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Fragility of randomized clinical trials of treatment of clavicular fractures

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Background: Statistical significance, as reported by the *P* value, has traditionally been the most commonly reported way to determine whether a difference exists between clinical interventions. Unfortunately, *P* values alone confer little about the robustness of a study's conclusions. An emerging metric, the fragility index (FI), helps to address this challenge by quantifying the number of events per outcome group that would need to be reversed to the alternative outcome in order to raise the *P* value above the 0.05 threshold.
Methods: Using systematic search strategy, we identified randomized controlled trials (RCTs) pertaining to clavicular fractures published in the last decade (2007-2017). Studies included for analysis involved 2 parallel arms, were published in English, allocated patients to treatment and control arms in a 1:1 ratio, and reported statistical significance ($P < .05$) for dichotomous variables. The FI was determined based on the Fisher exact test, using previously published methods.
Results: Fifteen RCTs were included. The median FI was 2 (range, 0-17). Eleven studies (73.3%) had an FI of 2 or less. Seven of the trials (46.7%) reported that the number of patients lost to follow-up exceeded the FI.
Conclusions: The median FI reported in the recent literature on clavicular fractures is only 2. The FI is a useful metric to analyze the robustness of study conclusions that should complement other methods of critical data evaluation, including the *P* value or effect sizes. Future efforts are needed to increase institutional collaboration and patient recruitment to strengthen the robustness of RCT conclusions, especially in the realm of clavicular fracture management.
Level of evidence: Level II; Systematic Review

Keywords: Evidence-based medicine; fragility index; clavicular fractures; randomized controlled trial; *P* value; dichotomous outcome variables

Several randomized controlled trials (RCTs) that focus on the management of clavicular fractures have recently been published, sparking controversy in appropriate management.[1,4,5,7-9,12,14-16,18,19,21,22,24] Adding further confusion are the myriad of fracture types and treatment modalities compared in such trials in addition to the "significant" findings or *P* values of <.05 reported in the results. Combining the factors of both significant findings and the gold standard of clinical study designs,[3] RCTs can strongly influence a reader's conclusions. Although RCTs are considered Level I evidence and *P* values are helpful for providing the probability of incorrectly rejecting the null hypothesis, these elements do not tell the whole story and are not enough to capture the

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robustness of a trial's conclusions nor do they represent methodological quality.

To address the challenge of conveying the robustness of a RCT's results, another metric, the fragility index (FI) has been described. The FI is calculated by sequentially exchanging events to nonevents or vice versa and recalculating the *P* value for each new scenario until the *P* value becomes >.05.[23] The FI can only be applied in situations of a statistically significant result of a dichotomous variable from a study containing 2 parallel arms in which patients are allocated equally to the treatment and control arms.

The FI has recently gained traction within the orthopedic surgery literature,[6,10] usually in the form of systematic reviews that summarize the range of FIs seen within RCTs published within each subspecialties' topics. Whether spine, sports, pediatrics, or hand surgery, the median FI has consistently been reported to have values from 1 to 3.[6,10,11] The trials included in these systematic reviews often contain small group sizes, and in many cases, the losses to follow-up exceed the FI by a substantial proportion. Such small-magnitude FIs are concerning because changing the results of just 1 to 3 patients in each of these instances would lead to a reversal of a study's conclusions. Given the recent proliferation of RCTs focusing on the management of clavicular fractures, coupled with their inconsistent results and conclusions, the primary aim of this study was to report the FI of these studies in an effort to provide more clarity to these data. We hypothesized that the median FI within the clavicular fracture literature will be ≤3, consistent with what has previously been reported throughout the orthopedic literature.

Materials and methods

A systematic search of the MEDLINE and Embase databases was performed. The Medical Subject Headings terms "clavicle," "collarbone," and "randomized controlled trials," along with synonymous keywords from January 1, 2007, to January 1, 2017, were queried. Appendix A outlines our exact search strategy. Two independent reviewers (J.J.R., S.K.) screened titles, abstracts, and manuscripts to identify RCTs containing parallel arms, allocating subjects in a 1:1 ratio to treatment or control groups,[20] published in English, and containing dichotomous primary or secondary outcome measures that reported a statistically significant result ($P < .05$). A third reviewer (R.C.R.) settled any discrepancies. If the FI could be calculated for multiple variables, the primary outcome variable was preferentially chosen, followed by the first reported secondary outcome variable.

