Letter to the Editor Regarding "Metformin as an Adjunct Treatment to Temozolomide for High-Grade Gliomas: A Systematic Review and Meta-Analysis"

To the Editor,

We read with great interest the systematic review and meta-analysis by de Assis et al., evaluating metformin (MET) as an adjunct to temozolomide in high-grade gliomas.[1] The reported survival benefit (HR 0.74) is notable, particularly in a domain where therapeutic gains are measured in weeks, not months. Yet, before such findings are translated into clinical practice, the evidentiary scaffold warrants a critical re-examination.

Upon review, 3 interlinked vulnerabilities emerge: methodologic fragility, molecular oversight, and mechanistic ambiguity.

To begin with methodologic fragility, the analysis leans heavily on retrospective studies. Only one randomized controlled trial was included—graded "some concerns" using the RoB-II tool—and 8 of 9 observational studies were rated as serious or critical risk of bias using ROBINS-I.[1] This introduces classic epidemiologic vulnerabilities such as immortal time bias and treatment indication bias, both of which are known to inflate survival estimates.[2] Adding further concern is the lack of consistency in MET dosing, which ranged from 400 to 2550 mg/day, with no standardized timing relative to temozolomide or radiation.[1] The lone randomized controlled trial examined recurrent glioblastoma, a biologically and prognostically distinct entity, limiting extrapolation to newly diagnosed cohorts. Pooling such heterogeneous data risks amplifying statistical noise over therapeutic signal.

When trials are uneven and dosing is erratic, the illusion of efficacy may be pharmacologic in name—but statistical in truth.

Turning to the molecular underpinnings, while the authors highlight a survival advantage in MGMT-methylated patients (HR 0.44), most studies failed to report co-occurring mutations such as IDH1/2, EGFRvIII, or TERT promoter status—each of which critically modulates glioma behavior and treatment response.[3] IDH-mutant gliomas, for instance, exhibit metabolic liabilities that may sensitize them to AMPK activation, offering a plausible but untested explanation for differential metformin sensitivity.[4] Further complicating interpretation is the fact that several studies used outdated histologic criteria, without alignment to the 2021 WHO CNS classification.[1] In modern neuro-oncology, molecular taxonomy is no longer optional—it is foundational.

Precision falters when we blur genotypes and group phenotypes—the genome, after all, is not a footnote but the frame.

The final layer of uncertainty lies in mechanistic ambiguity. MET is proposed to act through AMPK activation, mTOR inhibition, and MGMT suppression—yet most studies failed to report baseline glucose levels, HbA1c, or diabetic control status.[1,5] In the absence of metabolic profiling, one cannot distinguish between MET's direct antitumor effects and its systemic glycemic modulation. Notably, normoglycemic patients appeared to derive greater benefit than diabetics, despite similar MET exposure—a paradox that should raise flags, not confidence.

When the mechanism is murky and metrics are missing, the molecule risks becoming a myth.

Taken together, the findings in this meta-analysis are provocative—but not definitive. And the more sobering question remains unanswered: why has metformin, despite more than a decade of preclinical enthusiasm, failed to enter any major neuro-oncology guideline?

The reasons are not solely scientific—they are structural:

- No biomarker-driven trial has clarified which subset of patients truly benefits.
- No phase III randomized controlled trial has shown a robust overall survival advantage in newly diagnosed glioblastoma.
- The drug's mechanism remains speculative and inconsistently validated across contexts.
- And most damningly—metformin is too cheap to chase.

As an off-patent agent with razor-thin commercial margins, metformin offers little incentive for pharmaceutical sponsorship. No industry is likely to fund a $20–40 million trial to validate a molecule that cannot be monetized. In a cruel irony, the very affordability that makes metformin globally accessible also makes it scientifically orphaned. Until research funding models prioritize public health impact over proprietary gain, repurposed agents like metformin will continue to languish—rich in hypothesis, poor in hierarchy.

We are not rejecting metformin—we are diagnosing the ecosystem that sidelines it.

Metformin may be ready to join the glioma orchestra—but for now, it is still waiting for a formal invitation from the conductor.

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