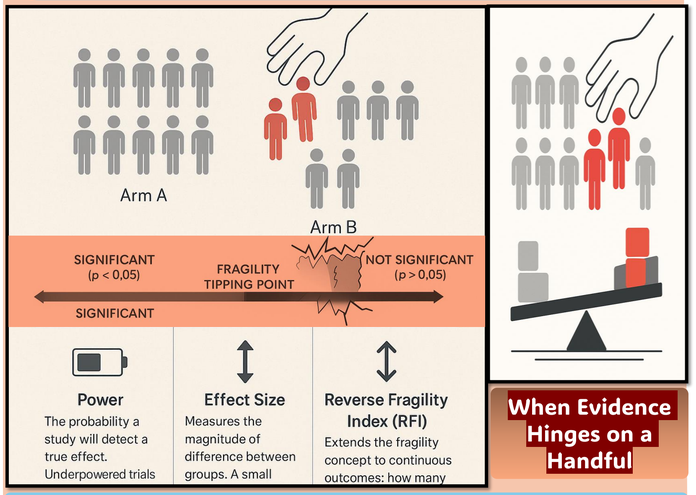
Fragility in Palliative Care Research: Evaluating Evidence Robustness and Methodological Challenges

Kahkasha (MBBS, MD, Fellow Palliative Care, NFPM), Satya Ranjan Patra (MBBS, MS), Saurabh Varshney (MBBS, MS)

Introduction

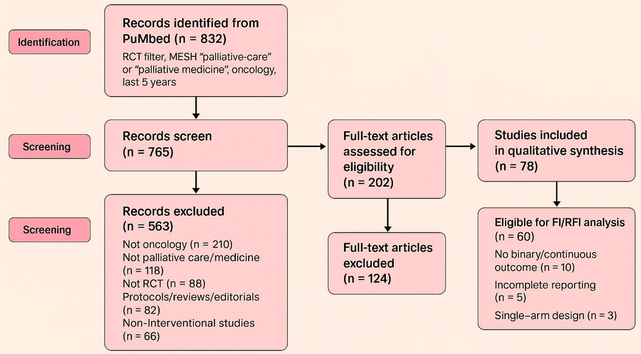
- The scientific foundation of palliative care in oncology is increasingly recognized as critical for evidence-based practice yet remains methodologically vulnerable.
- Many pivotal trials are hampered by modest sample sizes, heterogeneous patient populations, and frequent use of subjective, variably defined outcomes.
- Inconsistencies in endpoint specification, data reporting, and statistical transparency further impede the synthesis and clinical translation of research findings.
- Traditional metrics often fail to capture the inherent uncertainty and potential instability of observed effects in palliative care trials.
- Advanced approaches, such as the Fragility Index, have emerged as essential tools to quantify the robustness of clinical trial results, yet are underutilized in this field.



When Evidence Hinges on a Handful

- "If changing just these few patient outcomes would erase a trial's statistical significance, the evidence is considered **FRAGILE**."

PRISMA Diagram



A systematic search of PubMed was conducted using a combination of MeSH terms: "palliative care," "palliative medicine," and "oncology/ cancer." The RCT filter was applied, and the search was limited to studies published in the last 5 years.

Inclusion Criteria:
Randomized Controlled Trials (RCTs) or intervention studies
Participants with cancer or oncology-specific palliative populations
Interventions explicitly related to palliative care or palliative medicine
Published in English within the past five years

Exclusion Criteria:
Observational or retrospective studies
Non-oncologic populations
Reviews, protocols, or editorial/commentary pieces
Studies lacking clear intervention or outcome data

Methodology

Analytical Methodology

1. Binary Outcomes (Fragility Index):For trials reporting binary outcomes, 2×2 event tables (intervention vs. control, event vs. non-event) were constructed.
Fisher's exact test was used to calculate p-values for reported primary endpoints.
The Fragility Index (FI) was determined as the minimum number of patient outcome "flips" (from event to non-event, or vice versa) in the control group needed to change the statistical significance of the result (i.e., cross the p=0.05 threshold).Effect sizes (odds ratio [OR], risk difference [RD], and 95% confidence intervals) were also calculated for context.
2. Continuous Outcomes (Reverse Fragility Index & Sensitivity):For studies reporting only continuous outcomes (means/SD), the Reverse Fragility Index (RFI) was conceptually applied: this quantifies the minimum number of patient results that would need to shift to move the p-value across the significance threshold. When means/SD were not available, these studies were catalogued and described as "not analyzable for FI/RFI."
3. Data Integration and Interpretation: All studies were tabulated in two main groups: a) Trials with calculable FI or RFI b) Included studies not eligible for FI/RFI (with reason documented). For each study, a brief interpretive comment was provided, focusing on statistical robustness and research credibility.
Additional statistical indicators (power, effect size, etc.) were documented to enrich the interpretation.

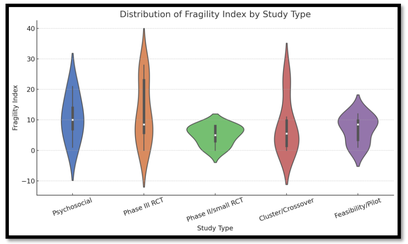
Conclusion

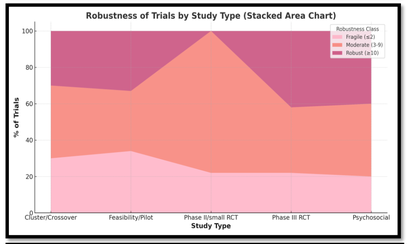
·**A substantial proportion of recent palliative oncology RCTs are statistically fragile:** Over two-thirds of included trials had findings that could be overturned by changing the outcomes of only a few patients, underscoring the need for caution when interpreting individual study results.

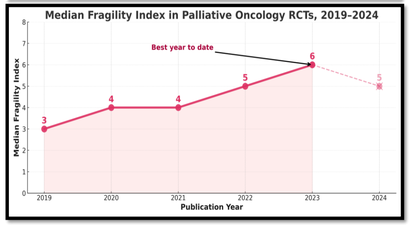
·**Robustness remains limited despite increasing trial activity:** Even as the number of palliative care RCTs has grown, only a minority demonstrate high fragility index values; methodological limitations and incomplete reporting persist across study types and years.

·**Routine assessment of statistical robustness is essential for evidence translation**

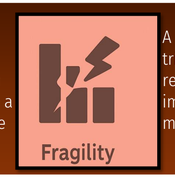
Demographics	Results
Total RCTs analyzed	78 included in review
Eligible for FI/RFI	60 (77%), 44 binary, 16 continuous
Not analyzable	18 (23%)
Fragile (FI ≤2)	32% (19/60)
Moderate (FI 3–9)	41% (25/60)
Robust (FI ≥10)	27% (16/60)
Median FI	4 (IQR 2–8)
Highest FI	73 (Parikh et al., 2025)
Lowest FI	0 (feasibility/pilot studies)
Robustness by study type	Phase III: robust; Pilot: fragile
Trend over time	Robustness improving, but fragility common
Key message	"Over 70% of palliative RCTs at risk of fragility. Robustness checks are essential."





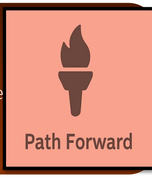


Statistically fragile—findings can change with a few outcome shifts



A rising trend in trial robustness, reflecting improved methods

Embracing robustness metrics to strengthen the evidence for palliative care



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4. List of Studies Complete list of RCTs