Mood Disorders and Immune-Related Adverse Event Related Treatment Discontinuation among Advanced Cancer Patients Receiving Immune Checkpoint Inhibitors

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ABSTRACT

Background: Cancer patients with anxiety and depression have increased health utilization and treatment with poorer quality of life, lower treatment adherence,[1,2] but higher overall health utilization[3]

Objective: To determine if insurance mediated the relationship between mood disorders and irAE-related treatment discontinuation (irAE-TxDx)

Study Design: Retrospective cohort study using a Flatiron Health electronic medical record-derived dataset

Sample: N=1,594 deceased patients with advanced cancers who received immune checkpoint inhibitors (ICI) and experienced irAEs

Measures:

Mood disorders: ICD-10 codes, medications (anxiety and depression)

IrAEs: ICD-10 codes;[4,5]

IrAE-TxDx:

- ICI patients with eligible cancers
- Positive irAE diagnosis
- Receipt of steroid or immunosuppressive treatment
- Did not receive a subsequent ICI

Analyses: Mediation analyses and logistic regression models were conducted in R

Key findings:

- Mood disorders (aOR=1.49 [95% CI: 1.14-1.93, p=0.003) and lung cancer (aOR=1.97 [1.47-2.64, p<0.001) were associated with higher odds of irAE-TxDx
- Older age, (aOR=0.99 [0.97-1.00], p=0.012) and being seen in a community practice setting (aOR=0.43 [0.33-0.55], p<0.001) was associated with lower odds of irAE-TxDx
- **Mediation analyses:** Significant total effect of mood disorders on irAE-TxDx (OR=1.08, [1.03, 1.15], p=0.004);

Conclusion: Better psychosocial support is needed for ICI patients experiencing irAEs

INTRODUCTION

- The population of patients treated with immune-checkpoint Inhibitors (ICIs) continues to grow
- ICIs are associated with immune-related adverse events (irAEs) that can be unpredictable in timing, severity, and chronicity
- Mood disorders are associated with poorer quality of life, lower treatment adherence,[1,2] but higher overall health utilization[3]
- This study builds on our previous analyses that observed increased odds of irAEs among ICI-treated patients with mood disorders, and that the relationship between mood disorders and irAEs was moderated by patients' insurance type[4]

- **Objective: We sought to determine if insurance mediated the relationship between mood disorders and irAE-related treatment discontinuation (irAE-TxDx)**

METHODS AND MATERIALS

Ethical Approvals: Approved by University of Utah (#00160252)

Study Design: Retrospective cohort study (2011-2022)

Dataset: US Flatiron Health electronic medical record-derived dataset

Cohort: N=1,594 deceased ICI-treated patients with advanced cancers who experienced irAEs (advanced melanoma, head and neck, lung, bladder, and

Measures:

- *Mood disorders:* Anxiety and depression medications and ICD-10 codes
- *IrAEs* ICD-10 codes associated with irAE-related autoimmune conditions, after ICI exposure[4,5]
- IrAE-TxDx:
  - *ICI patients with eligible cancers*
  - *Positive irAE diagnosis*
  - *Receipt of steroid or immunosuppressive treatment*
  - *Did not receive a subsequent ICI*
- **Analyses:** Mediation analyses and logistic regression models were conducted in R

RESULTS

- 33.5% of ICI-treated patients with irAEs (*N*=534) had been diagnosed or treated for mood disorders
- ICI-treated patients with irAEs and mood disorders, compared with ICI-treated patients with irAEs a no mood disorders were:
  - Younger (Mean=66 vs. 70, *p*<0.001)
  - Greater number of clinic visits (Mean=70 vs. Mean=98, *p*<0.001)
  - Female (51% vs. 40%, *p*<0.001)
  - White (90% vs. 85%, *p*=0.006)
  - *Ethnicity, socioeconomic status, cancer type, functional status, insurance type, and type of ICIs were not associated with mood disorders*

Higher Odds of irAE-TxDx:

- Mood disorders (aOR=1.49 [95% CI: 1.14-1.93, *p*=0.003), ref no mood disorder
- Lung cancer (aOR=1.97 [1.47-2.64, *p*<0.001), ref melanoma

Higher Odds of irAE-TxDx:

- Older age, (aOR=0.99 [0.97-1.00], *p*=0.012)
- Being seen in a community practice setting (aOR=0.43 [0.33-0.55], *p*<0.001), ref academic setting

