1241 CLUSTERS OF MULTI-ORGAN TOXICITIES ARE ASSOCIATED WITH IMPROVED SURVIVAL AMONG IMMUNE CHECKPOINT INHIBITOR RECIPIENTS: A POPULATION-LEVEL STUDY

[1]Wenxin Chen, [1]Guihong Wan, [1]Katie Roster, [2]Nga Nguyen, [1]Ahmad Rajesh, [1]Jayhyun Seo, [1]Hannah Rashdan, [1]Leyre Zubiri, [1]Kerry Reynolds, [1]Shadmehr Demehri, [3]Kun-Hsing Yu, [4]William Lotter, [4]Alexander Gusev, [4]Nicole R Leboeuf, [5]Shawn Kwatra, [1,3]Yevgeniy R Semenov*. *[1]Massachusetts General Hospital, Boston, MA, USA; [2]Massachusetts General Hospital, Fayetteville, NC, USA; [3]Harvard Medical School, Boston, MA, USA; [4]Dana-Farber Cancer Institute, Boston, MA, USA; [5]Johns Hopkins University, Baltimore, MD, USA*

Background Immune-related adverse events (irAEs) induced by immune checkpoint inhibitor (ICI) therapy can involve multiple organ systems, of which cutaneous irAEs (c-irAEs) are the most common.[1–5] Understanding co-occurrence patterns and prognostic outcomes of irAEs is critical for immunotherapy management. However, previous studies have been limited by cohort size, thus limiting generalizability.[6–8] In addition, the prior study approaches primarily utilized pairwise comparison analyses, which limited the examination of irAE relationships to two organ systems at a time. In this study, we leverage a population-level database and compare results to a multi-institutional cohort from a tertiary-level academic healthcare system to investigate the co-occurrence patterns irAEs and their impact on immunotherapy outcomes through non-negative matrix factorization (NMF),[9] which allows for multi-organ analyses.

Methods After propensity-matching in a 1:2 ratio based on demographic and cancer-related variables and exclusion of ambiguous cases, the study analyses included 9,273 patients in the Mass General Brigham Healthcare System (MGB) cohort and 23,689 patients in the TriNetX network (figure 1). The identification of irAEs was based on ICD codes. Pairwise correlation analysis and NMF were conducted to investigate the co-occurrence patterns. Multivariate landmark analyses were conducted to evaluate the associated impact on overall survival, adjusting for demographics, cancer type, and ICI type.

Results Characteristics of the TriNetX and MGB are shown in (table 1). Pairwise co-occurrence analyses showed patients with c-irAEs were at increased risk of developing an irAE in nine of the eleven organ systems evaluated. The co-occurrence of c-irAEs and non-cutaneous irAEs (nc-irAEs) was associated with improved survival (HR:0.68, CI, 0.61–0.76; $p<0.001$) (table 2). NMF identified four unique patient clusters, of which three were consistent between the TriNetX and MGB cohorts: c-irAEs, endocrine irAEs, and multiple internal organ irAEs (comprising mostly neurologic, respiratory, gastrointestinal irAEs) (figure 2). The Cutaneous and endocrine clusters showed strongly favorable prognoses across all landmark times (table 3). The endocrine-dominant cluster displayed a better prognosis (MGB: HR=0.48, $p<0.001$; TriNetX: HR=0.58, $p<0.001$) compared to the Cutaneous-dominant cluster (MGB: HR=0.55, $p<0.001$; TriNetX: HR=0.65, $p<0.001$).

Conclusions Our study demonstrates that patients who develop c-irAEs are at significantly increased risk of developing toxicities in other organs. This emphasizes the importance of monitoring, diagnosing, and managing c-irAEs given their valuable prognostic benefit. In addition, we specifically found a significant survival benefit among patients who develop cutaneous and endocrine irAEs. This may suggest underlying mechanisms that differ from other ICI and organ system interactions, which will require future studies to elucidate.

