopaedic Surgery, Westchester Medical Center, Valhalla, NY 10595, United States

**Nirav H Amin,** Department of Orthopaedic Surgery, Premier Orthopaedic and Trauma Specialists, Pomona, CA 91767, United States

**Joseph N Liu,** Department of Orthopedic Surgery, USC Epstein Family Center for Sports Medicine, Los Angeles, CA 90089, United States

**Corresponding author:** Joseph N Liu, MD, Assistant Professor, Department of Orthopedic Surgery, USC Epstein Family Center for Sports Medicine, 950 Downey Way, Los Angeles, CA 90089, United States. [josephnliu@gmail.com](mailto:josephnliu@gmail.com)

### Abstract

#### BACKGROUND

Despite recent meta-analyses of randomized controlled trials (RCTs), there remains no consensus regarding the preferred surgical treatment for humeral shaft fractures. The fragility index (FI) is an emerging tool used to evaluate the robustness of RCTs by quantifying the number of participants in a study group that would need to switch outcomes in order to reverse the study conclusions.

#### AIM

To investigate the fragility index of randomized control trials assessing outcomes of operative fixation in proximal humerus fractures.

#### METHODS

We completed a systematic review of RCTs evaluating the surgical treatment of humeral shaft fractures. Inclusion criteria included: articles published in English; patients randomized and allotted in 1:1 ratio to 2 parallel arms; and dichotomous outcome variables. The FI was calculated for total complications, each

complication individually, and secondary surgeries using the Fisher exact test, as previously published.

## RESULTS

Fifteen RCTs were included in the analysis comparing open reduction plate osteosynthesis with dynamic compression plate or locking compression plate, intramedullary nail, and minimally invasive plate osteosynthesis. The median FI was 0 for all parameters analyzed. Regarding individual outcomes, the FI was 0 for 81/91 (89%) of outcomes. The FI exceeded the number lost to follow up in only 2/91 (2%) outcomes.

## CONCLUSION

The FI shows that data from RCTs regarding operative treatment of humeral shaft fractures are fragile and does not demonstrate superiority of any particular surgical technique.

**Key Words:** Humerus fracture; Open reduction internal fixation; Intramedullary nail; Fragility index; Complications; Fragility index

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core Tip:** Humerus shaft fractures have been managed with intramedullary nail fixation and plate osteosynthesis. Multiple randomized control trials have been performed to compare outcomes, complications, reoperations, and union rates between both treatment modalities. Despite multiple randomized control trials, there remains a lack of consensus from the existing literature regarding surgical treatment of humeral shaft fractures. This manuscript aims to further assess the quality of the literature that guides treatment decisions by employing a new metric, the fragility index.

**Citation:** Morris SC, Gowd AK, Agarwalla A, Phipatanakul WP, Amin NH, Liu JN. Fragility of statistically significant findings from randomized clinical trials of surgical treatment of humeral shaft fractures: A systematic review. *World J Orthop* 2022; 13(9): 825-836

**URL:** <https://www.wjgnet.com/2218-5836/full/v13/i9/825.htm>

**DOI:** <https://dx.doi.org/10.5312/wjo.v13.i9.825>

## INTRODUCTION

Humeral shaft fractures represent approximately 3% of all long-bone fractures[1] with an incidence around 13 per 100000 people per year[2]. While the vast majority may be managed nonoperatively[1-5], surgical treatment is generally indicated for open fractures, polytrauma patients, ipsilateral humeral shaft and forearm fractures (floating elbow), segmental fractures, and cases of failed treatment in functional brace[3]. However, it is important to note that there are currently no defined gold standards for the treatment of humeral shaft fractures[6,7]. Surgical treatment options include external fixation, open reduction and plate osteosynthesis (ORPO), minimally invasive plate osteosynthesis (MIPO), and intramedullary nail (IMN). Implant options for both ORPO and MIPO include dynamic compression plate (DCP) and locking compression plate (LCP). Numerous recent systematic reviews, meta-analysis, and network meta-analysis (NMA) review papers have been published aiming to determine the efficacy of these treatment options in order to provide reliable evidence to guide clinical decision making[6,8-13]. Based on the lack of consensus from the existing literature regarding surgical treatment of humeral shaft fractures, this manuscript aims to further assess the quality of the literature that guides treatment decisions by employing a new metric, the fragility index (FI). The FI has been introduced to further evaluate the robustness (or fragility) of randomized control trial (RCT) results[14,15].

The evaluation of RCTs *via* systematic review, meta-analysis, or NMA represents level I evidence; however, the fact remains that many RCTs in orthopaedics, despite demonstrating statistically significant effects, are limited by small sample sizes and few outcome events[16-19]. Clinical studies are classically evaluated for statistical significance in the form of *P* values, and 95% confidence intervals, which help determine how likely observed effects would occur based solely on chance[20-22]. The FI represents the required number of participants in the RCT whose outcome would have to change from nonevent to event in order to convert a statistically significant result to nonsignificant. The FI is calculated by sequentially calculating the *P* value using the Fisher exact test while changing an outcome from nonevent to event between cycles until the calculated *P* value is not significant, or *P* > 0.05. Basically, the FI quantifies how many patients would be required to switch outcomes in order to change the study conclusions. In the case where a study reports a statistically significant result, but the FI is

calculated to be zero, this would indicate that the Fisher's exact test did not find a  $P$  value  $< 0.05$ , whereas the statistical method used in the paper did. In addition, the FI may be lower than the number of patients lost to follow-up, limiting the confidence one may have in the study conclusion[14]. The higher the FI the more confidence the reader can have that the result is robust. While there is no defined cut off for the FI value, if the FI is zero or less than the number of patients lost to follow up, then any statistically significant result should be considered fragile and interpreted with caution. By applying the FI metric to RCTs evaluating surgical outcomes in humeral shaft fractures we can determine how much confidence these studies should be given in guiding treatment decisions.

Due to this added value, the FI has been gaining traction in the literature with studies published across numerous medical specialties[15,23,32-35,24-31], in addition to orthopaedic subspecialties[25,36-40]. This valuable, new tool, the FI, can serve to increase our understanding of the literature regarding treatment of humeral shaft fractures, aiding in clinical decision making. Our primary objective was to determine the robustness of statistically significant findings in RCTs of the surgical treatment of humeral shaft fractures by systematically applying the FI. We sought to accomplish this objective by testing our hypothesis that the median FI in these RCTs would be less than the number lost to follow up and therefore would indicate fragile results.

