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The Reverse Fragility Index: Interpreting the Current Literature on Long-Term Survivorship of Computer-Navigated Versus Conventional TKA

A Systematic Review and Cross-Sectional Study of Randomized Controlled Trials

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Background: Despite the most recent American Academy of Orthopaedic Surgeons clinical practice guideline making a "strong" recommendation against the use of intraoperative navigation in total knee arthroplasty (TKA), its use is increasing. We utilized the concept of the reverse fragility index (RFI) to assess the strength of neutrality of the randomized controlled trials (RCTs) comparing the long-term survivorship of computer-navigated and conventional TKA.

Methods: A systematic review was performed including all RCTs through August 3, 2021, comparing the long-term outcomes of computer-navigated and conventional TKA. Randomized trials with mean follow-up of >8 years and survivorship with revision as the end point were included. The RFI quantifies the strength of a study's neutrality by calculating the minimum number of events necessary to flip the result from nonsignificant to significant. The RFI at a threshold of $p < 0.05$ was calculated for each study reporting nonsignificant results. The reverse fragility quotient (RFQ) was calculated by dividing the RFI by the study sample size.

Results: Ten clinical trials with 2,518 patients and 38 all-cause revisions were analyzed. All 10 studies reported nonsignificant results. The median RFI at the $p < 0.05$ threshold was 4, meaning that a median of 4 events would be needed to change the results from nonsignificant to significant. The median RFQ was 0.029, indicating that the nonsignificance of the results was contingent on only 2.9 events per 100 participants. The median loss to follow-up was 27 patients. In all studies, the number of patients lost to follow-up was greater than the RFI.

Conclusions: The equipoise in long-term survivorship between computer-navigated and conventional TKA rests on fragile studies, as their statistical nonsignificance could be reversed by changing the outcome status of only a handful of patients—a number that was always smaller than the number lost to follow-up. Routine reporting of the RFI in trials with nonsignificant findings may provide readers with a measure of confidence in the neutrality of the results.

Level of Evidence: Prognostic Level II. See Instructions for Authors for a complete description of levels of evidence.

The p value threshold of $p < 0.05$ is the primary tool utilized to determine significance in the scientific literature[1-3]. However, interpreting the clinical relevance of a study can be difficult, especially if the result is just above or below the $p < 0.05$ threshold[3-5]. Reliance on this threshold can be especially problematic in randomized controlled trials; because of the expensive and time-intensive nature of such a study design, they generally have smaller sample sizes and low event rates (relative to larger retrospective or registry studies), which may predispose them to a type-II error (false-negative result)[3-5]. In fact, assuming an alpha of 0.05 and a power of 80%, randomized trials are more likely to obtain a false-negative result than a false-positive one. Therefore, evaluating the strength of neutrality of studies reporting nonsignificant

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results should be considered, especially in instances where the consequences of a false-negative result are just as impactful as those of a false-positive result or more so[3].

While the fragility index (FI) has been extensively used to evaluate the robustness of significant results, only recently has the reverse fragility index (RFI), the number of events necessary to flip the results from nonsignificant to significant, been introduced as a way to evaluate the strength of neutrality of null trial results[3]. Applying the RFI to orthopaedic literature reporting nonsignificant results may help readers to better understand subtle nuances in the data, which are often overlooked in the traditionally black-and-white interpretation of the p value[3,6-8].

To our knowledge, there have been no studies that applied the RFI to compare the long-term survivorship of computer-navigated and conventional total knee arthroplasty (TKA). The most recent American Academy of Orthopaedic Surgeons (AAOS) clinical practice guideline states that there is “strong” evidence against using intraoperative navigation in TKA because of a lack of observed differences in outcomes or complications compared with conventional methods[9]. This is supported by multiple randomized trials suggesting that there may be no significant long-term differences in survivorship between the 2 techniques[10-12]. Despite these recommendations, the utilization of computer-navigated TKA continues to increase[13]. Given this trend, a critical appraisal of the available evidence regarding this topic is imperative[14]. Therefore, we utilized the concept of the RFI to assess the strength of neutrality of the randomized controlled trials (RCTs) comparing the survivorship of computer-navigated and conventional TKA. We hypothesized that the findings of these studies would be fragile.

