Qeios

Peer Review

Review of: "When Costs Eclipse Cure: Does Financial Toxicity Erode Survival Gains from Novel Cancer Therapies?"

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1. Independent researcher

This manuscript evaluates whether financial toxicity (FT) diminishes overall survival (OS) benefits associated with FDA-approved novel cancer therapies. By synthesizing HRs from a large meta-analysis of 234 RCTs and combining them with HRs from FT-related studies (including insurance status as a proxy), the author develops a multiplicative model to estimate net mortality impacts in different economic contexts. The topic is timely and highly relevant, especially given the rising global cost of oncology care. The article is clearly written, addresses an important public health concern, and provides an innovative modeling framework linking therapeutic efficacy and financial burden. Nevertheless, several key methodological assumptions require further justification, and certain interpretations may exceed what the data can confidently support. I outline major and minor concerns below.

Comments

1. **Reevaluating the suitability of the research methodology for the research question**

The research question appears to investigate whether financial toxicity (FT) diminishes the survival benefits of new cancer treatments by analyzing data from published studies.

Measuring survival outcomes is particularly challenging across different contexts because numerous variables can influence the results.

From the perspective of large meta-analyses, the reported overall survival (OS) improvement of 2.8 months may not accurately represent the survival benefits of novel cancer drugs. This is because only randomized controlled trials (RCTs) that designate OS as the primary endpoint provide reliable measures. If OS is considered a key secondary endpoint, the results may be biased due to the study design (e.g., control arm cross-over to the study arm is allowed after progression). I reviewed the first paper cited by

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the author (JCO, 2022), which examined 124 FDA-approved drugs across 374 indications, including 141 approved as combinations and 248 supported by randomized controlled trials (66%). Among these, 234 randomized trials had available data, with 188 reporting OS hazard ratios (HR) and 203 reporting progression-free survival (PFS) HRs. However, it is unclear whether the 188 OS HRs correspond to primary or key secondary endpoints.

Additionally, the study does not clearly define financial toxicity (FT). The author references other public studies related to FT to compare with the reported OS data, but these comparisons are made across different contexts. For example, the 2.8-month OS improvement likely comes from global studies, whereas the FT-related data may not. Given the many factors affecting survival—such as quality of medical care, use of combination versus single drugs, and varying indications—all of which significantly impact survival time, direct comparisons may not be appropriate.

2. Justification for assuming independence between drug efficacy HR and FT HR is insufficient

The central methodological step in this manuscript is multiplying the drug HR by the FT HR to estimate a "net HR." This requires the assumption that FT and drug efficacy act independently on the hazard function. However, FT may directly influence treatment adherence, dose intensity, or discontinuation rates, thereby interacting with therapeutic effect rather than acting independently.

2. Use of insurance status as a proxy for financial toxicity needs deeper discussion

In the synthesis of FT HRs, the meta-analysis by Tian et al. used insurance status as an FT surrogate. However, insurance coverage is an imperfect proxy for FT—many insured patients experience severe FT, and uninsured patients in some countries may still have low out-of-pocket burdens depending on local systems.

3. High heterogeneity ($I^2 \approx 85\%$) among the six FT studies is not adequately addressed

The six studies reporting FT-related HRs show substantial heterogeneity, but no subgroup or meta-regression analyses were performed.

4. Key assumptions in the 1,000-patient mortality model require further justification

The model assumes:

- A baseline 5-year mortality rate of 40% for advanced solid tumors,
- An exponential survival distribution,
- Fixed HRs across populations,

- Constant FT prevalence values (35% for HICs, 64% for LMICs).

These simplifying assumptions may not reflect real-world survival curves or FT dynamics.

5. Some conclusions may overstate the strength of the evidence

Statements such as “tens of thousands of excess global deaths annually” and “minimal or no net benefit in LMICs” may be interpreted as empirical findings, although they are model-based projections highly dependent on assumptions.

Minor Comments

1. **Clarify terminology.**

Terms such as “offset,” “modest trial gains,” and “overload” should be explicitly defined at first use to avoid ambiguity.

2. **Figures and tables could be improved for clarity.**

- Figure 1’s colors and categories would benefit from clearer visual separation.
- Consider adding offset percentages directly on the bars for better readability.

3. **Structure and flow.**

The Introduction and Discussion sections are lengthy. A summary of the study’s unique contribution at the end of the Introduction would help orient readers.

4. **Referencing inconsistencies.**

There are several instances where references are annotated with “a, b, c” superscripts or inconsistent formatting. Please standardize according to journal style.

1. **Limitations section.**

Although limitations are mentioned, they could be expanded, especially addressing bias from combining RCT-derived efficacy with observational FT data.

Recommendation

Major Revision

The manuscript addresses an important topic and has the potential to make a meaningful contribution to discussions on value-based oncology and global disparities. However, key methodological assumptions

require stronger justification, and several interpretations should be more cautiously framed.

Declarations

Potential competing interests: No potential competing interests to declare.