## MATERIALS AND METHODS

The systematic review was completed, and results reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines statement[41]. We began by evaluating all review articles about humeral shaft fractures published from 2000 to 2019[6,8-12] and extracting from those studies all included RCTs for analysis. We then performed a systematic review of the literature to identify randomized controlled trials dealing with surgical treatment of humeral shaft fractures that had been published since the most recent review articles. The Medline and EMBASE databases were searched for the dates of January 1, 2016 to April 1, 2019 using the following Medical Subject Headings terms: "humeral fractures". The Reference Citation Analysis (RCA) was also used to ensure high quality studies were included in the analysis. These dates were selected to identify new RCTs that would not have been included in prior systematic review articles. Titles and abstracts were screened, and full text manuscripts reviewed. Inclusion criteria included the following: patients randomized to 2 parallel arms, articles published in English, patient allocated to treatment and control arms in 1:1 ratio, reported statistical significance for dichotomous variables. Exclusion criteria included: published abstract only; studies without available full text, (non-English manuscripts; studies reporting patient data published previously; retrospective studies; and prospective studies that were not randomized.

Data was extracted from the included studies by individual review of each study by the primary author. Accuracy of data extraction was confirmed by independent review by the remaining authors separately, with any discrepancy resolved by group consensus. An electronic data form was developed and the following data were extracted for each included study: First author, journal, publication year, comparison groups, randomization parameters, initial sample size, total patients lost to follow up, final sample size, patients in study group 1, patients in study group 2, patients lost to follow up in group 1, patients lost to follow up in group 2, presence of power analysis, as well as the number of events for each outcome in each group and reported  $p$ -value for dichotomous outcomes (delayed union/nonunion, iatrogenic radial nerve palsy, infection, malunion, shoulder impingement, elbow stiffness, secondary surgeries). For our study lost to follow up included any patients initially enrolled in the study but not included in final analysis for any reason. The total number of events for all complications was defined as the sum of delayed union/nonunion, iatrogenic radial nerve palsy, infection, malunion, shoulder impingement, and elbow stiffness. The total number of events for all complications was calculated for each study group within each included study.

For each study the FI was then calculated for all complications, secondary surgeries, as well as each complication individually. The FI was calculated *via* the method described previously by Walsh *et al*[14] using a publicly available calculator found at <http://clincalc.com/Stats/FragilityIndex.aspx>. After inputting the total number of patients in the control group, experimental group, control group with primary endpoint, and experimental group with primary endpoint, this tool calculates the  $P$  value using the Fisher exact test. If the  $P$  value is significant ( $< 0.05$ ), the tool incrementally converts 1 outcome from nonevent to event and recalculates the  $P$  value until the  $P$  value increases above 0.05 and the result becomes insignificant. The methodological quality of each RCT was also assessed by calculating the Jadad scale[42], also known as the Oxford Quality Scoring System, for each trial.

## RESULTS

Our review of RCTs from recent review articles as well as systemic search strategy produced 415 records screened and 28 full text articles assessed (Figure 1). Of these, 15 studies met inclusion criteria (Table 1)[43-57]. The primary outcome was only defined in two studies, shoulder function defined by

Table 1 Included randomized controlled trials with characteristics

| First author (last name) | Journal   | Year | Comparison         | Patients enrolled | Patients lost to follow up | Final study, <i>n</i> | JADAD score | Power analysis |
|--------------------------|---|------|--------------------|-------------------|----------------------------|-----------------------|-------------|----------------|
| Kim                      | <i>J Orthop Trauma</i>                          | 2015 | ORPO (LCP) vs MIPO | 72                | 4                          | 68                    | 3           | Yes            |
| Esmailiejah              | <i>Trauma Mon</i>                               | 2015 | ORPO (DCP) vs MIPO | 68                | 3                          | 65                    | 3           | No             |
| Fan                      | <i>Orthopedics</i>                              | 2015 | ORPO (LCP) vs IMN  | 60                | 0                          | 60                    | 2           | Yes            |
| Hadhoud                  | <i>Menoufia Medical Journal</i>                 | 2015 | ORPO (LCP) vs MIPO | 30                | 0                          | 30                    | 2           | No             |
| Wali                     | <i>Strategies Trauma Limb Reconstr</i>          | 2014 | ORPO (DCP) vs IMN  | 50                | 0                          | 50                    | 2           | No             |
| Benegas                  | <i>J Shoulder Elbow Surg</i>                    | 2014 | MIPO vs IMN        | 41                | 1                          | 40                    | 3           | Yes            |
| Lian                     | <i>Orthopedics</i>                              | 2013 | MIPO vs IMN        | 56                | 9                          | 47                    | 3           | No             |
| Li                       | <i>J Shoulder Elbow Surg</i>                    | 2011 | ORPO (LCP) vs IMN  | 50                | 5                          | 45                    | 3           | Yes            |
| Iqbal                    | <i>Annals of King Edward Medical University</i> | 2011 | ORPO (DCP) vs IMN  | 40                | 0                          | 40                    | 3           | No             |
| Singiseti                | <i>Int Orthop</i>                               | 2010 | ORPO (DCP) vs IMN  | 45                | 9                          | 36                    | 1           | No             |
| Putti                    | <i>J Orthop Surg (Hong Kong)</i>                | 2009 | ORPO (DCP) vs IMN  | 34                | 0                          | 34                    | 2           | No             |
| Changulani               | <i>Int Orthop</i>                               | 2007 | ORPO (DCP) vs IMN  | 47                | 2                          | 45                    | 3           | No             |
| Kesemenli                | <i>Acta Orthop Traumatol Turc</i>               | 2003 | ORPO (DCP) vs IMN  | 60                | 0                          | 60                    | 2           | No             |
| McCormack                | <i>J Bone Joint Surg (Br)</i>                   | 2000 | ORPO (DCP) vs IMN  | 44                | 3                          | 41                    | 2           | No             |
| Chapman                  | <i>J Orthop Trauma</i>                          | 2000 | ORPO (DCP) vs IMN  | 89                | 5                          | 84                    | 3           | No             |

ORPO: Open reduction and plate osteosynthesis; DCP: Dynamic compression plate; LCP: Locking compression plate; IMN: Intramedullary nail; MIPO: Minimally invasive plate osteosynthesis.

University of California, Los Angeles (UCLA) scoring system in one study[43] and shoulder function defined by the American Shoulder and Elbow Surgeons (ASES) score in the other[56]. Table 2 contains summary characteristics for these trials. The mean initial sample size was 52.4 (range 30-89), mean lost to follow up of 2.7 (range 0-9), while the mean final sample size was 49.7 (range 30-84). The mean Jadad scale score was 2.5 (range 1-3). Power analysis was only reported in 4 studies (26.7%).

The most common comparison was between ORPO with DCP and IMN, found in 8 studies (53.3%). ORPO with LCP vs IMN, MIPO vs IMN, and ORPO with DCP vs IMN were the comparison groups of 2 studies each (13.3% each), and 1 study (6.7%) compared ORPO with DCP and MIPO. All 15 studies evaluated both the outcomes of delayed union/nonunion and iatrogenic radial nerve palsy. The majority of studies also reported incidence for infection (14 studies, 93.3%), secondary surgeries (11 studies, 73.3%), and shoulder impingement (10 studies, 66.7%). Malunion was a reported outcome in 7 studies (46.7%), while only 4 studies (26.7%) reported the outcome of elbow stiffness.