Materials and Methods

This systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement guidelines and included RCTs published in all journals through August 3, 2021 comparing the long-term outcomes of computer-navigated and conventional TKA methods. We queried the MEDLINE, Embase, and Cochrane Library online databases. The following keywords were used as search terms: “total knee arthroplasty,” “conventional,” “computer-navigated,” “computer-assisted,” and “survivorship.” We composed a list of articles and removed duplicates. We also reviewed the reference lists of relevant papers to identify other papers that were not found in our database searches.

Two reviewers (J.L.S., M.A.M.) independently examined the title and abstract of each potentially relevant article and selected those to be used in our study based on the following inclusion and exclusion criteria. Any discrepancies were arbitrated by a third author (M.J.S.). Inclusion criteria were (1) an RCT design, (2) mean follow-up of >8 years, and (3) implant survivorship with a binary end point of revision as an outcome. For this study, all-cause revision was the primary end point used to determine implant survivorship. A follow-up period of ≥8 years was chosen based on a recent meta-analysis published on this topic[12].

The 2 reviewers extracted data from the 10 included studies, including the names of the authors, year of publication, journal, sample size for each arm of the trial, implant and navigation systems used, mean follow-up, revision rate, and loss to follow-up of each study.

Statistical Analysis

The RFI was calculated by manipulating the reported outcome events in a 2 × 2 contingency table, while maintaining a constant number of participants, until significance was achieved[3]. The RFI was calculated for each TKA method, with the lowest RFI of the 2 groups used as the reported RFI of the study. In other words, the RFI was defined as the lowest number of event reversals needed to decrease p to <0.05[3]. Significance was defined using the $p < 0.05$ threshold and was calculated using the chi-square test or 2-tailed Fisher exact test, as appropriate. If events in 1 group reached 0 prior to reaching significance, the data were manipulated by adding events in the other group, while subtracting nonevents from that same group to keep the total number of participants constant, until significance was achieved. This is demonstrated in the example in Figure 1.

The reverse fragility quotient (RFQ) for each study was calculated by dividing the RFI by the sample size for that study[3]. One participant was defined as 1 knee, as some studies involved bilateral procedures (with 1 knee treated using each method). Loss to follow-up was compared with the RFI for each study, and it was noted whether the loss to follow-up exceeded the RFI. Deaths, when reported, were treated as a loss to follow-up. All analyses were performed with GraphPad Prism (version 9.2.0) and Microsoft Excel (version 16.54). A meta-analysis was not

	Revision	No Revision
CAN	0	41
Conv	2	38
P value		.24

	Revision	No Revision
CAN	0	41
Conv	5	35
P value		.03

Fig. 1
Reversal of significance in an example in which the number of outcome events in 1 group is zero. The reverse fragility index (RFI) is 3. This was calculated by adding outcome events to the other group, while subtracting nonevents from that same group to keep the number of participants constant, until significance is achieved. CAN = computer-navigated TKA, Conv = conventional total knee arthroplasty.

performed because fragility and RFIs are traditionally reported on an individual study basis. However, we also report the median RFI, RFQ, and loss to follow-up (with interquartile ranges [IQRs]) in order to provide an overall assessment of the results. Notably, while the fragility of a study with a significant result is defined as the minimum number of patients whose outcome would need to change in order to convert the result to a nonsignificant finding, the RFI is defined as the number of events that would need to change status in order to flip a nonsignificant result to a significant one. Furthermore, "strength of neutrality" was defined as the degree of confidence that one has in the nonsignificance of the result.

Source of Funding

No external funding was received for this study.

Results

Of the 1,459 studies that were initially screened, 10 RCTs were ultimately included for analysis after screening and application of the eligibility criteria[15-24] (Fig. 2). Table I summarizes the characteristics of each included study. Table II shows the number of revision events for each TKA method and the RFI, RFQ, and loss to follow-up in each study. All 10 RCTs reported a nonsignificant difference in TKA revision rates between groups and used $p < 0.05$ as the threshold for significance.