For each included study, several variables were extracted: journal name, publication year, sample size for each arm, losses to follow-up for each arm, number of events for each arm, reported *P* value, randomization parameters (ie, allocation, concealment, randomization method, and type of analysis), type of outcome included in the analysis (primary or secondary), type of primary outcome, presence of a power analysis, confidence intervals of the variable of interest, and recalculated FI using the Fisher exact test. Risk of bias for each trial was assessed with the Cochrane Risk of Bias Tool by two separate reviewers (J.J.R., S.K.) (Fig. 1). Discrepancies were resolved by a third independent reviewer (R.C.R.).

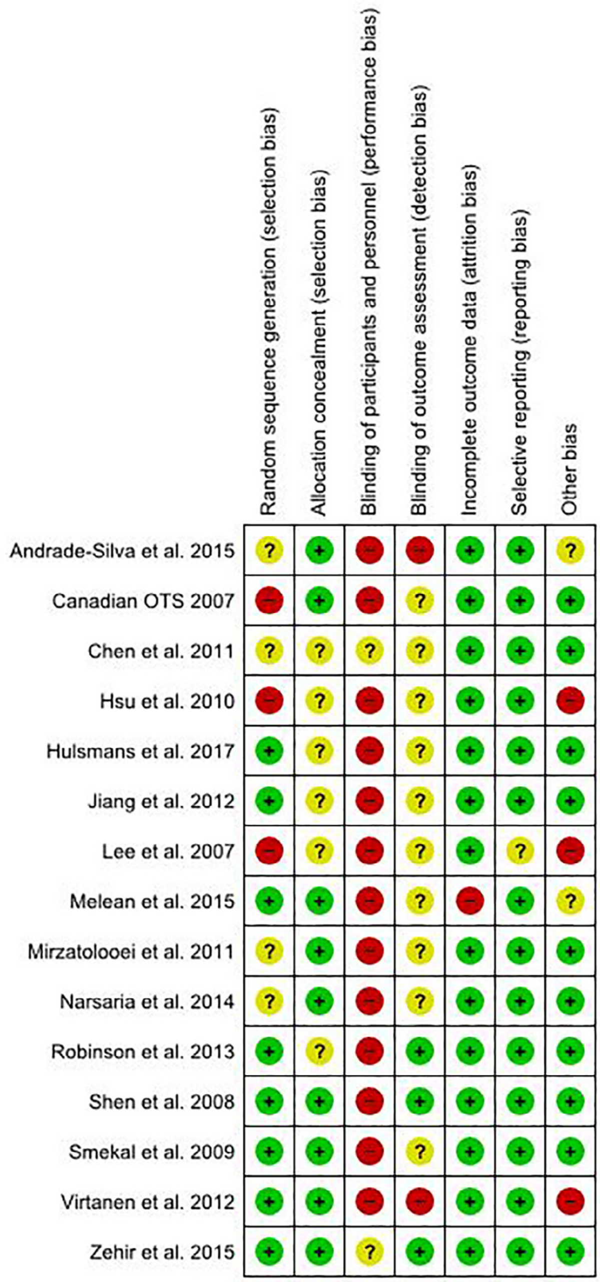

Figure 1 Risk of bias summary. (+), low risk; (–), high risk; (?), uncertain risk.

The FI for each study was calculated as described by Walsh et al[23] using the FI calculator found at http://clincalc.com/Stats/FragilityIndex.aspx. This free, publically accessible tool automates the process of calculating the FI, allowing for an easy, standardized calculation. After outcome proportions of both groups are entered, this calculator acts to incrementally convert 1 unit from the first outcome to the other dichotomous outcome sequentially until the *P* value, as calculated by the Fisher exact test, increases above .05 (Fig. 2).