The cumulative FI values for each outcome within each study are listed in Table 3 and presented graphically (Figure 2). The FI was found to be 0 for all individual outcomes except for iatrogenic nerve palsy in 1 out of 14 studies (higher rate with DCP compared with IMN), malunion in 1 of 7 studies (higher rate in IMN compared with LCP), shoulder impingement in 4 of 10 studies (higher rate in IMN compared with MIPO or DCP), elbow stiffness in 1 of 4 studies (higher rate in DCP compared with IMN), and secondary surgeries in 1 of 11 studies (higher rate with IMN compared with DCP). When totaling all complications for each study, the FI was >0 in 2 out of the 15 studies, with higher complication rates in IMN compared with MIPO or DCP. Overall, the FI was greater than 0 in only 9.8% (9/91) and was greater than the number lost to follow up in 2% (2/91) of outcomes studied.

The relationship between enrolled initial sample size and FI for all complications (Figure 3) was calculated using the Spearman correlation coefficient and was found to not be significant with a *P* value of 0.830. The majority of included RCTs reported continuous variable outcomes such as operative time,

Table 2 Summary characteristics of included randomized controlled trials

| Characteristic                | No.  | % or range |
|-------------------------------|------|------------|
| Initial sample size, mean No. | 52.4 | (30-89)    |
| Lost to follow up, mean No.   | 2.7  | (0-9)      |
| Final sample size, mean No.   | 49.7 | (30-84)    |
| Power analysis                | 4    | 26.7%      |
| Comparison groups             |      |            |
| ORPO (DCP) <i>vs</i> IMN      | 8    | 53.3%      |
| ORPO (LCP) <i>vs</i> IMN      | 2    | 13.3%      |
| MIPO <i>vs</i> IMN            | 2    | 13.3%      |
| ORPO (LCP) <i>vs</i> MIPO     | 2    | 13.3%      |
| ORPO (DCP) <i>vs</i> MIPO     | 1    | 6.7%       |
| Outcome assessed              |      |            |
| Delayed union/nonunion        | 15   | 100.0%     |
| Iatrogenic radial nerve palsy | 15   | 100.0%     |
| Infection                     | 14   | 93.3%      |
| Secondary surgeries           | 11   | 73.3%      |
| Shoulder impingement          | 10   | 66.7%      |
| Malunion                      | 7    | 46.7%      |
| Elbow stiffness               | 4    | 26.7%      |

ORPO: Open reduction and plate osteosynthesis; DCP: Dynamic compression plate; LCP: Locking compression plate; IMN: Intramedullary nail; MIPO: Minimally invasive plate osteosynthesis.

radiation exposure time, operative blood loss, length of hospital stay, time to union, and functional outcome scores such as the UCLA scoring system, Mayo elbow performance index, and the ASES score. The outcomes with reported differences between groups are summarized in [Table 4](#).

## DISCUSSION

Our systemic review looked at randomized control trials (RCTs) of the surgical treatment of humeral shaft fractures and discovered that the median FI for all outcomes was 0. In the studies with data leading to FI > 0, the FI exceeded the number lost to follow up in only two instances (2%): (1) Lower incidence of iatrogenic radial nerve palsy with IMN compared with ORPO[45]; and (2) Lower rate of overall total complication with ORPO compared with IMN[56]. Therefore, all evaluated outcomes (nonunion, radial nerve palsy, infections, malunion, malrotation, shoulder impingement, elbow stiffness, secondary surgeries, and overall complications) were extremely fragile and did not demonstrate superiority of one intervention (ORPO, MIPO, IMN) over another.

In analyzing all outcomes individually for humeral shaft fractures, the median FI was 0, and remained so when calculating median FI for all outcomes combined. This result is not surprising given the median FI ≤ 3 reported in the orthopaedic literature previously[36-40]. A recent study used FI to explore the literature on the treatment of clavicular fractures and found the median FI to be 2, with 46.7% of trials reporting the number of patients lost to follow-up exceeded the FI[40]. Sample sizes in an operative population are inherently lower. In addition, the cost, time, and resources required to complete RCTs with sufficiently large sample sizes often pose a significant challenge in orthopaedics, where the incidence of desired exposures and events can be low[18,58]. Simply increasing sample size alone, however, is not sufficient to guarantee increased FI values, as even very large sample size studies can still have fragile results if the between-group difference is very small[14].

While the FI was found to be > 0 in 9 outcomes total, the fact that the number lost to follow up exceeded the FI in 89/91 (98%) instances further confirms that those outcomes are quite fragile, and the significance of those conclusions should be called into question. When the number lost to follow up exceeds the FI this indicates that inclusion of the patients lost to follow up alone could have resulted in a nonsignificant *P* value. Kesemenli *et al*[45] reported significantly higher rate of iatrogenic radial nerve



**Table 3** Fragility index values for each outcome for included randomized controlled trials

| First author (last name) | Comparison         | Delayed union/ Nonunion | Iatrogenic radial nerve palsy | Infection | Malunion | Shoulder Impingement | Elbow Stiffness | All complications | Secondary surgeries |
|--------------------------|--------------------|-------------------------|-------------------------------|-----------|----------|----------------------|-----------------|-------------------|---------------------|
| Kim                      | ORPO (LCP) vs MIPO | 0                       | 0                             | 0         | 0        | NA                   | NA              | 0                 | 0                   |
| Esmailiejah              | ORPO (DCP) vs MIPO | 0                       | 0                             | 0         | 0        | NA                   | NA              | 0                 | 0                   |
| Fan                      | ORPO (LCP) vs IMN  | 0                       | 0                             | NA        | NA       | NA                   | NA              | 0                 | NA                  |
| Hadhoud                  | ORPO (LCP) vs MIPO | 0                       | 0                             | 0         | NA       | NA                   | NA              | 0                 | NA                  |
| Wali                     | ORPO (DCP) vs IMN  | 0                       | 0                             | 0         | NA       | 0                    | 0               | 0                 | 0                   |
| Benegas                  | MIPO vs IMN        | 0                       | 0                             | 0         | 0        | 0                    | NA              | 0                 | 0                   |
| Lian                     | MIPO vs IMN        | 0                       | 0                             | 0         | 0        | 1                    | 0               | 4                 | NA                  |
| Li                       | ORPO (LCP) vs IMN  | 0                       | 0                             | 0         | 2        | NA                   | NA              | 0                 | NA                  |
| Iqbal                    | ORPO (DCP) vs IMN  | 0                       | 0                             | 0         | NA       | 0                    | NA              | 0                 | 0                   |
| Singiseti                | ORPO (DCP) vs IMN  | 0                       | 0                             | 0         | NA       | 0                    | 0               | 0                 | 0                   |
| Putti                    | ORPO (DCP) vs IMN  | 0                       | 0                             | 0         | NA       | 0                    | NA              | 0                 | 0                   |
| Changulani               | ORPO (DCP) vs IMN  | 0                       | 0                             | 0         | NA       | 1                    | NA              | 0                 | 0                   |
| Kesemenli                | ORPO (DCP) vs IMN  | 0                       | 1                             | 0         | NA       | 0                    | NA              | 0                 | 0                   |
| McCormack                | ORPO (DCP) vs IMN  | 0                       | 0                             | 0         | 0        | 2                    | NA              | 6                 | 1                   |
| Chapman                  | ORPO (DCP) vs IMN  | 0                       | 0                             | 0         | 0        | 2                    | 1               | 0                 | 0                   |