A total of 2,518 participants and 38 all-cause revisions were analyzed. The sample size ranged from 61 to 1,040. The median follow-up time was 10.9 years (IQR, 10.33 to 11.75 years). The median RFI was 4 (IQR, 3 to 5.75). The lowest RFI was for computer-navigated TKA in 6 trials, conventional TKA in 1 trial, and neither method in 3 trials. The median RFQ was 0.029 (IQR, 0.013 to 0.053), meaning that the nonsignificance of the results was contingent on 2.9 events per 100 participants. The RFQ for each study is illustrated in Figure 3. The median number of participants lost to follow-up was 27 (IQR, 10 to 33.5). In all studies, the loss to follow-up was larger than the RFI. The sample size, loss to follow-up, and RFI in each study are compared in Figure 4. Deaths were reported in 6 studies: Cip et al.[15] (67), Kim et al.[17] (5), Kim et al.[18] (3), Kim et al.[19] (3), Ollivier et al.[21] (7), and Hsu et al.[24] (4). Even when deaths were not considered as loss to follow-up, 8 of the 10 studies were found to have a loss to follow-up greater than the RFI.

Discussion

This study provides further evidence that the $p < 0.05$ threshold is an imperfect measure to rely on when determining clinical relevance[3,25]. At face value, all RCTs to date comparing survivorship between computer-navigated and conventional TKA at a minimum of 8 years of follow-up showed no significant difference. However, our analysis found that these results are fragile, with a median RFI of 4 and RFQ of 0.029, meaning that only 4 events or 2.9% of the study population would have needed to have a different outcome in order to change the significance of these results. Furthermore, loss to follow-up was greater than the RFI in all 10 of the included studies. A loss to follow-up larger than the RFI is a strong indicator of a fragile study, as the outcomes of the patients lost to follow-up could alter the significance of the results[3,26,27]. Our findings of a relatively small