Mediation analyses

- Significant total effect of mood disorders on irAE-TxDx (OR=1.08, [1.03, 1.15], *p*=0.004)
- Insurance type did not mediate this relationship (OR=1.00, [1.00, 1.00], p=0.828)
- Total effect was almost all due to the significant direct effect of mood disorders on irAE-TxDx

	Unadjusted Regression			Adjusted Regression[1]		
Characteristic	**OR[1]**	**95% CI[2]**	**p-value**	**OR[1]**	**95% CI[2]**	**p-value**
Any Mood Disorder, ref none	2.25	1.82, 2.79	<0.001	1.49	1.14, 1.93	0.003
Age at Advanced Diagnosis	0.99	0.98, 1.00	0.003	0.99	0.97, 1.00	0.012
Male Gender, ref female	0.73	0.60, 0.89	0.002	1.06	0.84, 1.33	0.6
Cancer Type, ref Melanoma						
Bladder	0.99	0.64, 1.54	>0.9	1.49	0.93, 2.39	0.10
Colorectal	0.76	0.35, 1.61	0.5	0.86	0.38, 1.90	0.7
Head and Neck	0.00	0.00, 0.00	>0.9	0.00	0.00, 0.00	>0.9
Lung	1.58	1.22, 2.05	<0.001	1.97	1.47, 2.64	<0.001
Practice Type, ref any acad.						
Community Only	0.41	0.33, 0.51	<0.001	0.43	0.33, 0.55	<0.001
Visits after Adv. Diagnosis	1.01	1.00, 1.01	<0.001	1.01	1.00, 1.01	<0.001

[1]Models adjusted for insurance type, race; [2]OR = Odds Ratio, CI = Confidence Interval

Table 1. Unadjusted and adjusted logistic regression examining characteristics associated with irAE-TxDx

DISCUSSION

- **Risk factors for irAE-TxDx:** Mood disorder, younger age, lung cancer
- **Practice considerations:** Treatment discontinuation was associated with greater overall clinic visits and varies by practice type
- **Strengths:** Causal modeling approach, large real-world dataset
- **Limitations:** Possible bidirectionality of findings, data may underrepresent patients with lower help-seeking behaviors for irAEs or mood disorders, unable to study lower severity symptoms that may meaningfully impact quality of life and influence treatment discontinuation

CONCLUSIONS

- Suggests that patients with irAEs and mood disorders may be at risk for discontinuing ICI therapy
- Implications for the need for more integrative physical and psychosocial symptom monitoring, support, and management for patients with irAEs and mood disorders-- particularly younger patients with lung cancer, across care settings

REFERENCES

1. Smith HR. Depression in cancer patients: Pathogenesis, implications and treatment. Oncology letters. 2015;9(4):1509-1514.

2. Goerling U, Hinz A, Koch-Gromus U, Hufeld JM, Esser P, Mehnert-Theuerkauf A. Prevalence and severity of anxiety in cancer patients: Results from a multi-center cohort study in Germany. Journal of Cancer Research and Clinical Oncology. 2023;149(9):6371-6379.

3. Grassi L, Caruso R, Riba M, et al. Anxiety and depression in adult cancer patients: ESMO Clinical Practice Guideline. *ESMO open*. 2023;8(2):101155

4. Tay, D., Dubose, K., Hidayatullah Fadlullah, M. Z., Guo, J. W., Tan, A. C., Young, A., ... & Sheng, X. (2024). Immune-related adverse events, mood disorders, and the impact of social determinants of health among a national cohort of patients receiving immunotherapy

5. Wang F, Yang S, Palmer N, et al. Real-world data analyses unveiled the immune-related adverse effects of immune checkpoint inhibitors across cancer types. NPJ Precision Oncology. 2021;5(1):82

This study was funded by a Flatiron Health Equity award from Flatiron Health (DT, JG) and an American Cancer Society intramural grant award (DT). The support and resources from the Center for High Performance Computing at the University of Utah are gratefully acknowledged. The computational resources used were partially funded by the NIH Shared Instrumentation Grant 1S10OD021644-01A1. This study was also partially supported by the Huntsman Cancer Institute Comprehensive Cancer Center at the University of Utah P30CA042014, utilizing the Cancer Biostatistics and Cancer Bioinformatics Shared Resources. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.