The Reverse Fragility Index for Mortality Endpoints in Randomized Trials Comparing Uncemented and Cemented Hemiarthroplasty for Intracapsular Hip Fractures

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INTRODUCTION: Intracapsular hip fractures represent a global health issue that places a substantial socioeconomic burden on healthcare systems, and the incidence of these fractures has been projected to increase to over 6 million annually by 2050.[1] Treatment of displaced intracapsular hip fractures often consists of hemiarthroplasty with surgical resection of femoral head and neck and implantation of a prosthesis using a cemented or uncemented fixation technique. However, there remains debate as to which fixation method is superior, with a substantial number of randomized controlled trials (RCTs) being published in recent years. Mortality is a commonly studied endpoint in these studies considering the high risk population being treated, and confidence in the results and quality of published RCTs have wide clinical implications as surgeons may choose to alter their treatment approaches based on the statistical significance of reported findings. Fragility is therefore an important statistical concept to consider when interpreting the results of a clinical trial, as a small number of events may entirely alter the conclusions of a study should the data be fragile. Understanding the fragility of the study may appropriately caution the interpretation of study findings where the P-value is susceptible to methodological limitations. The primary objective of this study was to evaluate the robustness of statistically insignificant events from RCTs comparing hemiarthroplasty fixation and mortality by using the reverse fragility index (RFI).

METHODS: RCTs were systematically identified using Pubmed, OVID/Medline, and Cochrane databases. Mortality endpoints were extracted and stratified into three categories: 1) within 30-days, 2) within 90-days, and 3) at latest reported follow up. The RFI was defined as the number of events required in order to change a nonsignificant association between hemiarthroplasty fixation and mortality to a significant one. The RFI for each individual study was derived by manipulating reported mortality events utilizing a contingency table while maintaining a constant number of participants. This was performed for each cohort (cemented and uncemented hemiarthroplasty), with the lowest number of event reversals that yielded statistical significance selected to represent the RFI for the study. In cases where mortality events in one group reached 0 prior to a statistically significant association being observed, data was further manipulated by adding events in the other group until significance was achieved. To determine whether the manipulation yielded statistical significance, a 2-tailed Fischer exact test or Chi-squared test was implicated as appropriate depending on the number of events in the contingency table. For each study, the RFI was also compared to the number of participants lost to follow up at that respective timepoint. An extension of the RFI, the reverse fragility quotient (RFQ), was also defined for each study. This metric is defined by dividing the RFI by the total study population size for the respective study. All metrics were reported using the median and interquartile range (IQR) to provide a measure of statistical dispersion and global representation of data.

RESULTS: Eight RCTs (2,494 participants) were included **(Table 1)**. The median RFI and RFQ within 30-days was 3.0 (IQR:3.0–6.0) and 0.016 (IQR:0.015–0.021), suggesting that nonsignificant findings were contingent on only 1.6 mortality events/100 participants. The median RFI and RFQ within 90-days was 6.0 (IQR:4.0–7.0) and 0.028 (IQR:0.024–0.038), suggesting that nonsignificant findings were contingent on only 2.8 mortality events/100 participants. At latest follow up, the median RFI and RFQ was 7.0 (IQR:6.0–12.0) and 0.038 (IQR:0.029–0.054), suggesting that nonsignificant findings were contingent on only 3.8 mortality events/100 participants. Median loss to follow up was 16.0 (IQR:11.0 – 58.0), which was 228% greater than the RFI, and exceeded the RFI in 6/7 (85.7%) studies **(Figure 1**).

DISCUSSION AND CONCLUSION: This cross-sectional study found that a relatively small number of events (median of 7) was required to convert a statistically nonsignificant finding to one that is significant for the primary endpoint of mortality. The median loss to follow up exceeded the median RFI by greater than 200%, with 85.7% of studies reporting loss to follow up exceeding the RFI, suggesting methodological limitations such as patient allocation could significantly alter conclusions. These findings suggest that clinical decision making should not depend on individual results of RCTs for hip hemiarthroplasty.

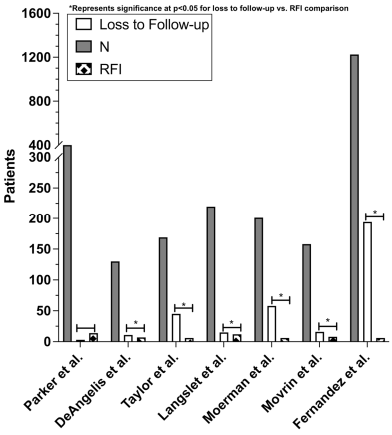

Table 1. Included randomized trials evaluating mortality endpoints after hip hemiarthroplasty for intracapsular hip fractures

Article	Year	Cemented	Uncemented	Inclusion Criteria	Exclusion Criteria
Figved et al.	2009	112	108	Minimum age 70 years with displaced intracapsular hip fracture	Medically unfit for procedure, pre-existing osteoarthritis, pathologic fracture, ongoing infectious disease, inability to ambulate prior to injury
Parker et al.	2010	200	200	Minimum age 60 years with displaced intracapsular hip fracture	Nondisplaced or minimally displaced fractures, age less than 60 year or age 60-75 years with no mobility restriction at time of injury, senile dementia where consent could not be obtained, pathologic fractures, previous treatment to same hip for a fracture, medically unfit for procedure, treatment with THA
DeAngelis et al.	2012	66	64	Minimum age 55 years with displaced intracapsular hip fracture and ability to ambulate 10 feet prior to injury	Pathologic fractures, inability to ambulate greater than 10 feet prior to injury, multiple extremity trauma, acute MI within 30 days of enrollment, presence of symptoms associated with anemia or preexisting metabolic bone disease
Taylor et al.	2012	80	80	Minimum age 70 years with displaced intracapsular hip fracture	Pathologic fracture, prior ipsilateral hip fracture, treatment with THA
Langslet et al.*	2014	112	108	Minimum age 70 years with displaced intracapsular hip fracture	Medically unfit for procedure, pre-existing osteoarthritis, pathologic fracture, ongoing infectious disease, inability to ambulate prior to injury
Moerman et al.	2017	110	91	Minimum age 70 years with displaced intracapsular hip fracture	Pathologic fracture, fracture older than 7 days, ASA IV-V
Movrin et al.	2020	79	79	Minimum age ≥76 years with displaced intracapsular hip fracture	Medically unfit for procedure, pre-existing arthritis, prior ipsilateral hip fracture, cognitive impairment, inability to ambulate prior to injury
Fernandez et al.	2022	610	615	Minimum age 60 years with a displaced intracapsular hip fracture	Age less than 60 years, non-operative management, treatment with THA

*Only used for calculation of latest follow-up metrics as this was a long-term follow-up of the Figved et al. trial.