This systematic review was performed and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. SPSS 22 software (2013; IBM,

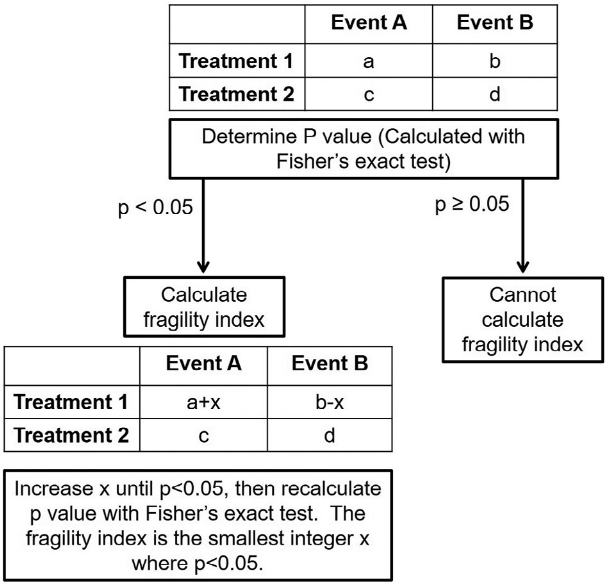

Figure 2 Calculation of the fragility index.

Armonk, NY, USA) was used to determine the Spearman correlation coefficient for the relationship between sample size and FI.

Results

Our search identified 481 unique articles for potential inclusion: 121 from MEDLINE and 478 from Embase, of which 15 met the inclusion criteria (Fig. 3, Table I).[1,4,5,7-9,12,14-16,18,19,21,22,24] Summary characteristics for these trials are presented in Table II. The mean trial size was 79.5 (range, 45-178) with a mean group size of 39 (range, 21-92), and the median FI was 2 (range 0-17; Fig. 4), affirming our hypothesis. In 9 of 15 (60%) of the included trials, a prestudy power analysis was not performed to determine sample size, and 9 trials did not specify the primary outcome measurement. Only 2 studies (13%) reported confidence intervals of the variable of interest. As reported in Table II, the outcome most commonly assessed for the FI calculation, found in 46.7% of the trials, was whether the operative intervention resulted in increased clavicular union. The second most commonly assessed outcome was patient satisfaction of appearance after surgical or nonsurgical treatment. Other outcome variables included proportion of malunions, symptomatic hardware/removal, complications, aesthetics, and subacromial erosion.

Metrics of the included trials are summarized in Table II. Fig. 5 demonstrates the relationship between sample size and FI. For this comparison, the Spearman correlation coefficient was 0.254, but this did not reach statistical significance ($P = .379$). Participant loss to follow-up was reported in 8 of 15 studies (53.3%), and the losses to follow-up in 7 of these studies (46.7%) exceeded their corresponding FIs.

The FIs in 4 publications were 0 (Fig. 4); meaning, that when a 2-sided Fisher exact test was applied to the reported numbers from the trial, the calculated P value was >.05. Zehir et al[24] reported the rate of cosmetic dissatisfaction as a secondary outcome for the treatment of midshaft clavicular fractures with an intramedullary pin vs. open reduction internal fixation (ORIF). In the group undergoing intramedullary pinning, 4 of 24 patients were dissatisfied with the appearance; whereas, 9 of 21 patients undergoing ORIF were dissatisfied. The authors reported a P value of .05 for this comparison. They reported in their statistical analysis that "categorical data were compared using chi square test or Fisher exact test where appropriate"; however, when the P value for these proportions is recalculated using the Fisher exact test, which is the more appropriate test in instances when one of the groups contains ≤5 items,[13] the value is .098.

In the second study, Narsaria et al[16] reported the rate of hypertrophic scarring as one of their secondary outcomes for the treatment of midshaft clavicular fractures with an elastic intramedullary nail vs. precontoured plate. In the group undergoing elastic intramedullary nail, 4 of 32 patients developed a hypertrophic scar; whereas, none of the 32 patients undergoing ORIF developed this complication. The authors reported a P value of .04 for this comparison. Unfortunately, they did not report the type of statistical test that was performed. When the P value for these proportions is calculated using the Fisher exact test, "significance" is lost with a P value of .053.