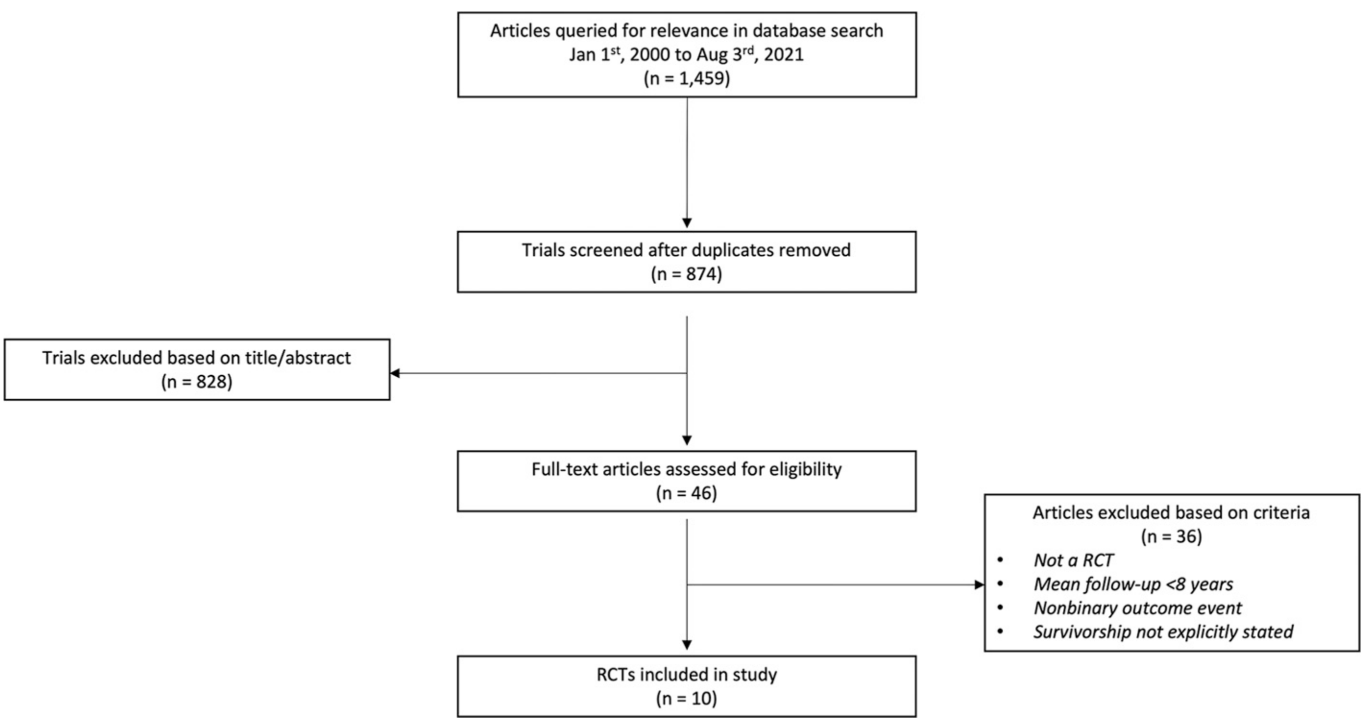

Fig. 2

Study identification flowchart. RCT = randomized controlled trial.

TABLE I Study Characteristics

Study	Year	Country	Computer-Navigated*	Conventional*	Implant	Navigation System	Follow-up†
Cip[15]	2018	Austria	100 (54)	100 (47)	NexGen MBK (Zimmer), NexGen LPS-Flex Mobile (Zimmer)	VectorVision CT-free Knee (Brainlab)	12
d'Amato[16]	2019	Italy	60 (48)	60 (47)	Scorpio PS (Stryker), Optetrak PS (Exactech)	Stryker Navigation (Stryker-Leibinger)	10.3
Kim[17]	2012	Republic of Korea	536 (520)	536 (520)	PFC Sigma CR mobile-bearing (DePuy), NexGen LPS-Flex (Zimmer)	VectorVision CT-free Knee (Brainlab)	10.8
Kim[18]	2017	Republic of Korea	170 (162)	170 (162)	NexGen CR-Flex (Zimmer)	VectorVision CT-free Knee (Brainlab)	12.3
Kim[19]	2018	Republic of Korea	296 (282)	296 (282)	NexGen PS (Zimmer)	VectorVision CT-free Knee (Brainlab)	15
Lacko[20]	2018	Slovakia	49 (30)	46 (31)	e.motion (B. Braun)	OrthoPilot (B. Braun/Aesculap)	11
Ollivier[21]	2018	France	40 (35)	40 (36)	NexGen LPS-Flex (Zimmer)	Not reported	11
Song[22]	2016	Republic of Korea	45 (41)	43 (40)	e.motion CR (B. Braun)	OrthoPilot (B. Braun/Aesculap)	10.4
Zhu[23]	2016	Singapore	52 (30)	56 (37)	PFC Sigma (DePuy)	Ci Total Knee Replacement (DePuy/Brainlab)	9.1
Hsu[24]	2019	Taiwan	60 (56)	60 (56)	PFC Sigma CR (DePuy)	VectorVision CT-free Knee (Brainlab)	8.1

*Number of knees enrolled for total knee arthroplasty, with the number of followed knees in parentheses. †The values are given as the mean in years.

RFI (median of 4) and large loss to follow-up (median of 27) suggest that the published RCTs comparing long-term survivorship of computer- navigated and conventional TKA are fragile, and thus should be interpreted with caution.

