

ABSTRACTS

Association of Antidepressant Use With Survival and Clinical Outcomes in Lung Cancer Patients Receiving PD-1/PD-L1 Immunotherapy

Banuja M., MD¹, Emmanuel Maame, MD¹, Muhammad Sajawal, MD², Muhammad Asim Agha, MD², Rawan Elkomi Elkomi, MD³, Syed Fahad Gillani, MD³, Nicholas Azinge, MD, FACP³, Miriam Michael, MD³

¹ Howard college of medicine, ² Internal Medicine, Howard University Hospital, ³ Howard University Hospital

Keywords: PD-1/PD-L1 inhibitors, Depression, psycho-oncology, healthcare utilization, palliative care, corticosteroids, real-world evidence

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Lung cancer is a leading cause of cancer mortality. Immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1) or programmed death-ligand 1 (PD-L1) improve outcomes, but associations between antidepressant exposure and immunotherapy effectiveness remain uncertain.

Abstract

Background: Lung cancer is a leading cause of cancer mortality. Immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1) or programmed death-ligand 1 (PD-L1) improve outcomes, but associations between antidepressant exposure and immunotherapy effectiveness remain uncertain.

Objective: To evaluate associations between antidepressant prescribing and all-cause mortality, hospitalization, corticosteroid initiation, and palliative care encounters among adults with lung cancer who are receiving PD-1/PD-L1 inhibitors.

Methods: In this retrospective TriNetX cohort, antidepressant exposure was defined as having an antidepressant prescription on record within 3 months before or after PD-1/PD-L1 inhibitor initiation. TriNetX is a searchable online data platform of real-world, deidentified patient electronic health records. The antidepressant exposure window captured prescribing near the time of PD-1/PD-L1 treatment initiation; prescription records served as a surrogate for medication exposure. Antidepressant classes and exposures (before or after PD-1/PD-L1) were pooled. We used propensity score matching to pair adults with lung cancer who were exposed vs unexposed to antidepressants. Outcomes were assessed from immunotherapy initiation through available patient follow-up.

Results: Each cohort (exposed vs unexposed) included 27,553 patients. Median survival was shorter among antidepressant-exposed vs unexposed patients (448 vs 643 days). The unexposed cohort had a lower mortality hazard relative to the exposed cohort (hazard ratio, 0.80; 95% CI, 0.78-0.82;

$P < .001$), although end-of-follow-up survival probabilities were similar (18.1% for unexposed vs 18.6% for exposed). Antidepressant-exposed patients also had earlier hospitalization, corticosteroid initiation, and palliative care use.

Conclusion: Antidepressant prescribing within 3 months before or after PD-1/PD-L1 inhibitor initiation was associated with shorter median survival and earlier healthcare utilization but had a similar survival probability through available patient follow-up as having no antidepressant prescription. Depression severity, cancer burden, patient characteristics, healthcare access, exposure timing, and antidepressant class may contribute to these findings. Further research should examine these factors before causal conclusions are drawn.

Keywords: Depression; Psycho-oncology; Healthcare Utilization; Palliative Care; Corticosteroids; Real-World Evidence

Peer Review

Reviewer 1

Minor comments:

- Line 44: “...within 3 months before or after immune checkpoint inhibitor initiation...” The exposure definition 3 months before and after encompasses patients with several different temporal relationships between antidepressant use and immune checkpoint inhibitor therapy initiation. Was the intention to capture concomitant antidepressant use or any antidepressant exposure surrounding immune checkpoint inhibitor therapy initiation? If it was concomitant use, then it would be helpful to clarify the rationale for grouping these patients together. If it was to capture exposure around immune checkpoint inhibitor initiation, maybe add a brief statement like: the 3-month window was selected to capture antidepressant use surrounding immune checkpoint inhibitor therapy initiation.
- Line 44: “...antidepressant prescriptions...” It would be helpful to clarify whether antidepressant prescription records were used as a surrogate for antidepressant exposure, as prescription records may not necessarily reflect active medication use.
- Line 45: “Primary outcome was all-cause mortality; secondary...” The abstract could benefit from specifying the follow-up period over which the primary and secondary

outcomes were assessed to interpret results. For example, over what time frame were these outcomes assessed: within 30 days, at 1 year, during treatment, all of the above?

Reviewer 2

Comments:

- Line 47: Were there any other methods used for matching beyond propensity score matching? If so, please include these in the comments. If space is needed, you can remove the coding tags from the methods. You can also remove “which aggregates... organizations” (line 40), as this adds unnecessary info that someone can look up on their own.
- Line 53: Please also include that there is no difference in survival probability at end of study in the Conclusions as not including this is burying the lead a bit.
- Line 54: Additionally, I would say “further research is warranted to clarify biologic mechanisms *and patient characteristics* so that this information may guide integration of oncologic and psychiatric care.” The reason I would say this is because patient characteristics could also be a driver of who is and who is not accessing antidepressants to begin with and may further complicate the relationship with healthcare utilization.

Reviewer 3

Minor Comments:

- Line 33: Consider defining programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1) when introduced for readers who may be less familiar with these targets.
- Line 38: Consider specifying the “clinical outcomes” being investigated to improve clarity and better align the objective with the outcomes.
- Line 43: Consider specifying whether different types of antidepressant classes were analyzed together or individually.
- Line 53: Consider expanding the discussion of further research to include investigation of whether the observed association is due to antidepressant effects themselves or other underlying factors like depression severity, cancer burden, etc.

Major Comments:

- Line 43: Consider evaluating outcomes separately among patients who initiated antidepressants before vs after PD-1/PD-L1 inhibitor therapy, as these groups may be clinically distinct subpopulations. Consider evaluating these outcomes separately or acknowledging this limitation.
- Line 49: As currently written, the hazard ratio for mortality appears to be inconsistent with the reported median survival statistics presented in line 48. A hazard ratio of 0.80 suggests lower mortality for the antidepressant group, whereas the stated median survival (448 vs 643 days) suggests poorer survival in this group. Please clarify this discrepancy as this affects interpretation of the results.

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Funding

None.

Conflict of interest

The authors declare no conflicts of interest.

IRB approval/exemption

Data were obtained by executing prespecified queries within TriNetX. The platform returned de-identified, aggregate data, and no directly identifiable patient information was accessed. As such, it was granted exemption by the Western Institutional Review Board, and no additional institutional review board approval or informed consent was required.

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