Jiang et al[9] reported that the rate of satisfaction with appearance when comparing minimally invasive to standard ORIF of midshaft clavicular fractures was significantly greater for the minimally invasive cohort (30 of 32 patients vs. 25 of 32 patients). They reported that the χ^2 test was used to compare these 2 groups. When the more appropriate Fisher exact test is used,[13] the new calculated P value is .148.

Finally, the fourth study with an FI of 0 is from Smekal et al,[21] who reported the rate of delayed unions in 30 patients treated operatively with an intramedullary implant vs. 30 patients treated nonoperatively. Delayed union occurred in 1 patient in the operative group and in 6 in the nonoperative group. For this comparison, the authors reported a P value of .02 when the χ^2 test was used for the analysis. Recalculating this comparison using Fisher exact test again leads to a reversal of significance with a $P = .103$.

Discussion

The median FI for RCTs focusing on the treatment of clavicular fractures is 2. In other words, if 2 participants exhibited a change in their results, the findings would no longer have a P value of <.05 and would not be reported as "significant." Furthermore, nearly 60% of the trials included did not perform a power analysis to determine sample size or name a primary outcome variable, a significant methodological flaw undermining the findings.

The FI value of 2 reported in this systematic review remains consistent with other reports within orthopedics, with all studies thus far citing median FIs of ≤3.[6,10,11] Although most of the

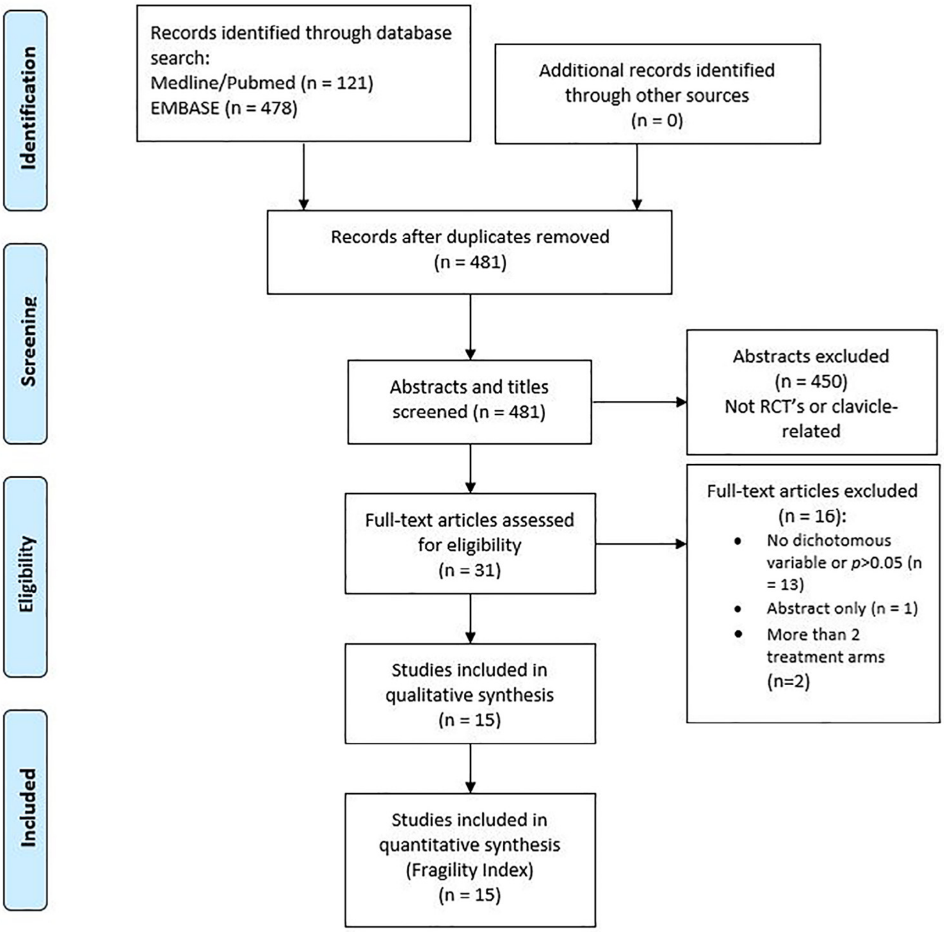

Figure 3 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of included studies. *RCT*, randomized controlled trial.