The United States has the highest rate of TKA, with projected increases by as much as 143% between 2016 and 2050[28]. The current AAOS clinical practice guideline and RCT data suggest that the increased cost and operative time associated with the utilization of computer navigation do not result in improved functional outcomes or implant survivorship[14]. However, this is a topic of debate, as the RCT data are in conflict with studies utilizing population-based data from the Australian Orthopaedic Association National Joint Replacement Registry showing that use of computer navigation in that larger sample was associated with lower revision rates in patients <65 years old[29]. Other studies utilizing large, registry-level databases found that computer navigation was associated with lower rates of major aseptic revision[30] and revision for mechanical failure[31]. Additionally, 1 recent simulation-based power analysis noted that it would take >5,000 participants to detect a long-term survivorship benefit resulting from use of computer navigation in TKA[32]. The largest RCT included in the present systematic review, by Kim et al.[17], had 1,040 participants, which is an impressive number but still far smaller than the projected >5,000 participants needed to detect a difference in this type of study.

There are many possible reasons why the current RCTs comparing long-term survivorship between computer-navigated and conventional TKA methods had nonsignificant findings.

TABLE II Reverse Fragility Analysis of Included Studies*

Study	Revisions, CAN	Revisions, Conv.	RFI	RFQ	Loss to FU
Cip[15]	1	4	1	0.010	99
d'Amato[16]	2	5	2	0.021	25
Kim[17]	6	4	4	0.004	32
Kim[18]	0	0	6	0.019	16
Kim[19]	2	2	6	0.011	28
Lacko[20]	1	4	3	0.049	34
Ollivier[21]	1	2	5	0.070	7
Song[22]	0	2	3	0.037	7
Zhu[23]	0	2	4	0.058	41
Hsu[24]	0	0	6	0.054	8

*Revisions = number of all-cause revision events, CAN = computer-navigated TKA, Conv. = conventional TKA, RFI = lowest reverse fragility index needed to demonstrate significant results, RFQ = reverse fragility quotient, FU = follow-up.