ORPO: Open reduction and plate osteosynthesis; DCP: Dynamic compression plate; LCP: Locking compression plate; IMN: Intramedullary nail; MIPO: Minimally invasive plate osteosynthesis.

palsy among the DCP group compared with the IMN group. Of note, this study reported no patients lost to follow up. While this suggests a robust outcome, the fact remains that the other 14/15 studies showed no difference among treatment groups regarding iatrogenic radial nerve palsy. Regarding all complications combined, two studies[55,56] resulted in FI > 0, but the FI exceeded the number lost to follow up in only one[56].

The difference between treatment options may possibly be captured only by continuous variables, and not by dichotomous variables. There is precedence for this in the orthopaedic literature, as Bhandari *et al*[58] recommended that when orthopaedic surgeons anticipate small sample sizes they can optimize their study's statistical power by choosing a continuous outcome variable. In reviewing 76 orthopaedic RCTs, these authors found significantly greater study power in RCTs reporting continuous variables compared with studies reporting dichotomous variables ( $P = 0.042$ ), despite similar mean sample size in each group ( $P > 0.05$ ). The difference in treatment options for humeral shaft fractures, however, has been reported and analyzed by continuous variables previously. As summarized in this review in Table 4, the majority of included RCTs reported on continuous variable outcomes. The FI is not designed to evaluate continuous variables, and therefore all these continuous outcomes fell outside the scope of our review. As such, application of the FI does not add to the commentary favoring any one treatment over the others on the basis of these continuous variables.

Our study has potential weaknesses, with some inherent to the requirements of the FI. In order to calculate an FI, a study must compare 2 treatment arms, randomize patients to those arms in 1:1 ratio, and report dichotomous outcomes. These inclusion criteria limit both the number of studies that can be included for analysis, as well as the number of outcomes or results that can be analyzed from the included studies. Another requirement of the FI is that a study must be a prospective, randomized trial.

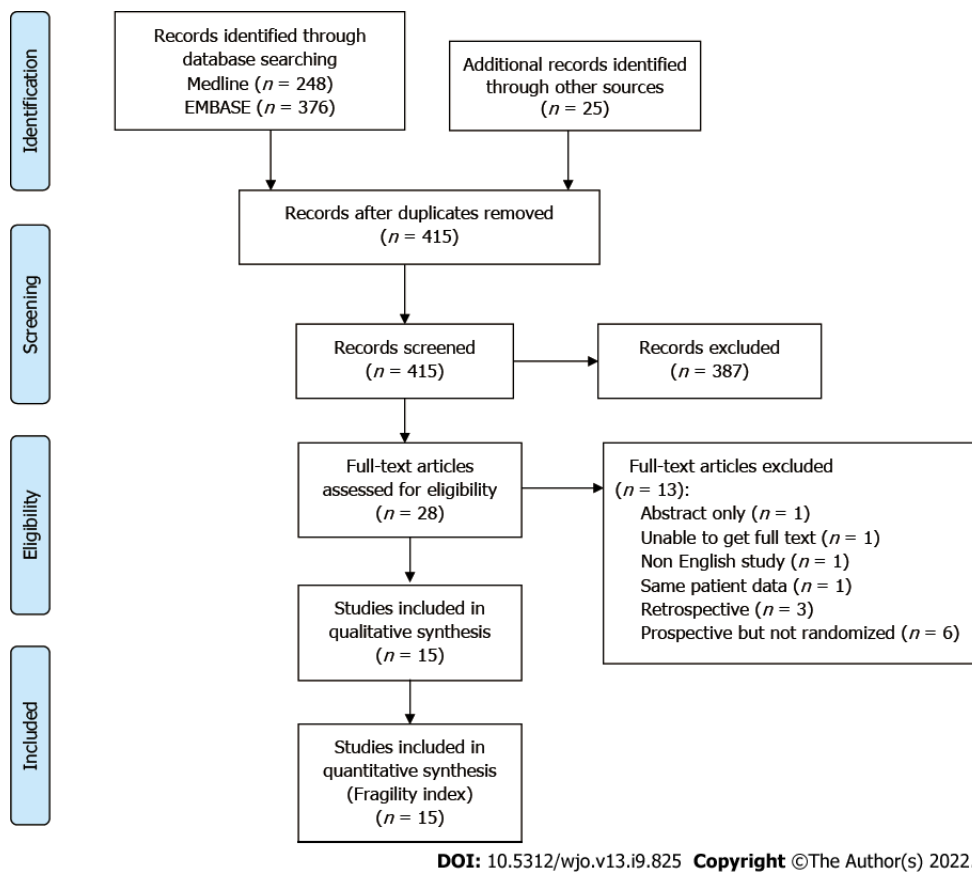


Figure 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of included studies.

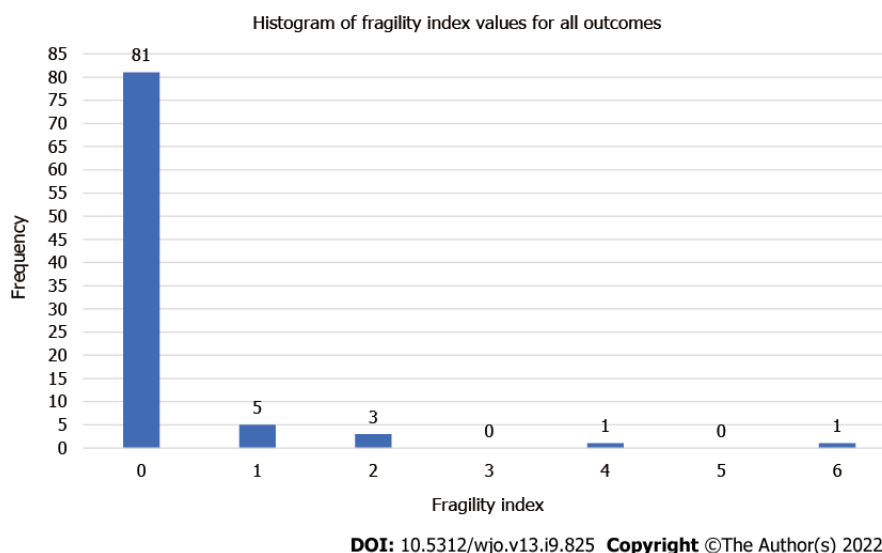


Figure 2 Distribution of fragility indices from all studies and for all outcomes.