REFERENCES

1. Ramos-Casals M, Brahmer JR, Callahan MK, *et al*. Immune-related adverse events of checkpoint inhibitors. *Nat Rev Dis Primers*. 2020;**6**(1):1–21. Doi:10.1038/s41572–020-0160–6
2. Puzanov I, Diab A, Abdallah K, *et al*. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer*. 2017;**5**(1):95. Doi:10.1186/S40425–017-0300-Z
3. Brahmer JR, Lacchetti C, Schneider BJ, *et al*. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American society of clinical oncology clinical practice guideline. *Journal of Clinical Oncology*. 2018;**36**(17):1714–1768. Doi:10.1200/JCO.2017.77.6385
4. Le TK, Brown I, Goldberg R, *et al*. Cutaneous Toxicities Associated with Immune Checkpoint Inhibitors: An Observational, Pharmacovigilance Study. *J Invest Dermatol*. 2022;**142**(11):2896–2908.e4. doi:10.1016/J.JID.2022.04.020
5. Wongvibulsin S, Pahalyants V, Kalinich M, *et al*. Epidemiology and risk factors for the development of cutaneous toxicities in patients treated with immune-checkpoint inhibitors: A United States population-level analysis. *J Am Acad Dermatol*. 2022;**86**(3):563–572. Doi:10.1016/J.JAAD.2021.03.094
6. Chieng JHL, Htet ZW, Zhao JJ, *et al*. Clinical Presentation of Immune-Related Endocrine Adverse Events during Immune Checkpoint Inhibitor Treatment. *Cancers (Basel)*. 2022;**14**(11):2687. Doi:10.3390/CANCERS14112687
7. Yamada K, Nakamura M, Yamamura T, *et al*. Clinical characteristics of gastrointestinal immune-related adverse events of immune checkpoint inhibitors and their association with survival. *World J Gastroenterol*. 2021;**27**(41):7190. Doi:10.3748/WJG.V27.I41.7190
8. Asdourian MS, Shah N, Jacoby T V, *et al*. Development of multiple cutaneous immune-related adverse events among cancer patients after immune checkpoint blockade. *J Am Acad Dermatol*. 2023;**88**(2):485–487. Doi:10.1016/j.jaad.2022.06.030
9. Pedregosa FABIANPEDREGOSA F, Michel V, Grisel OLIVIERGRISEL O, *et al*. Scikit-learn: Machine Learning in Python. *Journal of Machine Learning Research*. 2011;**12**(85):2825–2830. Accessed February 24, 2023. http://jmlr.org/papers/v12/pedregosa11a.html

Ethics Approval Reviewed and approved by Mass General Brigham IRB (Protocol #2020P002179)

