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Review

The statistical fragility of outcomes in calcaneus fractures: A systematic review of randomized controlled trials

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ABSTRACT

Introduction: The purpose of this study was to utilize the fragility index to assess the robustness of randomized controlled trials (RCTs) evaluating the management of calcaneus fractures. We hypothesize that the dichotomous outcomes in calcaneus fracture literature will be statistically fragile and comparable to other orthopedic specialties.

Methods: We performed a PubMed search for calcaneus fracture RCTs from 2000 to 2022 using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The fragility index (FI) of each outcome was calculated through the reversal of a single outcome event until significance was reversed. The fragility quotient (FQ) was calculated by dividing each fragility index by study sample size. The interquartile range (IQR) was also calculated for the FI and FQ.

Results: Of the 3003 studies screened, 97 met the search criteria, with 19 RCTs evaluating calcaneus fractures included in the analysis. Seventy-nine dichotomous outcomes with 30 significant ($P < 0.05$) outcomes and 49 with nonsignificant ($P \geq 0.05$) outcomes were identified. The overall FI and FQ of all outcomes were 6 (IQR 3–8) and 0.067 (IQR 0.032–0.100), respectively.

Conclusions: The literature surrounding calcaneus fractures may not be as statistically stable as previously thought. The sole reliance on the *P* value may depict misleading results. We, therefore, recommend reporting the *P* value in conjunction with the FI and FQ to give a robust contextualization of clinical findings in the calcaneus fracture literature.

1. Introduction

Calcaneus fractures are the most commonly occurring fractures involving tarsal bones and are associated with high-energy mechanisms such as motor vehicle crashes [1]. Fractures of the calcaneus occur with an annual incidence of 11.5 per 100,000 person-years and involve the articular facet in two-thirds of all calcaneal fractures [2]. Calcaneus fractures comprise 1.2% of all fractures in the human body and 62.4% of all tarsal bone fractures in the foot [3]. These fractures were historically managed nonoperatively, but as surgical interventions advanced, operative management has become more prevalent. Nonoperative management of these fractures has been associated with arthritis, chronic heel

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deformity, and malalignment of the mechanical axis [4,5]. The surgical management of calcaneus fractures explores the use of an open reduction and internal fixation (ORIF) of the limb. Different surgical approaches include the lateral extensile incision which was first used and described by Zwipp and colleagues in 1989, the sinus tarsi approach which was originally described and used by Palmer in 1948, and the percutaneous approach [6–8]. However, research has shown mixed opinions regarding the optimal treatment of calcaneus fractures because of the inconclusive and contradicting findings surrounding operative or nonoperative management [9]. The lack of significant overall superiority in management across prospective randomized controlled trials has raised questions about a more optimal approach [10–12]. Some debate surrounding the surgical management reveals that minimally invasive approaches and percutaneous reduction and fixation methods are superior to open reduction methods minimizing soft-tissue complications [13].

Evidence-based medicine drives the treatment protocols and surgical indications for all fields of medicine and has always served as a guide for clinical decision-making. To ensure proper data-driven decisions, statistically significant findings from randomized controlled trials (RCTs) are utilized as the basis for treatment modalities and surgical management. These statistically significant findings are often presented with *P* values, where the null hypothesis (H_0) is rejected in favor of the alternate hypothesis (H_1). An arbitrary threshold is chosen most popularly with an alpha of 0.05. This threshold indicates that the observed difference holds a 5% probability that it is due to chance. While the *P* value has emerged consistently as a powerful statistical tool to evaluate outcomes in research, it fails to provide information concerning effect size, strength of association or applicability of a research outcome to a specific population [14]. In addition, the *P* value may not correlate with clinical significance and may be misinterpreted if the data sample has a substantial loss to follow-up lacks sufficient statistical power or contains confounding variables [15–18].

