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Germline prediction of immune checkpoint inhibitor discontinuation for immune-related adverse events

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ABSTRACT

Introduction Immune checkpoint inhibitors (ICIs) can yield remarkable clinical responses in subsets of patients with solid tumors, but they also commonly cause immune-related adverse events (irAEs). The predictive features of clinically severe irAEs leading to cessation of ICIs have yet to be established. Given the similarities between irAEs and autoimmune diseases, we sought to investigate the association of a germline polygenic risk score for autoimmune disease and discontinuation of ICIs due to irAEs.

Methods The Genetics of immune-related adverse events and Response to Immunotherapy (GeRI) cohort comprises 1302 patients with non-small cell lung cancer (NSCLC) who received ICI therapy between 2009 and 2022 at four academic medical centers. We used a published polygenic risk score for autoimmune diseases (PRS_{AD}) in the general population and validated it in the All of Us. We then assessed the association between PRS_{AD} and cessation of ICI therapy due to irAEs in the GeRI cohort, using cause-specific and Fine-Gray subdistribution hazard models. To further understand the differential effects of type of therapy on the association between PRS_{AD} and cessation of ICI due to irAEs, we conducted a stratified analysis by type of ICI therapy.

Results Using a competing risk model, we found an association between PRS_{AD} and ICI cessation due to irAEs (HR per SD=1.24, p=0.004). This association was particularly strong in patients who had ICI cessation due to irAEs within 3 months of therapy initiation (HR per SD=1.40, p=0.005). Individuals in the top quintile of PRS_{AD} had 4.8% ICI discontinuation for irAEs by 3 months, compared with 2% discontinuation by 3 months among patients in the bottom quintile (log-rank p=0.03). In addition, among patients who received combination programmed cell death protein-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors and cytotoxic T-lymphocyte associated protein 4 (CTLA4) inhibitors, ICI discontinuation for irAEs by 3 months occurred in 4 of the 13 patients (30.8%) with high PRS_{AD} genetic risk (top quintile) versus 3 of 21 patients (14.3%) with low PRS_{AD} genetic risk (bottom quintile).

Conclusions We demonstrate an association between a polygenic risk score for autoimmune disease and early ICI discontinuation for irAEs. Our results suggest that germline genetics may be used as an adjunctive tool for risk stratification around ICI clinical decision-making in solid tumor oncology.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Clinically severe immune-related adverse events (irAEs) from immune checkpoint inhibitors (ICIs) can lead to treatment discontinuation, yet no predictive biomarkers exist. Since irAEs mimic autoimmune diseases, this study sought to investigate whether genetic predisposition to autoimmunity influences the risk of ICI cessation due to irAEs.

WHAT THIS STUDY ADDS

⇒ Our study demonstrates that genetic predisposition to overall autoimmunity is associated with an increased risk of developing clinically severe irAEs, leading to an early cessation of ICI therapy in patients with non-small cell lung cancer.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings could aid in risk stratification that could influence the management and treatment of patients with cancer receiving ICIs, particularly in early-stage cancers.

INTRODUCTION

Immune checkpoint inhibitors (ICIs), including anti-programmed cell death protein-1 (PD-1)/programmed death-ligand 1 (PD-L1) and anti-cytotoxic T-lymphocyte associated protein 4 (CTLA-4)-based therapies,[1–3] have revolutionized treatment landscapes across a wide spectrum of solid tumors including cutaneous,[4 5] lung,[6 7] genitourinary,[8 9] hepatobiliary,[10] and many other malignancies, and can lead to durable clinical responses in subsets of patients. However, in the clinic, the predicted benefit of ICIs must be balanced by the risk of incumbent

immune-related adverse events (irAEs) resulting from enhanced immune system activation, with irAEs of any grade estimated to occur in approximately 30–40% of patients treated with ICIs across indications.[11–13] Although irAEs are often mild-to-moderate in severity, the incidence of high-grade irAEs has been estimated to be up to 8–20% for anti-PD-1/PD-L1 monotherapy[14–16] and up to 18–59% for combination anti-PD-1 and anti-CTLA-4 therapy.[4 16] In some cases, irAEs can lead to severe morbidity and even patient death,[17 18] and subsets of irAEs have been shown to be irreversible.[19] The development of clinically significant irAEs can therefore often necessitate cessation of ICI therapy in the clinic.