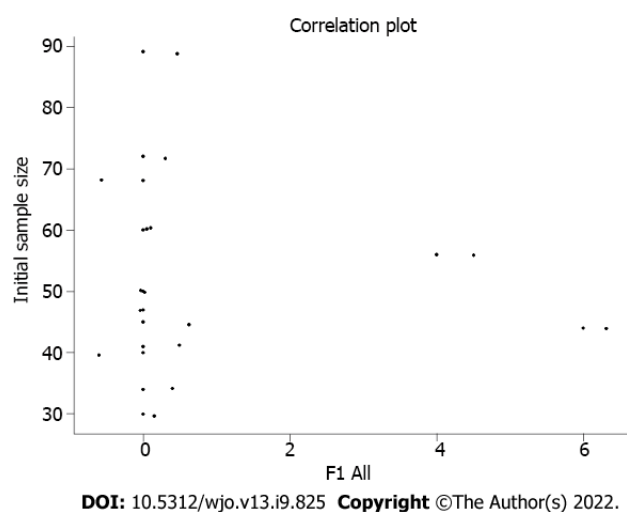
Due to this requirement, we excluded 3 retrospective studies and another 9 prospective studies that were not randomized. While this represents a loss in the number of included studies, and associated decrease in number of included patient outcomes, we do not feel this represents a significant loss as it means that the included studies represent the highest level of data availability.

Another potential weakness relates to the FI itself, which is not without inherent weakness or controversy. RCTs with small samples and in which the event of interest is rare, are common in orthopaedics and tend to be inherently fragile. The FI revolves around the statistical threshold of using  $P < 0.05$  as a strict criterion of correct inference. While this cutoff is necessary for making statistical determinations, the actual judging of the quality of inference is a complex activity with more nuance

**Table 4 Summary of outcomes with reported differences between groups**

| Continuous variable        | Superior treatment | Inferior treatment | First author (last name) |
|----------------------------|--------------------|--------------------|--------------------------|
| Time to union              | IMN                | ORPO               | Changulani               |
| Time to union              | IMN                | ORPO               | Fan                      |
| Operative time             | IMN                | ORPO               | Fan                      |
| Operative time             | IMN                | ORPO               | Wali                     |
| Operative time             | MIPO               | IMN                | Lian                     |
| Operative time             | MIPO               | ORPO               | Hadhoud                  |
| Intraoperative blood loss  | IMN                | ORPO               | Fan                      |
| Intraoperative blood loss  | IMN                | ORPO               | Wali                     |
| Intraoperative blood loss  | MIPO               | IMN                | Lian                     |
| Hospital stay              | IMN                | ORPO               | Fan                      |
| Hospital stay              | IMN                | ORPO               | Wali                     |
| Constant scores            | MIPO               | IMN                | Li                       |
| Rodriguez-Merchan criteria | DCP                | IMN                | Singiseti                |
| Shoulder ROM               | MIPO               | IMN                | Li                       |
| Shoulder ROM               | DCP                | IMN                | Chapman                  |
| Elbow ROM                  | IMN                | DCP                | Chapman                  |

ORPO: Open reduction and plate osteosynthesis; DCP: Dynamic compression plate; LCP: Locking compression plate; IMN: Intramedullary nail; MIPO: Minimally invasive plate osteosynthesis.

**Figure 3 Relationship between initial sample size and FI for all outcomes.**

than is afforded in having a *P* value slightly greater of less than 0.05[59]. The misinterpretation of statistical tests extends beyond just the FI[60].

## CONCLUSION

The FI represents a valuable tool that can aid in the interpretation of results from RCTs. Along with *P* value and confidence intervals, the FI provides a quantitative metric regarding the robustness of the reportedly significant results. In applying the FI to RCTs comparing surgical treatment options for humeral shaft fractures, this study has shown that there is a significant lack of robust data to recommend one treatment option over another on the basis of delayed union/nonunion, iatrogenic



radial nerve palsy, infection, malunion, shoulder impingement, elbow stiffness, or secondary surgeries. The results published in the literature for treatment of humeral shaft fractures should be interpreted cautiously. This study, while limited in the analysis of functional outcome, suggests no clear benefit of one surgical technique over another with respect to dichotomous outcomes. Plate and nail techniques should both be considered as options for surgical treatment of humeral shaft fractures.

## ARTICLE HIGHLIGHTS

### Research background

Humeral shaft fractures are a common injury which could be managed non-operatively or operatively. There is a lack of clear evidence to support open reduction internal fixation *vs* intramedullary nail fixation.

### Research motivation

Identify the fragility index, which identifies the number of patients have a change in outcome from a significant to non-significant. This is important as higher level studies guide management in orthopedics.

### Research objectives

Applying the fragility index to humeral shaft fractures will aid in clinical decision making on treatment of humeral shaft fractures.

### Research methods

A systematic review of randomized controlled trials (RCTs) evaluating the surgical treatment of humeral shaft fractures was conducted. The fragility index (FI) was calculated for total complications, each complication individually, and secondary surgeries using the Fisher exact test, as previously published.

### Research results

Fifteen RCTs were included in the analysis comparing open reduction plate osteosynthesis with dynamic compression plate or locking compression plate, intramedullary nail, and minimally invasive plate osteosynthesis. The median FI was 0 for all parameters analyzed. Regarding individual outcomes, the FI was 0 for 81/91 (89%) of outcomes. The FI exceeded the number lost to follow up in only 2/91 (2%) outcomes.

### Research conclusions

The FI shows that data from RCTs regarding operative treatment of humeral shaft fractures are fragile and does not demonstrate superiority of any particular surgical technique.

### Research perspectives

Further research is needed to delineate whether open reduction internal fixation or intramedullary nail fixation is superior in the management of humeral shaft fractures.

## FOOTNOTES

**Author contributions:** Morris SC is responsible for the data collection; Morris SC and Gowd AK analyze the data; Phipatanakul WP, Liu JN and Amin NH are responsible for the study conception; all authors participate in the manuscript preparation.

**Conflict-of-interest statement:** All authors report no relevant conflict of interest for this article.

**PRISMA 2009 Checklist statement:** The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

**Country/Territory of origin:** United States

**ORCID number:** Stephen Craig Morris 0000-0001-9462-7821; Anirudh K Gowd 0000-0001-7151-6459; Avinash Agarwalla 0000-0001-5056-6780; Wesley P Phipatanakul 0000-0002-5110-1931; Nirav H Amin 0000-0002-1862-4669; Joseph N Liu 0000-0002-3801-8885.