Feinstein in 1990 proposed the concept of the fragility index (FI) and developed it to address the limitations of the *P* value; the FI represents the number of event reversals required to change a study's significance [19]. The FI is calculated by the stepwise alteration of the outcome status of patients in one study arm until the recalculated *P* value changes from statistically significant ($P < 0.05$) to statistically nonsignificant ($P \geq 0.05$) or vice versa. A low FI indicates that the outcome is fragile, indicating that the outcome could be altered with a few events. Conversely, a large FI suggests a statistically robust outcome, suggesting that many events have to be altered to change its result. In addition, the fragility quotient (FQ), has also been applied to aid in understanding the

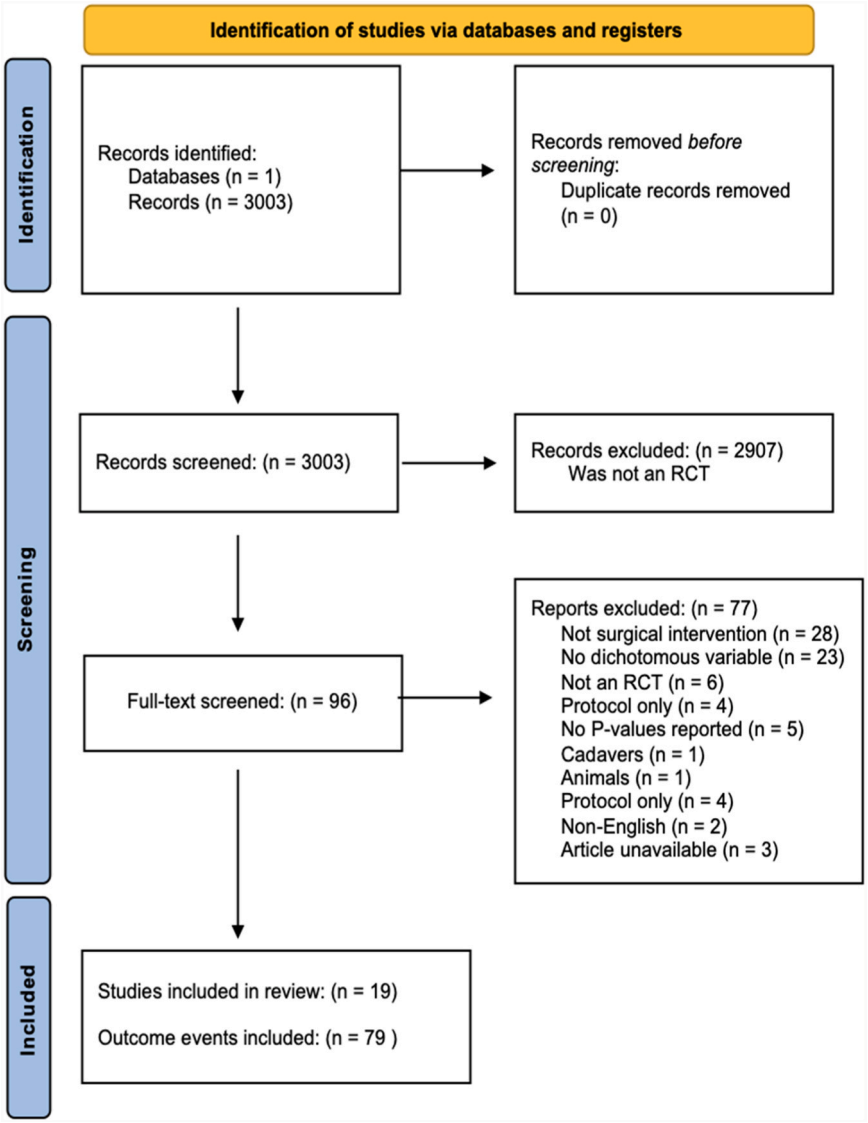

Fig. 1. PRISMA flow diagram of included studies.

FI. The FQ was first introduced by Ahmed et al., and has been used to determine the relative measure of fragility by dividing the FI by the study sample size [20]. In conjunction with *P* value analysis, the FI and FQ provides a more comprehensive interpretation of the trial fragility and robustness. Thus, studies that possess low susceptibility to fragility are stronger in conclusions than studies with high susceptibility to fragility allowing readers to critically evaluate the literature and make clinical decisions through evidence-based principles.