Abstract 1241 Table 1 Characteristics of the MGB and TriNetX cohorts

	TrinetX (N=23689)	MGB (N=9273)	P-value
Age at ICI Initiation			
Median [IQR]	66.0 [58.0,74.0]	66.7 [58.1,74.5]	<0.001
Gender			
Female	10644 (44.9%)	4191 (45.2%)	0.674
Male	13045 (55.1%)	5082 (54.8%)	
Race			
White	21104 (89.1%)	8379 (90.4%)	<0.001
Black or African American	787 (3.3%)	249 (2.7%)	
Asian	689 (2.9%)	283 (3.1%)	
Other/Unavailable	1109 (4.7%)	362 (3.9%)	
Ethnicity			
Hispanic	823 (3.5%)	250 (2.7%)	0.00163
Not Hispanic	21059 (88.9%)	8314 (89.7%)	
Unavailable	1807 (7.6%)	709 (7.6%)	
Charlson Comorbidity Index			
0	274 (1.2%)	73 (0.8%)	<0.001
1-2	3081 (13.0%)	1293 (13.9%)	
3-4	2025 (8.5%)	672 (7.2%)	
>=5	18309 (77.3%)	7235 (78.0%)	
Cancer Type			
Breast	1167 (4.9%)	530 (5.7%)	<0.001
Digestive	2885 (12.2%)	1157 (12.5%)	
Eye/Brain/Nervous	798 (3.4%)	408 (4.4%)	
Female Genital	1062 (4.5%)	407 (4.4%)	
Lymphoid/Hematopoietic	1144 (4.8%)	434 (4.7%)	
Thoracic	5823 (24.6%)	2398 (25.9%)	
Lip/Oral/Pharynx	1011 (4.3%)	347 (3.7%)	
Male Genital/Urinary	3049 (12.9%)	1245 (13.4%)	
Melanoma	3313 (14.0%)	1100 (11.9%)	
Other Skin Malignancy	1484 (6.3%)	528 (5.7%)	
Other	1953 (8.2%)	719 (7.8%)	
Secondary Cancer Type			
Multiple Sites	14230 (60.1%)	5697 (61.4%)	<0.001
Lymph Nodes	1259 (5.3%)	588 (6.3%)	
Respiratory/Digestive	1431 (6.0%)	633 (6.8%)	
Other	2042 (8.6%)	679 (7.3%)	
No	4727 (20.0%)	1676 (18.1%)	
Pre-ICI Treatment			
Conventional Chemotherapy	5495 (23.2%)	2565 (27.7%)	<0.001
Targeted Therapy	923 (3.9%)	708 (7.6%)	

Abstract 1241 Table 2 Survival outcomes of multi-organ toxicity among patients with c-irAEs

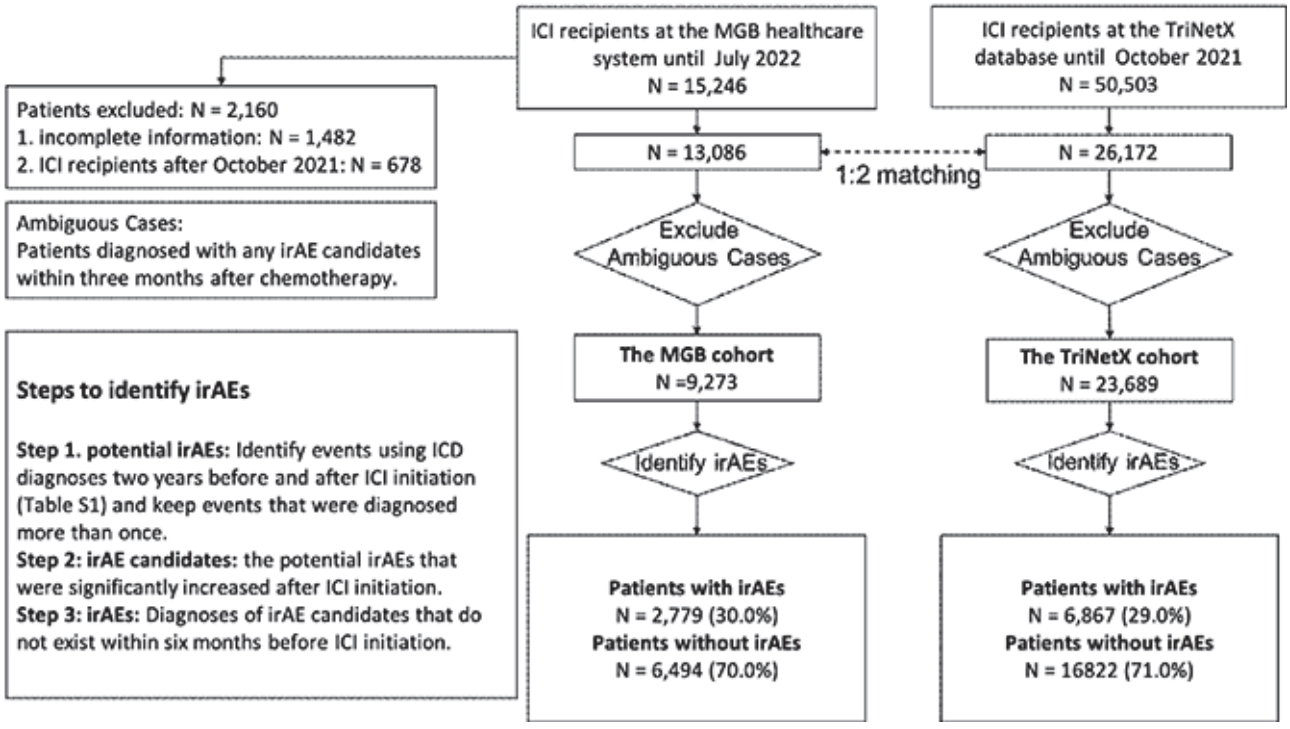
Landmark Time	Cohort	HR [95% CI]		
		c-irAE only	c-irAE + nc-irAE	nc-irAE only
3	TriNetX	0.54 [0.48,0.61]***	0.52 [0.47,0.58]***	0.74 [0.70,0.79]***
	MGB	0.43 [0.35,0.53]***	0.52 [0.44,0.61]***	0.71 [0.65,0.77]***
6	TriNetX	0.62 [0.54,0.70]***	0.68 [0.61,0.76]***	0.85 [0.79,0.91]***
	MGB	0.47 [0.37,0.59]***	0.57 [0.48,0.69]***	0.73 [0.66,0.80]***
9	TriNetX	0.71 [0.61,0.82]***	0.84 [0.74,0.95]**	0.94 [0.87,1.02]
	MGB	0.52 [0.41,0.67]***	0.71 [0.59,0.85]***	0.78 [0.69,0.87]***