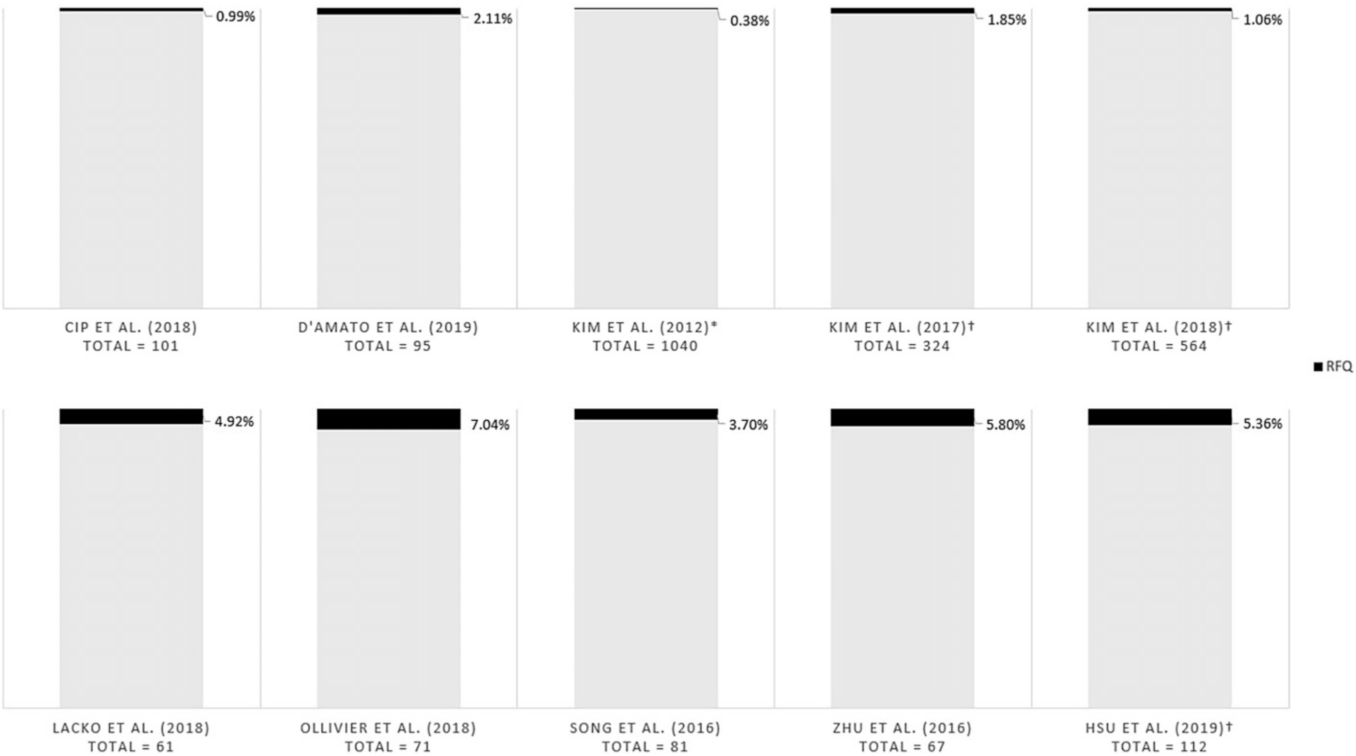

Fig. 3

Illustration of the reverse fragility quotient (RFQ) in each study. The black area represents the percentage of participants needed to change the study significance. * = RFQ favors conventional total knee arthroplasty, † = RFQ is equal for both groups. RFQ favors computer-navigated total knee arthroplasty for all other studies.

While studies certainly may be underpowered or biased, it is also possible that they did not follow the patients for a sufficient length of time to detect a difference (e.g., benefits of computer navigation may manifest at 20 to 30 years). Perhaps studying a younger, more active patient population would yield greater benefit from the improved precision of postoperative alignment[10-12] resulting from computer-navigated TKA. Notably, in 9 of the 10 included studies[15-19,21-24] the surgery was performed

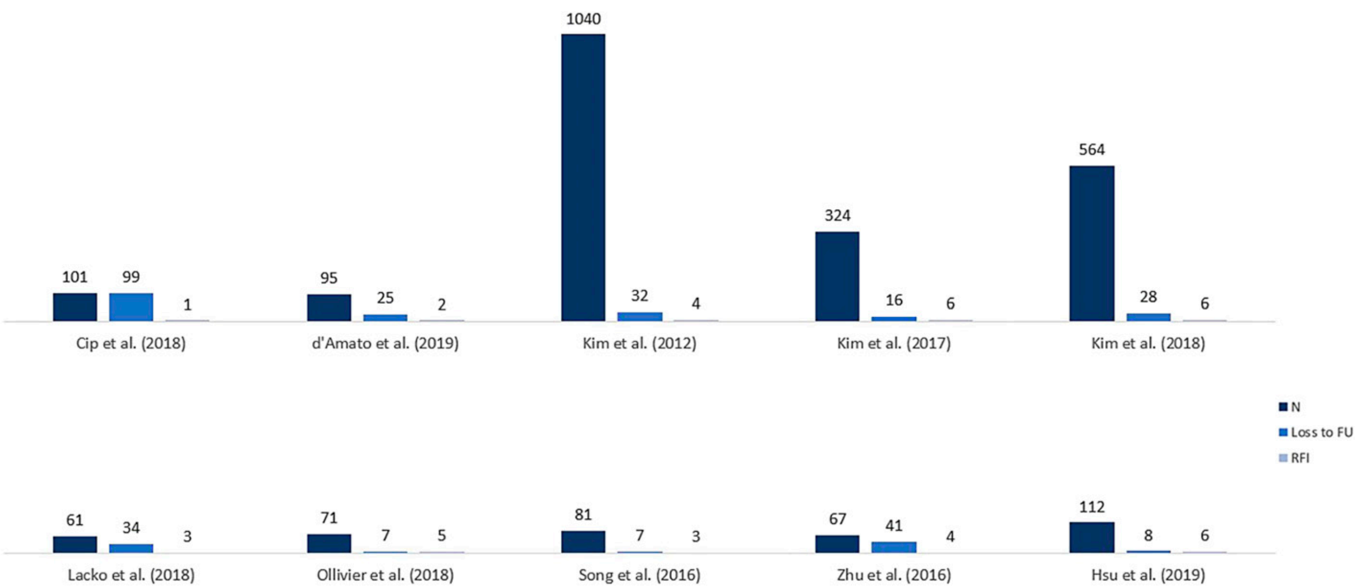

Fig. 4

Comparison of sample size (N), loss to follow-up (FU), and reverse fragility index (RFI) for each study.

by an experienced surgeon, which may confound results by decreasing overall revision rates, as there are data showing that computer navigation can improve the quality of TKAs performed by less-experienced surgeons[33]. Furthermore, recent advances in computer-navigated TKA technology may provide a greater advantage than the technology utilized in the included studies.