Despite these risks, however, there remain no clear predictive features for the risk of development of clinically significant irAEs routinely considered in practice, apart from a history of prior autoimmune disease. Development of such predictive features would help optimize patient selection for ICI treatment, particularly in settings in which there remains clinical equipoise around the magnitude of predicted ICI benefit.[20 21] Efforts to characterize potential predictors of irAE development have included investigation of shared antigens in tumors and index organs experiencing irAE toxicity,[22] comprehensive gut microbiome profiling,[23] and evaluation of baseline serum autoantibodies by proteomics[24] in individual tumor types.

Multiple recent studies have highlighted the impact of germline genetic variation on the risk of irAE development across solid tumors.[25 26] In particular, polygenic risk scores (PRS) for autoimmune diseases have been shown to be associated with the development of irAEs. For example, recent work from our group and others has demonstrated that PRS for hypothyroidism is associated with ICI-induced thyroiditis,[27 28] PRS for ulcerative colitis is associated with ICI-induced colitis,[29] and PRS for psoriasis is associated with ICI-induced rash.[30] These findings suggest that pre-existing genetic susceptibility can unmask underlying autoimmunity, leading to the onset of irAEs in patients treated with ICIs. Since many autoimmune syndromes have overlapping susceptibility variants, we sought to evaluate whether a PRS for overall autoimmune susceptibility may be of value in predicting the development of irAEs, particularly clinically severe irAEs leading to discontinuation of ICI therapy. Here, using a large pooled cohort of patients with non-small cell lung cancer (NSCLC) treated with ICIs, we demonstrate the utility of a germline PRS for autoimmune disease[31] in predicting cessation of ICIs due to irAEs.

METHODS

Study sample

An overview of the Genetics of immune-related adverse events and Response to Immunotherapy (GeRI) study and analytical pipeline is shown in figure 1. The GeRI study is a cohort of 1,302 patients with NSCLC who were treated with ICIs across four medical centers: Vanderbilt