aforementioned literature was focused on RCTs that were published within an entire orthopedic subspecialty, this study differs in its specific, problem-focused clinical context. Understanding the median FI for this narrow context can provide a clinician with better sense of the robustness of evidence for a specific clinical setting, which is more useful than broad subspecialty reporting.

The topic of clavicular fracture management is especially pertinent to FI reporting. Although almost all of these fractures heal with low complication rates and high patient satisfaction, the method of treatment, whether nonoperative vs. operative, or even regarding the type of operative management (single plate, dual plate, intramedullary nail, etc) for most varieties of these fractures remains controversial.

In an effort to influence evidence-based decision making on this process, a series of RCTs[1,4,5,7-9,12,14-16,18,19,21,22,24] were recently published and gained widespread attention. Given our results, the FI can be helpful not only for interpreting the findings of each individual study's findings but also for providing evidence, when examining the topic on the whole, that the need remains for further high-quality investigation into this topic. For example, most of the included studies have a fragility index of 2 or less, in other words, reversing the outcomes of just 2 patients has the potential to neutralize the reported "statistical significance" of that outcome; however, given that 9 of the 15 included studies did not report a prestudy power analysis, it is likely that the low overall FI is a reflection of methodologic quality rather than clinical variations seen in clavicle fractures that are difficult to control.[22]

This study has several weaknesses, most originating from the inherent limitations of calculating the FI. Some of these requirements, including dichotomous outcome variables and *P* values of <.05, act to limit the breadth of studies that can be included in this type of analysis. As can be seen in Fig. 3, 13 of 16 studies were excluded due to these requirements alone. An additional consequence of these requirements is that many of the primary outcomes were eliminated, which resulted in an analysis of secondary outcomes in nearly one-third of the RCTs.

Another potential limitation includes the constraints of reports published in the prior 10-year period or those published in the English language. Given the median FI of 2, a value consistent to other reports within the orthopedic literature, expanding the search to include more years or other

Table I Included randomized controlled trials with characteristics

Authors	Pub. year	Journal name	Type of comparison	Outcome assessed	Primary outcome (category of variable)	Reported relative risk (95% CI)
Hulsmans et al.[8]	2017	CORR	IMN vs. Plate	NA	Unspecified	0.61 (0.5-0.8)
Andrade-Silva et al.[1]	2015	JBJS	IMN vs. superior plate	Secondary	DASH (continuous)	NA
Melean et al.[14]	2015	JSES	Conservative vs. surgical	NA	Unspecified	NA
Zehir et al.[24]	2015	Arch Orthop Trauma Surg	IMN vs. Plate	Secondary	*Quick*DASH (continuous)	NA
Narsaria et al.[16]	2014	J Orthop Traumat	Plate vs. elastic nail	NA	unspecified	NA
Robinson et al.[18]	2013	JBJS	Non-op vs. ORIF	Primary	Union (binary)	0.07 (0.01-0.5)
Jiang et al.[9]	2012	Ortho Traumatol Surg Res	Minimally invasive percutaneous plate vs. ORIF	NA	Unspecified	NA
Virtanen et al.[22]	2012	JBJS	Sling vs. ORIF	Secondary	Constant and DASH (continuous)	NA
Chen et al.[5]	2011	Chinese J Trauma	Elastic nailing vs. Sling	NA	Unspecified	NA
Mirzatolooei et al.[15]	2011	Acta Ortho Traumaol Turc	Non-op vs. operative	NA	Unspecified	NA
Hsu et al.[7]	2010	Orthopedics	Tension band vs. hook plate	NA	Unspecified	NA
Smekal et al.[21]	2009	JOT	Elastic IMN vs. non-op	NA	Unspecified	NA
Shen et al.[19]	2008	Bone Joint J	3D plate vs. superior plate	NA	Unspecified	NA
Lee et al.[12]	2007	Orthopedics	Knowles pin vs. plate	Secondary	Constant score (continuous)	NA
Canadian OTS[4]	2007	JBJS	Non-op vs. Plate	Secondary	DASH (continuous)	NA

