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Model-Free Survival Fragility Restores Robustness in Clinical Trials Reporting the Survival-Inferred Fragility Index

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Abstract

The Survival-Inferred Fragility Index (SIFI), introduced in 2020 and now applied to first-line metastatic renal cell carcinoma immunotherapy trials, extends the fragility concept into time-to-event oncology outcomes by iteratively reassigning long-surviving patients between trial arms until statistical significance is lost. This reassignment rule is model-dependent: the choice of which survivors to move and in what order embeds distributional assumptions about the survival tail, so SIFI values are path-dependent and therefore have limited cross-trial comparability. The Survival Fragility Quotient, derived from the Cox regression z-statistic and paired with the Survival Robustness Quotient on the neutrality boundary, provides a model-free survival fragility measure without iterative reassignment, requires only the reported hazard ratio and its confidence interval, and completes the p–fr–nb triplet for time-to-event outcomes. Oncology randomized trial reporting should adopt the model-free pair to support cross-trial comparability of the quality of survival evidence.

Keywords

survival fragility, robustness in clinical trials, neutrality boundary framework, survival-inferred fragility index, p-fr-nb, model-free statistics, oncology trial methodology, hazard ratio

The Survival-Inferred Fragility Index (SIFI) was introduced to extend the fragility concept to time-to-event oncology outcomes and has since been applied to first-line metastatic renal cell carcinoma immunotherapy trials [1,2], but SIFI inherits the same model-dependent pathology that has already troubled iterative continuous-outcome fragility calculations, and a model-free survival counterpart is available. The argument that follows is not that survival fragility is unimportant — quite the opposite — but that the survival domain deserves a metric whose values are reproducible from published summary statistics and comparable across trials.

The classical fragility index was defined for binary outcomes as the minimum number of outcome reversals required to change the Fisher exact test classification [3]. When the same iterative logic was carried over to continuous outcomes using the Caldwell-style continuous fragility index (CFI) [4], the procedure became model-dependent because each iteration requires assumptions about the next data point's mean and variance, as well as the reassignment order. The lesson generalizes: whenever a fragility metric requires the analyst to choose which observation to alter next, the resulting value is conditional on that choice, and inter-trial comparison loses its anchor. The Continuous Fragility Quotient (CFQ) was proposed precisely to recover model-freedom: CFQ derives classification stability from the Welch t-geometry without any iterative data modification, and it is bounded on the unit interval [5]. Specifically, given the Welch t-statistic T and critical value t*, the continuous fragility score $CFS = ||T| - t^*|$, and $CFQ = CFS / (1 + CFS)$.

SIFI repeats the CFI iterative pattern in the survival domain. As applied to four phase 3 immunotherapy combinations in first-line metastatic renal cell carcinoma, the procedure reassigns the longest-surviving patients from the experimental arm to the control arm until the overall-survival p-value crosses the significance threshold [2]. Two methodological consequences follow directly. First, the reassignment selects exchangeable survivors by tail position, which assumes that the rightmost observations are the appropriate ones to perturb; this is a distributional assumption about where survival evidence is located. Second, the reported SIFI count is path-dependent: reassigning the longest survivor first changes the next-step Cox likelihood, so the order of reassignment alters the index value. The published SIFI numbers (with some overall-survival values as low as 2.2%) therefore reflect a specific iterative path through a specific reconstructed dataset, not a transferable summary of how far the trial sits from the significance boundary.

In the Heston neutrality boundary framework, robustness refers to the distance from therapeutic neutrality [6]. This p–fr–nb framework provides model-free survival metrics

derived directly from the reported Cox results [7]. The Survival Fragility Quotient (SFQ) is defined as |z_HR − 1.96| / (1 + |z_HR − 1.96|), where z_HR is the Cox regression z-statistic obtained from the hazard ratio and its 95% confidence interval via ln(HR) divided by the symmetric standard error implied by the confidence-interval width. SFQ requires no patient-level reconstruction, no Kaplan-Meier digitization, and no iterative data modification. Its companion robustness metric, the Survival Robustness Quotient (SRQ), is |ln(HR)| / (1 + |ln(HR)|) and measures geometric distance from the neutrality boundary at HR = 1 on the same 0–1 scale used elsewhere in the neutrality boundary framework [6]. Reporting both together completes the p–fr–nb triplet for survival outcomes: the p-value indicates significance, SFQ indicates classification stability, and SRQ indicates distance from therapeutic neutrality (robustness in clinical trials).

Three concrete properties separate SFQ from SIFI in the way that CFQ separates from the CFI. First, the structural parallel is exact: both pairs replace iterative outcome modification with a closed-form transformation of the published test statistic, so the same model-free principle that already disciplines continuous-outcome fragility now disciplines survival-outcome fragility. Second, SFQ is bounded on the unit interval and is symmetric around the significance boundary, so a value reported in one oncology trial is directly comparable to a value reported in any other oncology trial, irrespective of sample size or median follow-up. Third, the four trials currently being graded by SIFI — covering nivolumab plus ipilimumab, nivolumab plus cabozantinib, pembrolizumab plus axitinib, and pembrolizumab plus lenvatinib in first-line metastatic renal cell carcinoma — all report hazard ratios with 95% confidence intervals for overall survival, which is the complete input set required to compute SFQ and SRQ from the published manuscripts alone, with no patient-level reconstruction step required.

Oncology randomized trial reporting should pair the SFQ with the SRQ as the default survival-outcome implementation of the p–fr–nb triplet, both for prospective trial reports and for retrospective reanalyses of the SIFI-published cohort. A side-by-side reanalysis of the four first-line metastatic renal cell carcinoma trials would calibrate the empirical relationship between SIFI percentages and SFQ values across a clinically consequential dataset and would establish whether the published SIFI ordering of "more robust" versus "less robust" combinations survives the move to a model-free, cross-trial-comparable metric. The discipline imposed by model freedom is what makes survival fragility a transferable property of the evidence rather than of the analyst's reassignment path.

Declarations

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