The purpose of the present study was to perform a fragility analysis utilizing the FI and FQ to evaluate the statistical strength of randomized controlled trials in calcaneus fracture literature. We hypothesized that dichotomous outcomes in calcaneus fracture literature will be statistically fragile and comparable to other orthopedic specialties.

2. Methods

2.1. Search strategy

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 1). The goal of the search was to identify articles examining calcaneus fracture management. The search ("calcaneus fractures" OR "calcaneal fractures") was conducted between 2000 and 2022. No filters were applied to maximize our search strategy. The included studies came from these orthopedic journals: *Journal of Foot and Ankle Surgery, Journal of Injury, Journal of Orthopedic Science, American Journal Translational Research, Journal of International Orthopedics, International Journal of Bone Trauma, Journal of Bone and Joint Surgery, International Journal of Foot and Ankle Surgery, Journal of Orthopedic Surgery, Journal of Orthopedic Surgery and Research, BMC Musculoskeletal Disorders, Acta Orthopedica, European Review for Medical and Pharmacological Sciences, Foot and Ankle International Journal* and *Journal of Orthopedic Trauma*.

2.2. Inclusion and exclusion criteria

Three independent authors (SS, EM, HM) screened each search result to determine if it met the inclusion and exclusion criteria. Each article was then examined, and studies were included if they included dichotomous data and reported associated *P* values on the surgical management of calcaneus fractures. Studies involving cadaveric, animal, and non-dichotomous data along with nonsurgical interventions, non-randomized controlled trials, protocols, and trials with more than 2 treatment arms were excluded from analysis.

2.3. Risk-of-bias assessment

Two authors (EM, SS) independently evaluated each study, and a Cochrane Risk bias of assessment was also performed for each of the individual studies (Fig. 2). Seven items were utilized to assess bias risk: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), complete outcome data (attrition bias), selective reporting (reporting bias) and other bias. A series of Cochrane signaling questions were applied to each article and a score was provided via the Cochrane algorithm, with each category scored as having a risk of bias that was low, high or unclear. Any conflicts or issues were resolved by a review of the article and the senior author (MM) made the final decision.

2.4. Data analysis

Multiple data points were recorded for each dichotomous outcome in a study: first author, PMID, journal title, year of publication, RCT, primary or secondary outcome measure, intervention, loss to follow-up, and *P* value. Outcomes were considered primary if they were explicitly stated as such or if they were reported within the abstract unless otherwise specified; all other outcomes were considered secondary. The reported *P* value was verified for accuracy using the 2-tailed Fisher exact test. Fragility analysis was performed by manipulating the reported outcome until a significant reversal was achieved. A *P* value of less than 0.05 was considered statistically significant. For outcomes with a *P* value of less than 0.05 no. of events required to raise the above significance was determined and for studies where outcomes with a *P* value above 0.05 no. of events required to lower the *P* value below 0.05 was calculated. The number of events needed to reverse the outcome was considered as the fragility index (FI) for the outcome (Table 1). This was applied to each outcome identified in the search and a median FI was calculated. The fragility quotient (FQ) of each outcome was calculated by dividing FI by the total sample size of each study and the median FQ was calculated. Interquartile ranges (IQR) ranges for both FI and FQ were calculated. The IQR was the difference between the 75th and the 25th percentiles. Fragility analysis was performed on the following subgroups: (1) primary versus secondary outcomes, (2) total complications, infection/wound complications, performance activities, (3) significant vs non-significant outcomes, and (4) studies published from 2000 to 2005, 2006–2011, 2012–2017, and 2017–2022 (Table 2).