Authors	Power analysis	Specific outcome assessed	Patients enrolled (No.)	Patients lost to follow-up (No.)	Risk of bias	Fragility index
Hulsmans et al.[8]	No	Implant removal	118	4	L	9
Andrade-Silva et al.[1]	Yes	Minor complications	54	5	L	1
Melean et al.[14]	No	Fracture healing at 12 weeks	76	NA	U	17
Zehir et al.[24]	Yes	Cosmetic dissatisfaction	45	0	L	0
Narsaria et al.[16]	No	Hypertrophic scar	66	0	L	0
Robinson et al.[18]	Yes	Nonunion	178	22	L	6
Jiang et al.[9]	No	Satisfaction with appearance	64	0	H	0
Virtanen et al.[22]	Yes	Union	51	9	U	2
Chen et al.[5]	No	Delayed or nonunion	60	0	L	2
Mirzatolooei et al.[15]	Yes	Malunion	50	10	H	7
Hsu et al.[7]	No	Subacromial erosion	65	0	L	2
Smekal et al.[21]	No	Delayed union	60	8	H	0
Shen et al.[19]	No	Delayed union	133	0	L	1
Lee et al.[12]	No	Symptomatic hardware	62	7	L	2
Canadian OTS[4]	Yes	Nonunion	111	15	L	1

CI, confidence interval; *CORR*, Clinical Orthopedics and Related Research; *IMN*, Intramedullary nail; *NA*, not available; *L*, low; *JBJS*, Journal of Bone and Joint Surgery; *DASH*, Disabilities of the Arm, Shoulder and Hand; *JSES*, Journal of Shoulder and Elbow Surgery; *U*, uncertain; Quick*DASH*, 11-item version of the Disabilities of the Arm, Shoulder and Hand; *H*, high; *JOT*, Journal of Orthopaedic Trauma; *ORIF*, open reduction internal fixation.

Table II Summary characteristics of included randomized controlled trials

Characteristic	No. (% or range)
Reported *P* value	
.01-.05	10 (66.7)
≤.01	5 (33.3)
Included outcome	
Unspecified	9 (60)
Primary	1 (6.7)
Secondary	5 (33.3)
Patients in study, mean No.	79.5 (45-178)
Fragility index, median	2 (0-17)
Patients lost to follow-up, mean No.	5.7 (0-22)
Outcome assessed	
Delayed/nonunion	7 (46.7)
Malunion	1 (6.7)
Symptomatic hardware or removal	2 (13.3)
Complications	1 (6.7)
Aesthetics	3 (20)
Subacromial erosion	1 (6.7)

languages would not likely have significantly affected this study's findings.

A cursory analysis of why the FIs reported in these studies tended to be of small magnitude reveals the obvious point: the mean group size of the included RCTs is only 39 patients. Although the positive correlation between total sample size and FI in this study was not found to be statistically significant, a positive relationship has been demonstrated in multiple prior systematic reviews,[6,11,17,23] and it is likely that larger RCTs do result in more robust findings.

Unfortunately, the costly and resource-consuming nature of performing a surgically based RCT certainly limits the ability to execute large clinical trials. As a result, the limited number of small RCTs reporting fragile yet statistically significant results is hazardous,[2] because it may disproportionately influence large-scale clinical decision making. This scenario demonstrates why the FI is extremely useful, especially when confidence intervals are sparingly reported, as in this series, where only 13% of trials reported confidence intervals of the variable of interest.