**S-Editor:** Wu YXJ

**L-Editor:** A

**P-Editor:** Wu YXJ

## REFERENCES

- 1 Attum B, Obremskey W. Treatment of Humeral Shaft Fractures: A Critical Analysis Review. *JBJS Rev* 2015; **3** [PMID: 27490668 DOI: 10.2106/JBJS.RVW.N.00119]
- 2 Updegrave GF, Mourad W, Abboud JA. Humeral shaft fractures. *J Shoulder Elbow Surg* 2018; **27**: e87-e97 [PMID: 29292035 DOI: 10.1016/j.jse.2017.10.028]
- 3 Walker M, Palumbo B, Badman B, Brooks J, Van Gelderen J, Mighell M. Humeral shaft fractures: a review. *J Shoulder Elbow Surg* 2011; **20**: 833-844 [PMID: 21393016 DOI: 10.1016/j.jse.2010.11.030]
- 4 Klenerman L. Fractures of the shaft of the humerus. *J Bone Joint Surg Br* 1966; **48**: 105-111 [DOI: 10.1302/0301-620X.48B1.105]
- 5 Sarmiento A, Zagorski JB, Zych GA, Latta LL, Capps CA. Functional bracing for the treatment of fractures of the humeral diaphysis. *J Bone Joint Surg Am* 2000; **82**: 478-486 [PMID: 10761938 DOI: 10.2106/00004623-200004000-00003]
- 6 Ouyang H, Xiong J, Xiang P, Cui Z, Chen L, Yu B. Plate versus intramedullary nail fixation in the treatment of humeral shaft fractures: an updated meta-analysis. *J Shoulder Elbow Surg* 2013; **22**: 387-395 [PMID: 22947239 DOI: 10.1016/j.jse.2012.06.007]
- 7 Gosler MW, Testroote M, Morrenhof JW, Janzing HM. Surgical versus non-surgical interventions for treating humeral shaft fractures in adults. *Cochrane Database Syst Rev* 2012; **1**: CD008832 [PMID: 22258990 DOI: 10.1002/14651858.CD008832.pub2]
- 8 Kurup H, Hossain M, Andrew JG. Dynamic compression plating versus locked intramedullary nailing for humeral shaft fractures in adults. *Cochrane Database Syst Rev* 2011; CD005959 [PMID: 21678350 DOI: 10.1002/14651858.CD005959.pub2]
- 9 Hu X, Xu S, Lu H, Chen B, Zhou X, He X, Dai J, Zhang Z, Gong S. Minimally invasive plate osteosynthesis vs conventional fixation techniques for surgically treated humeral shaft fractures: a meta-analysis. *J Orthop Surg Res* 2016; **11**: 59 [PMID: 27169580 DOI: 10.1186/s13018-016-0394-x]
- 10 Hohmann E, Glatt V, Tetsworth K. Minimally invasive plating versus either open reduction and plate fixation or intramedullary nailing of humeral shaft fractures: a systematic review and meta-analysis of randomized controlled trials. *J Shoulder Elbow Surg* 2016; **25**: 1634-1642 [PMID: 27522336 DOI: 10.1016/j.jse.2016.05.014]
- 11 Zhao Y, Wang J, Yao W, Cai Q, Wang Y, Yuan W, Gao S. Interventions for humeral shaft fractures: mixed treatment comparisons of clinical trials. *Osteoporos Int* 2017; **28**: 3229-3237 [PMID: 28780727 DOI: 10.1007/s00198-017-4174-1]
- 12 Zhao JG, Wang J, Meng XH, Zeng XT, Kan SL. Surgical interventions to treat humerus shaft fractures: A network meta-analysis of randomized controlled trials. *PLoS One* 2017; **12**: e0173634 [PMID: 28333947 DOI: 10.1371/journal.pone.0173634]
- 13 Qiu H, Wei Z, Liu Y, Dong J, Zhou X, Yin L, Zhang M, Lu M. A Bayesian network meta-analysis of three different surgical procedures for the treatment of humeral shaft fractures. *Medicine (Baltimore)* 2016; **95**: e5464 [PMID: 28002327 DOI: 10.1097/MD.00000000000005464]
- 14 Walsh M, Srinathan SK, McAuley DF, Mrkobrada M, Levine O, Ribic C, Molnar AO, Dattani ND, Burke A, Guyatt G, Thabane L, Walter SD, Pogue J, Devereaux PJ. The statistical significance of randomized controlled trial results is frequently fragile: a case for a Fragility Index. *J Clin Epidemiol* 2014; **67**: 622-628 [PMID: 24508144 DOI: 10.1016/j.jclinepi.2013.10.019]
- 15 Tignanelli CJ, Napolitano LM. The Fragility Index in Randomized Clinical Trials as a Means of Optimizing Patient Care. *JAMA Surg* 2019; **154**: 74-79 [PMID: 30422256 DOI: 10.1001/jamasurg.2018.4318]
- 16 Freedman KB, Back S, Bernstein J. Sample size and statistical power of randomised, controlled trials in orthopaedics. *J Bone Joint Surg Br* 2001; **83**: 397-402 [PMID: 11341427 DOI: 10.1302/0301-620x.83b3.10582]
- 17 Sabharwal S, Patel NK, Holloway I, Athanasiou T. Sample size calculations in orthopaedics randomised controlled trials: revisiting research practices. *Acta Orthop Belg* 2015; **81**: 115-122 [PMID: 26280864]
- 18 Abdullah L, Davis DE, Fabricant PD, Baldwin K, Namdari S. Is There Truly "No Significant Difference"? *J Bone Joint Surg Am* 2015; **97**: 2068-2073 [PMID: 26677241 DOI: 10.2106/JBJS.O.00012]
- 19 Mundi R, Chaudhry H, Mundi S, Godin K, Bhandari M. Design and execution of clinical trials in orthopaedic surgery. *Bone Joint Res* 2014; **3**: 161-168 [PMID: 24869465 DOI: 10.1302/2046-3758.35.2000280]
- 20 Dorey F. Statistics in brief: Interpretation and use of p values: all p values are not equal. *Clin Orthop Relat Res* 2011; **469**: 3259-3261 [PMID: 21918804 DOI: 10.1007/s11999-011-2053-1]
- 21 Porcher R. Reporting results of orthopaedic research: confidence intervals and p values. *Clin Orthop Relat Res* 2009; **467**: 2736-2737 [PMID: 19565303 DOI: 10.1007/s11999-009-0952-1]
- 22 Parisien RL, Trofa DP, Dashe J, Cronin PK, Curry EJ, Fu FH, Li X. Statistical Fragility and the Role of P Values in the Sports Medicine Literature. *J Am Acad Orthop Surg* 2019; **27**: e324-e329 [PMID: 30325880 DOI: 10.5435/JAAOS-D-17-00636]
- 23 Brown J, Lane A, Cooper C, Vassar M. The Results of Randomized Controlled Trials in Emergency Medicine Are Frequently Fragile. *Ann Emerg Med* 2019; **73**: 565-576 [PMID: 30551894 DOI: 10.1016/j.annemergmed.2018.10.037]