3. Results

Of the 3003 studies screened, 97 met the search criteria with 19 randomized controlled trials (RCTs) included in the analysis (Fig. 1). There were a total 79 total outcome events with 30 significant ($P < 0.05$) outcomes and 49 with nonsignificant ($P \geq 0.05$) outcomes identified. For the 30 outcomes that were reported as significant, the median number of events required to change the significance was only 3 (IQR, 1–5.25) (Table 2) with an FQ of 0.027 (IQR, 0.013–0.040). For the 49 outcomes that were reported as nonsignificant, the number of events required to change significance was 8 (IQR, 6–11) with an FQ of 0.104 (IQR, 0.069–0.152). Therefore statistically significant outcomes were 62.5% more fragile than nonsignificant outcomes. A subanalysis evaluating infection/wound complications demonstrated a FI of 7 (IQR, 1.5–8) and an associated FQ of 0.098 (IQR, 0.020–0.122). Accounting for sample size, the FQ for infection/wound complications accounts for 9.8% of outcome events. Outcomes relating to performance activities (14 events) demonstrated a similar level of fragility of 7 (IQR, 4–11) and FQ of 0.019 (IQR, 0.009–0.040). In addition, total complications outcomes (11 events) demonstrated a FI of 3 (IQR, 2–14) and an FQ of 0.039 (IQR, 0.021–0.099). Further fragility subanalysis per year of publication identified a FI of 5.5 from 2000 to 2005, a FI of 12 from 2006 to 2011, a FI of 6 from 2012 to 2017, and a FI of 6.5 from 2017 to 2022 (Table 2).

The overall FI, incorporating 79 events from 19 RCTs was 6 (IQR, 3–8). The overall FQ was 0.067 (IQR, 0.032–0.100), indicating the reversal of only 6.7 patients of 100 is required to alter the significance of all studies when accounting for sample size. Of the 19 included studies, 36.8% (7) reported a loss to follow-up (LTF) greater than or equal to the overall FI of 6.

4. Discussion

In the present evaluation of RCTs regarding calcaneus fractures, the overall FI was 6 and the overall FQ was 0.067. An FI of 6 indicates that the reversal of an outcome of 6 patients would be enough to reverse significance and an FQ of 0.067 suggests that just 7 of 100 patients would be required to reverse significance across 79 events. For statistically significant outcomes, the FI and FQ were 3 and 0.027 respectively. Throughout the RCTs in the calcaneus fracture literature, there has been consistent FI between 5.5 and 6.5 over the 20-year period. However, low median FI and FQ demonstrate the calcaneus fracture literature to be more fragile than previously recognized thus confirming our hypothesis. This study, therefore, adds to the growing body of evidence that suggests the fragility of statistical significance and thus supports the inclusion of the FI and FQ into RCTs that guide clinical decision-making.

Fig. 2. Cochrane Risk of Bias Assessment.

Table 1
Demonstration of reversal of significance with a Fragility Index of 1.

	Outcome A	Outcome B	*P* value
Scenario 1			
Treatment A	3	22	
Treatment B	***9***	***13***	***0.04***
Scenario 2			
Treatment A	3	22	
Treatment B	***8***	**14**	***0.08***

Table 2
Fragility Data Based on Trial and Outcome Characteristics.

Characteristic	Events	Fragility Index (IQR)	Fragility Quotient (IQR)
All trials	79	6 (3–8)	0.067 (0.032–0.100)
Outcomes			
Total complications	11	3 (2–14)	0.039 (0.021–0.099)
Infection/wound complications	17	7 (1.5–8)	0.098 (0.020–0.122)
Performance activities	14	7 (4–11)	0.019 (0.009–0.040)
Reported *P* value			
$P < 0.05$	30	3 (1–5.25)	0.027 (0.013–0.040)
$P \geq 0.05$	49	8 (6–11)	0.104 (0.069–0.152)
Year of publication			
2000 – 2005	16	5.5 (4–10.75)	0.013 (0.009–0.023)
2006 – 2011	1	12	0.133
2012 – 2017	24	6 (2–9)	0.079 (0.021–0.109)
2017 – 2022	38	6.5 (4–10)	0.103 (0.056–0.159)