Each row corresponds to a separate multivariate CoxPH model adjusted by age at ICI initiation, gender, race, ethnicity, cancer type, and ICI type. The reference group in each analysis was a cohort of patients without any irAEs. (***: p<0.001; **:p<0.01; *:p<0.05)

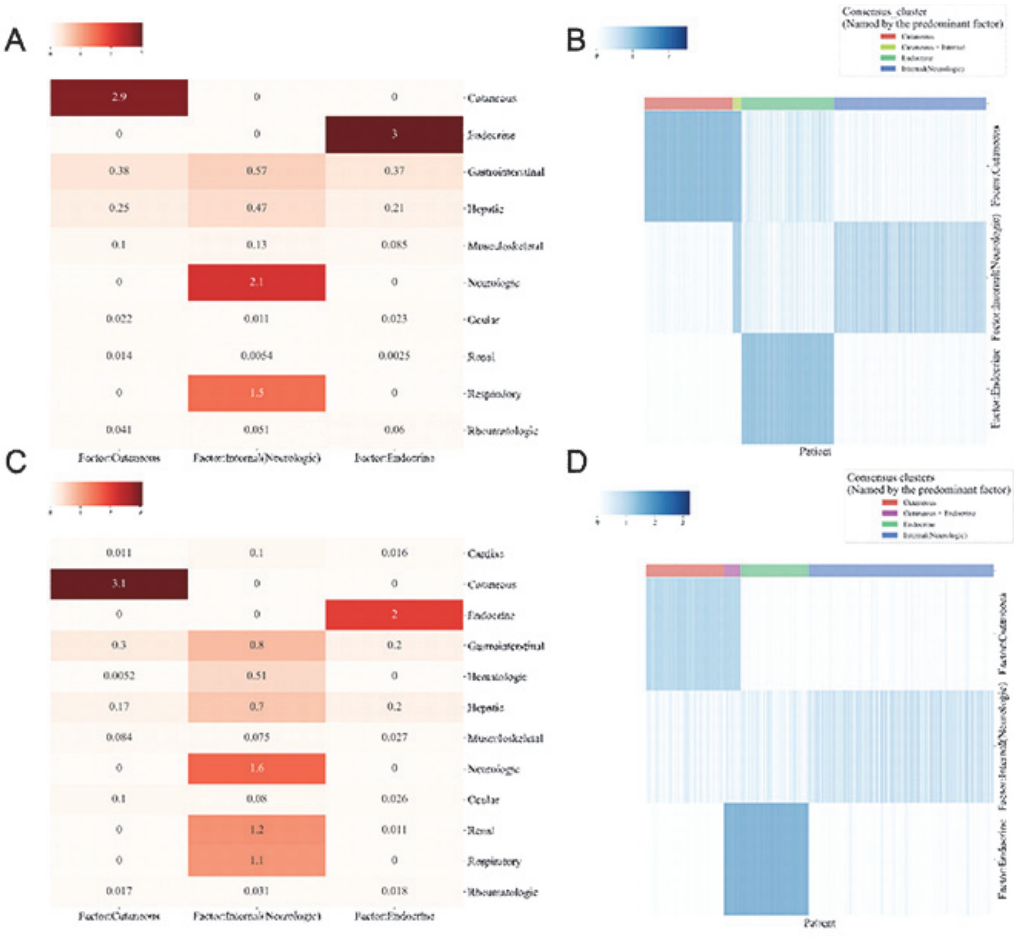
Abstract 1241 Table 3 Survival outcomes of patients cluster identified by NMF