- 24 **Gnech M**, Lovatt CA, McGrath M, Rickard M, Sanger S, Lorenzo AJ, Braga LH. Quality of reporting and fragility index for randomized controlled trials in the vesicoureteral reflux literature: where do we stand? *J Pediatr Urol* 2019; **15**: 204-212 [PMID: 31060965 DOI: 10.1016/j.jpuro.2019.02.014]
- 25 **Grolleau F**, Collins GS, Smarandache A, Pirracchio R, Gakuba C, Boutron I, Busse JW, Devereaux PJ, Le Manach Y. The Fragility and Reliability of Conclusions of Anesthesia and Critical Care Randomized Trials With Statistically Significant Findings: A Systematic Review. *Crit Care Med* 2019; **47**: 456-462 [PMID: 30394920 DOI: 10.1097/CCM.00000000000003527]
- 26 **Matics TJ**, Khan N, Jani P, Kane JM. The Fragility of Statistically Significant Findings in Pediatric Critical Care Randomized Controlled Trials. *Pediatr Crit Care Med* 2019; **20**: e258-e262 [PMID: 31013262 DOI: 10.1097/PCC.0000000000001922]
- 27 **Matics TJ**, Khan N, Jani P, Kane JM. The Fragility Index in a Cohort of Pediatric Randomized Controlled Trials. *J Clin Med* 2017; **6** [PMID: 28805717 DOI: 10.3390/jcm6080079]
- 28 **Narayan VM**, Gandhi S, Chrouser K, Evaniew N, Dahm P. The fragility of statistically significant findings from randomised controlled trials in the urological literature. *BJU Int* 2018; **122**: 160-166 [PMID: 29569390 DOI: 10.1111/bju.14210]
- 29 **Noel CW**, McMullen C, Yao C, Monteiro E, Goldstein DP, Eskander A, de Almeida JR. The fragility of statistically significant findings from randomized trials in head and neck surgery. *Laryngoscope* 2018; **128**: 2094-2100 [PMID: 29683494 DOI: 10.1002/lary.27183]
- 30 **Ridgeon EE**, Young PJ, Bellomo R, Mucchetti M, Lembo R, Landoni G. The Fragility Index in Multicenter Randomized Controlled Critical Care Trials. *Crit Care Med* 2016; **44**: 1278-1284 [PMID: 26963326 DOI: 10.1097/CCM.0000000000001670]
- 31 **Sato K**, Toda T, Iwata A. Fragility Index in Randomized Controlled Trials of Ischemic Stroke. *J Stroke Cerebrovasc Dis* 2019; **28**: 1290-1294 [PMID: 30765294 DOI: 10.1016/j.jstrokecerebrovasdis.2019.01.015]
- 32 **Shen C**, Shamsudeen I, Farrokhyar F, Sabri K. Fragility of Results in Ophthalmology Randomized Controlled Trials: A Systematic Review. *Ophthalmology* 2018; **125**: 642-648 [PMID: 29241744 DOI: 10.1016/j.ophtha.2017.11.015]
- 33 **Skinner M**, Tritz D, Farahani C, Ross A, Hamilton T, Vassar M. The fragility of statistically significant results in otolaryngology randomized trials. *Am J Otolaryngol* 2019; **40**: 61-66 [PMID: 30472124 DOI: 10.1016/j.amjoto.2018.10.011]
- 34 **Wayant C**, Meyer C, Gupton R, Som M, Baker D, Vassar M. The Fragility Index in a Cohort of HIV/AIDS Randomized Controlled Trials. *J Gen Intern Med* 2019; **34**: 1236-1243 [PMID: 31037544 DOI: 10.1007/s11606-019-04928-5]
- 35 **Shen Y**, Cheng X, Zhang W. The fragility of randomized controlled trials in intracranial hemorrhage. *Neurosurg Rev* 2019; **42**: 9-14 [PMID: 28634832 DOI: 10.1007/s10143-017-0870-8]
- 36 **Evaniew N**, Files C, Smith C, Bhandari M, Ghert M, Walsh M, Devereaux PJ, Guyatt G. The fragility of statistically significant findings from randomized trials in spine surgery: a systematic survey. *Spine J* 2015; **15**: 2188-2197 [PMID: 26072464 DOI: 10.1016/j.spinee.2015.06.004]
- 37 **Khan M**, Evaniew N, Gichuru M, Habib A, Ayeni OR, Bedi A, Walsh M, Devereaux PJ, Bhandari M. The Fragility of Statistically Significant Findings From Randomized Trials in Sports Surgery: A Systematic Survey. *Am J Sports Med* 2017; **45**: 2164-2170 [PMID: 27895038 DOI: 10.1177/0363546516674469]
- 38 **Khormae S**, Choe J, Ruzbarsky JJ, Agarwal KN, Blanco JS, Doyle SM, Dodwell ER. The Fragility of Statistically Significant Results in Pediatric Orthopaedic Randomized Controlled Trials as Quantified by the Fragility Index: A Systematic Review. *J Pediatr Orthop* 2018; **38**: e418-e423 [PMID: 29979332 DOI: 10.1097/BPO.0000000000001201]
- 39 **Ruzbarsky JJ**, Khormae S, Daluiski A. The Fragility Index in Hand Surgery Randomized Controlled Trials. *J Hand Surg Am* 2019; **44**: 698.e1-698.e7 [PMID: 30420197 DOI: 10.1016/j.jhsa.2018.10.005]
- 40 **Ruzbarsky JJ**, Khormae S, Rauck RC, Warren RF. Fragility of randomized clinical trials of treatment of clavicular fractures. *J Shoulder Elbow Surg* 2019; **28**: 415-422 [PMID: 30771826 DOI: 10.1016/j.jse.2018.11.039]
- 41 **Panic N**, Leoncini E, de Belvis G, Ricciardi W, Boccia S. Evaluation of the endorsement of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement on the quality of published systematic review and meta-analyses. *PLoS One* 2013; **8**: e83138 [PMID: 24386151 DOI: 10.1371/journal.pone.0083138]
- 42 **Jadad AR**, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials* 1996; **17**: 1-12 [DOI: 10.1016/0197-2456(95)00134-4]
- 43 **Benegas E**, Ferreira Neto AA, Gracitelli ME, Malavolta EA, Assunção JH, Prada Fde S, Bolliger Neto R, Mattar R Jr. Shoulder function after surgical treatment of displaced fractures of the humeral shaft: a randomized trial comparing antegrade intramedullary nailing with minimally invasive plate osteosynthesis. *J Shoulder Elbow Surg* 2014; **23**: 767-774 [PMID: 24768221 DOI: 10.1016/j.jse.2014.02.010]
- 44 **Changulani M**, Jain UK, Keswani T. Comparison of the use of the humerus intramedullary nail and dynamic compression plate for the management of diaphyseal fractures of the humerus. A randomised controlled study. *Int Orthop* 2007; **31**: 391-395 [PMID: 16900354 DOI: 10.1007/s00264-006-0200-1]
- 45 **Kesemenli CC**, Subaşı M, Arslan H, Necmioğlu S, Kapukaya A. [Comparison between the results of intramedullary nailing and compression plate fixation in the treatment of humerus fractures]. *Acta Orthop Traumatol Turc* 2003; **37**: 120-125 [PMID: 12704250]
- 46 **Putti AB**, Uppin RB, Putti BB. Locked intramedullary nailing versus dynamic compression plating for humeral shaft fractures. *J Orthop Surg (Hong Kong)* 2009; **17**: 139-141 [PMID: 19721138 DOI: 10.1177/230949900901700202]
- 47 **Singiseti K**, Ambedkar M. Nailing versus plating in humerus shaft fractures: a prospective comparative study. *Int Orthop* 2010; **34**: 571-576 [PMID: 19506868 DOI: 10.1007/s00264-009-0813-2]
- 48 **Wali MG**, Baba AN, Latoo IA, Bhat NA, Baba OK, Sharma S. Internal fixation of shaft humerus fractures by dynamic compression plate or interlocking intramedullary nail: a prospective, randomised study. *Strategies Trauma Limb Reconstr* 2014; **9**: 133-140 [PMID: 25408496 DOI: 10.1007/s11751-014-0204-0]
- 49 **Hadhoud MM**, Darwish AE MM. Minimally invasive plate osteosynthesis vs open reduction and plate fixation of humeral