In this review evaluating calcaneus fractures, the overall FI for nonsignificant and significant findings was 8 and 3 respectively. These findings are consistent with the developing body of evidence within the orthopedic literature evaluating significance and fragility [21–33]. Megafu et al., in their evaluation of the fragility of dichotomous outcomes in distal radius fractures, found an overall FI of 9 and an FI of significant outcomes of 4 [21]. Megafu et al. applied a fragility analysis to distal femur fractures research and demonstrated a FI of 5 but an FI of 1 regarding significant outcomes [22]. Parisien et al. in the evaluation of cartilage restoration of the knee revealed a significant outcome FI of 3 [23]. Parisien et al. searched through the shoulder literature and reported an overall FI of 4 [24]. Parisien et al. reported an overall FI of 5 within the orthopedic trauma literature [25] and an FI of 4 in the platelet-rich plasma rotator cuff literature [26]. In the sports medicine literature, a fragility analysis applied to 339 outcomes revealed an FI of 5 [27]. A fragility analysis conducted across Achilles injury research [28] and hip arthroscopy [29] literature demonstrated an FI of 4 and 3.5 respectively. Fackler et al. examined single-row versus double-row anchoring techniques for rotator cuff repairs and revealed an FI of 2 [30]. Fackler et al. also applied a fragility analysis to Achilles tendon rupture regarding operative versus nonoperative techniques and reported an FI of 4 [31]. Constant et al. examined the patellofemoral instability research and reported an FI of 3 [32]. Lastly, a fragility analysis utilizing tourniquets in total knee arthroplasties revealed an FI of 4 [33]. Thus, our calculated FI within RCTs of calcaneus fractures is consistent with the results from the orthopedic literature and reveals the impact that statistically fragile results may have on clinical decision-making.

This paper is the first to analyze the fragility in calcaneus fracture literature and has many strengths related to the findings. This study was informed by the PRISMA guidelines to incorporate the inclusion of primary and secondary outcome measures, total complications, infections/wound complications, performance activities, significant *P* values, and nonsignificant *P* values. In addition, the exclusive use of RCTs adds to the robustness and validity of these findings making the application of the FI and FQ generalizable. Lastly, this review utilized a two-directional fragility analysis where the fragility index and the reverse fragility index were calculated for the calcaneus fracture literature, providing a comprehensive overview over the past 20 years. As with many fragility studies, limitations included the use of dichotomous RCTs, thus excluding many continuous outcomes. As such, many potential variables were left out of our analysis as many RCTs utilize continuous outcomes such as pain scales. Lastly, this study examined only surgical interventions for calcaneus fractures and narrowed our scope of view.

RCTs play a crucial role in furthering our knowledge base and improving clinical care delivery. Evidence from studies related to particular treatment is shared widely and clinicians are able to collectively work on standardizing treatments. This entire process is underpinned by objective data and therefore it is important to ensure both the data and the results are accessible and understandable. The *P* value has been considered the lynchpin for these studies. However, the utilization of the *P* value does not take into account sample size, or LTF data and can be malleable to study designs. This leaves findings susceptible to unintentional type I (alpha) errors. Thus, the *P* value should not be used as the only measure of effect but should be supplemented to aid in the interpretation of evidence, taking into account study design and methodological integrity. The American Academy of Orthopedic Surgeons (AAOS) reported that an FI of 2 published clinical guidelines for evaluating research and reported an FI of 2 to be consistent with "strong evidence" in support of the reported findings [34]. However, the analyses within orthopedic literature have been fragile. Countless authors have reported FI and FQ findings similar to the overall median FI and FQ of this paper [21–33]. Although there is an increase in research regarding the statistical fragility literature, there are no clear thresholds that indicate optimal FI and FQ. As this area of research further develops, researchers can look at combining other statistical tools like minimally clinically important difference, substantial clinical benefit, and patient-acceptable symptomatic state with recommended FI and FQ for statistically significant outcomes. The development of these new tools will take time; however, the inclusion of FI and FQ in the analysis of fragility in RCTs can provide clinicians with a more comprehensive and accurate understanding of the trial's significance and reported significant outcomes.

5. Conclusions

The peer-reviewed literature on calcaneus fractures may not be as statistically stable as previously thought. With the utilization of a *P* value of 0.05 indicating the cutoff for statistical significance, clinical decision-making cannot rely solely on this statistical tool as it has proven misleading. Therefore, we recommend the triple reporting of the *P* value along with the FI and FQ to provide a comprehensive understanding and interpretation of the statistical robustness in the calcaneus fracture literature.

Declaration of Competing Interest

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