Cohort	Landmark Time	HR [95% CI]			
		Cutaneous	Internal(Neurologic)	Endocrine	Cutaneous + Internal
TriNetX	3	0.55 [0.50, 0.60]***	0.90 [0.84, 0.96]**	0.48 [0.43, 0.52]***	0.54 [0.41, 0.72]***
	6	0.65 [0.59,0.72]***	1.03 [0.95,1.11]	0.58 [0.52,0.64]***	0.68 [0.51, 0.92]*
	9	0.76 [0.68,0.86]***	1.14 [1.04,1.25]**	0.68 [0.61,0.77]***	0.81 [0.59, 1.12]
		Cutaneous	Internal(Neurologic)	Endocrine	Cutaneous + Endocrine
MGB	3	0.50 [0.44, 0.58]***	0.85 [0.78, 0.93]***	0.42 [0.36, 0.50]***	0.28 [0.19, 0.41]***
	6	0.55 [0.47,0.65]***	0.88 [0.79,0.97]*	0.48 [0.40,0.58]***	0.32 [0.21, 0.48]***
	9	0.64 [0.54,0.76]***	0.93 [0.83,1.05]	0.57 [0.47,0.69]***	0.41 [0.27, 0.61]***

Each row corresponds to a separate multivariate CoxPH model adjusted by age at ICI initiation, gender, race, cancer type, ICI type, and ICI initiation year. The reference group in each analysis is a cohort of patients without any irAEs. (***: p<0.001; **:p<0.01; *:p<0.05)



Abstract 1241 Figure 1 The study population



Abstract 1241 Figure 2 The results of NMF and hierarchical clustering on the consensus matrix. (A, B) The NMF results and clusters on the TriNetX cohort; C-D: The NMF results and clusters on the MGB cohort. The NMF decomposed the irAE count matrix into two low-rank matrices, representing the organ-level irAE factors (referred to as 'basis'; A, C) and the weights of irAE factors that comprise each patient (referred to as 'weight'; B and D), respectively. For the basis matrix, rows are organ systems, and columns are the irAE factors, each named by the dominant organ systems. For the weight matrix, columns are patients, rows are irAE factors, and the clustering results are presented at the top. Similar patterns were observed between the two basis matrices (A, C). Patients in both cohorts could be categorized into four groups (B, D) Cutaneous, Cutaneous + Internal

http://dx.doi.org/10.1136/jitc-2023-SITC2023.1241