Regardless, it is critical to keep in mind that, given the growing number of TKAs performed annually[28,34,35], even a small difference in long-term revision rates can lead to a considerable reduction in the number of revisions. Assuming that 500,000 TKAs are performed in the United States each year in patients <65 years of age[28,35], a 1.1% difference in survivorship at 10 years—as evidenced by recent Australian registry data in this age group[36]—could lead to approximately 5,500 fewer revisions annually with the widespread adoption of this technology (if the observed difference in survivorship found in the Australian registry can be entirely attributed to the use of robotic surgery). However, it should be noted that the added cost of computer-navigated TKA must be considered when choosing whether to implement this technology in practice[37].

This systematic review has several strengths, one of which is the inclusion of only RCTs. This study is also the first, to our knowledge, to apply the RFI to comparisons of long-term TKA survivorship between computer-navigated and conventional techniques, a topic that has generated considerable interest and debate over the past 2 decades. This study adds to the growing orthopaedic literature on fragility analyses[6-8] and highlights the benefit of the RFI as a supplemental tool to help interpret nonsignificant RCT results. Interestingly, although a study can decrease the probability of a type-II error by increasing its power (e.g., from 0.8 to 0.9), it may still remain susceptible to fragile results. Thus, the interpretation of nonsignificant results should use a combination of factors (e.g., RFI, power, effect size measures, p values) to determine the efficacy of an intervention. In fact, multiple prior studies have cautioned against an overreliance on p values in this setting[1,3,5,38,39]. Moving forward, in cases in which the consequences of a false-negative result are severe, researchers should consider increasing the power of their study and reporting the calculated RFI and RFQ and the loss to follow-up. Loss to follow-up is especially salient when the reported p value is just above the 0.05 threshold of significance[3]. Future studies should consider investigating the reverse fragility for topics that have historically demonstrated equivalent outcomes (e.g., management of Achilles tendon ruptures or deep venous thrombosis prophylaxis after lower-limb arthroplasty). The reverse fragility of many RCTs in the orthopaedic literature may also partially explain the findings of a recent article suggesting that there is no high-quality evidence supporting operative management over nonoperative alternatives for common orthopaedic conditions (e.g., rotator cuff tear, spinal stenosis)[40]. Lastly, this study highlights the potential shortcomings of RCTs, which are traditionally considered to be the "gold standard" in scientific literature. Specifically, when studying outcomes with low event rates, RCTs may be prone to false-negative results when underpowered. Thus, other study designs (e.g., use of data from a large registry) may prove to be more useful in these scenarios.

This study has certain limitations. As in other fragility analyses, the RFI and RFQ can only evaluate categorical data with binary end points. Survivorship with the primary end point of revision can be easily analyzed, but other continuous variables such as functional outcomes and component alignment cannot be evaluated. Additionally, use of the dichotomous outcome of revision rate to determine TKA survivorship is inherently flawed, as there are a variety of factors that lead to revision that may not be related to the TKA technique. Furthermore, our study does not include data from observational studies, as we only included RCTs. We acknowledge the utility of observational data and recommend that physicians consider all available data on a topic prior to making treatment decisions. Additionally, given the median 11-year follow-up of the included studies, our data do not represent the newest computer navigation technology of each medical device company. We encourage additional RCTs evaluating data from the most up-to-date technology with a minimum decade-long follow-up. Lastly, given the low rate of revision at mid-term follow-up, future studies on this topic should consider utilizing more sensitive outcomes (e.g., radiographic loosening, patient-reported outcome scores). ■

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