- shaft fractures. *Menoufia Med J* 2015; **28**: 154-161 [DOI: [10.4103/1110-2098.155974](https://doi.org/10.4103/1110-2098.155974)]
- 50 **Chapman JR**, Henley MB, Agel J, Benca PJ. Randomized prospective study of humeral shaft fracture fixation: intramedullary nails versus plates. *J Orthop Trauma* 2000; **14**: 162-166 [PMID: [10791665](https://pubmed.ncbi.nlm.nih.gov/10791665/) DOI: [10.1097/00005131-200003000-00002](https://doi.org/10.1097/00005131-200003000-00002)]
- 51 **Esmailieh AA**, Abbasian MR, Safdari F, Ashoori K. Treatment of Humeral Shaft Fractures: Minimally Invasive Plate Osteosynthesis Versus Open Reduction and Internal Fixation. *Trauma Mon* 2015; **20**: e26271 [PMID: [26543844](https://pubmed.ncbi.nlm.nih.gov/26543844/) DOI: [10.5812/traumamon.26271v2](https://doi.org/10.5812/traumamon.26271v2)]
- 52 **Fan Y**, Li YW, Zhang HB, Liu JF, Han XM, Chang X, Weng XS, Lin J, Zhang BZ. Management of Humeral Shaft Fractures With Intramedullary Interlocking Nail Versus Locking Compression Plate. *Orthopedics* 2015; **38**: e825-e829 [PMID: [26375542](https://pubmed.ncbi.nlm.nih.gov/26375542/) DOI: [10.3928/01477447-20150902-62](https://doi.org/10.3928/01477447-20150902-62)]
- 53 **Kim JW**, Oh CW, Byun YS, Kim JJ, Park KC. A prospective randomized study of operative treatment for noncomminuted humeral shaft fractures: conventional open plating versus minimal invasive plate osteosynthesis. *J Orthop Trauma* 2015; **29**: 189-194 [PMID: [25210833](https://pubmed.ncbi.nlm.nih.gov/25210833/) DOI: [10.1097/BOT.0000000000000232](https://doi.org/10.1097/BOT.0000000000000232)]
- 54 **Li Y**, Wang C, Wang M, Huang L, Huang Q. Postoperative malrotation of humeral shaft fracture after plating compared with intramedullary nailing. *J Shoulder Elbow Surg* 2011; **20**: 947-954 [PMID: [21440461](https://pubmed.ncbi.nlm.nih.gov/21440461/) DOI: [10.1016/j.jse.2010.12.016](https://doi.org/10.1016/j.jse.2010.12.016)]
- 55 **Lian K**, Wang L, Lin D, Chen Z. Minimally invasive plating osteosynthesis for mid-distal third humeral shaft fractures. *Orthopedics* 2013; **36**: e1025-e1032 [PMID: [23937748](https://pubmed.ncbi.nlm.nih.gov/23937748/) DOI: [10.3928/01477447-20130724-18](https://doi.org/10.3928/01477447-20130724-18)]
- 56 **McCormack RG**, Brien D, Buckley RE, McKee MD, Powell J, Schemitsch EH. Fixation of fractures of the shaft of the humerus by dynamic compression plate or intramedullary nail. A prospective, randomised trial. *J Bone Joint Surg Br* 2000; **82**: 336-339 [PMID: [10813165](https://pubmed.ncbi.nlm.nih.gov/10813165/) DOI: [10.1302/0301-620x.82b3.9675](https://doi.org/10.1302/0301-620x.82b3.9675)]
- 57 **Iqbal M**, Nawaz A, Mahmood T, Manzoor S, Siddiq AB. A Comparative Study of Treatment of Humeral Shaft Fractures using Interlocking Nail vs. AO Dynamic Compression Plate Fixation. *Ann KING EDWARD Med Univ* 2011; **17** [DOI: [10.21649/akemu.v22i1.793](https://doi.org/10.21649/akemu.v22i1.793)]
- 58 **Bhandari M**, Lochner H, Tornetta P 3rd. Effect of continuous versus dichotomous outcome variables on study power when sample sizes of orthopaedic randomized trials are small. *Arch Orthop Trauma Surg* 2002; **122**: 96-98 [PMID: [11880910](https://pubmed.ncbi.nlm.nih.gov/11880910/) DOI: [10.1007/s004020100347](https://doi.org/10.1007/s004020100347)]
- 59 **Andrade C**. The Use and Limitations of the Fragility Index in the Interpretation of Clinical Trial Findings. *J Clin Psychiatry* 2020; **81** [PMID: [32237291](https://pubmed.ncbi.nlm.nih.gov/32237291/) DOI: [10.4088/JCP.20f13334](https://doi.org/10.4088/JCP.20f13334)]
- 60 **Greenland S**, Senn SJ, Rothman KJ, Carlin JB, Poole C, Goodman SN, Altman DG. Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations. *Eur J Epidemiol* 2016; **31**: 337-350 [PMID: [27209009](https://pubmed.ncbi.nlm.nih.gov/27209009/) DOI: [10.1007/s10654-016-0149-3](https://doi.org/10.1007/s10654-016-0149-3)]



Published by **Baishideng Publishing Group Inc**  
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

**Help Desk:** <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