Conclusion

In addition to *P* values, confidence intervals, and effect sizes, the FI should be a part of the reader's systematic approach to interpreting the results and conclusions of every RCT. In reporting some of the methodological flaws, including a frequent lack of a power analyses in addition to the low median FI in clavicular fracture RCTs, a goal of this report is to provide a sense of the robustness of evidence in this specific clinical context and also to increase awareness of the need for improving study designs for orthopedic clinical trials. In addition to opting for other well-performed study designs when a RCT is not feasible, larger sample sizes aided by better funded studies and multicenter collaboration have the potential to increase FIs, ultimately providing stronger conclusions and better guidance to clinical care.

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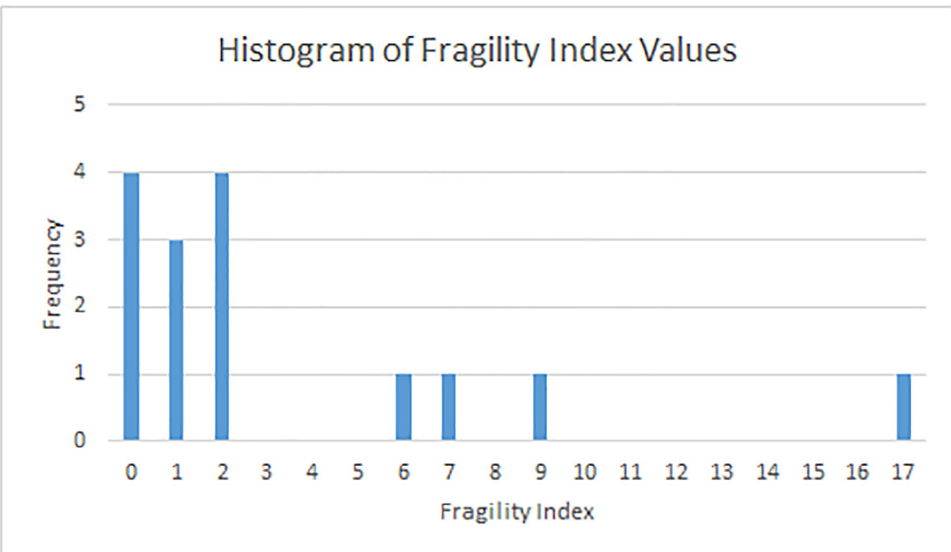

Figure 4 Distribution of the fragility indices.

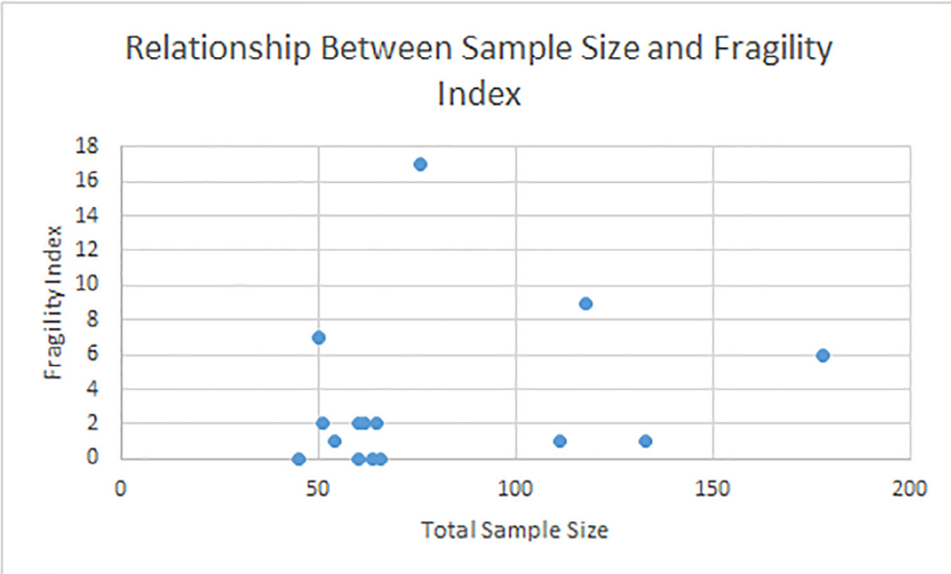

Figure 5 Relationship between sample size and the fragility index.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jse.2018.11.039

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