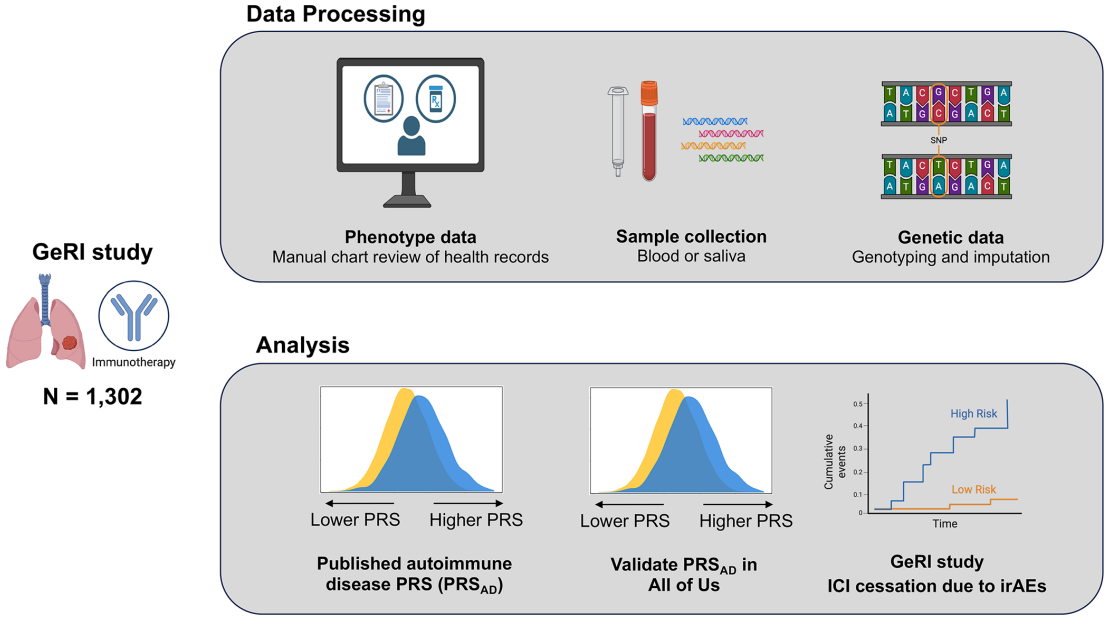

Figure 1 Brief overview of the GeRI study and the analytical pipeline. The GeRI study comprises 1302 patients with non-small cell lung cancer treated with at least one dose of immune checkpoint inhibitor (ICI) therapy. Phenotype data was manually curated from health records, and each participant provided either a blood or saliva sample for genotyping. Genotyping was performed using the Affymetrix Precision Medicine Diversity Array and imputed to the 1,000 genomes reference panel (phase 3 version 5). We used a published polygenic risk score for autoimmune diseases (PRS$_{AD}$)[1] in the general population and validated it in the All of Us. Next, association analysis between the PRS$_{AD}$[1] and ICI cessation due to immune-related adverse events (irAEs) was conducted using the Cox proportional hazards model and Fine-Gray subdistribution hazards models (to account for competing risks) in the GeRI study. Cumulative incidence curves were obtained by genetic risk based on PRS$_{AD}$ percentile. GeRI, Genetics of immune-related adverse events and Response to Immunotherapy.

University Medical Center (VUMC), Princess Margaret Cancer Center (PM), University of California, San Francisco (UCSF), and Memorial Sloan Kettering Cancer Center (MSK). All patients were administered at least one dose of either anti-PD-1 or anti-PD-L1 monotherapy or combined with anti-CTLA-4 and/or chemotherapy (online supplemental table 1). Briefly, the PM cohort comprises 306 ICI-treated patients enrolled between 2011 and 2022, while the VUMC cohort includes 242 patients who underwent ICI therapy between 2009 and 2019. VUMC participants were part of BioVU, Vanderbilt's biomedical DNA repository linked to the de-identified health records. The MSK cohort consists of 677 patients treated with ICIs between 2011 and 2022. The UCSF cohort includes 77 patients who received ICIs between 2019 and 2021. Local Institutional Review Boards approved the study at each center. All patients provided written informed consent.

Clinical and demographic data, including treatment dates and reasons for ICI therapy discontinuation, were extracted from each medical center through a manual review of medical, laboratory, and pharmacy records. None of the patients reported any prior or existing history of autoimmune disease. For the cause-specific hazards model, cessation of ICI therapy was coded as a dichotomous variable (1: cessation of therapy due to irAEs, 0: no cessation of therapy due to irAEs), and time-to-cessation for irAEs was assessed from the start of the ICI therapy to the date of ICI discontinuation due to irAEs. Patients who had ICI therapy cessation due to any other reason (eg, progression of the disease, death) were censored at the time of discontinuation of therapy due to that reason or the last follow-up date if the treatment was ongoing. In competing risk models, cessation of therapy due to reasons other than irAEs, such as progression of disease or death, was treated as competing risks.

Genotyping and quality control

Patients from all recruiting centers provided either blood or saliva samples for genotyping. Extracted DNA was genotyped using the Affymetrix Precision Medicine Diversity Research array. The array includes over 850,000 single nucleotide polymorphisms (SNPs), offering genome-wide coverage and is enriched for markers associated with known disease risks, including cancer, autoimmune disorders, and blood diseases.[32] It features an imputation-aware design, incorporating nearly 800,000 markers from phase III of the 1,000 Genomes Project to enhance genomic coverage. Furthermore, the markers were strategically selected to optimize representation across diverse ancestral populations, ensuring broad applicability and inclusivity in genetic studies. Genotype data were imputed to the 1,000 genomes reference panel (phase 3 version 5) using the Michigan Imputation Server. Samples with a call rate <95% were excluded from the analysis. Similarly, variants with genotyping rate <95%, Hardy-Weinberg equilibrium $p<1\times10^{-5}$, imputation quality INFO<0.30, and minor allele frequency (MAF)<1% were excluded.

Polygenic risk score for autoimmune disease

We used a previously developed polygenic risk score for autoimmune disease developed by Weissbrod *et al*.[31] (PRS_{AD}) to evaluate the association between PRS_{AD} and ICI discontinuation due to irAEs. Briefly, a dichotomous autoimmune disease phenotype was created by combining a series of autoimmune diseases, and a cross-population genome-wide PRS was developed using the PolyPred method.[31] PolyPred is a Bayesian approach to develop genome-wide PRS by applying functionally informed fine-mapping to estimate the weights of the SNPs. The PRS_{AD} comprises 159,127 genetic variants with an MAF>1% and was validated in an independent cross-population data set.

Replication of the PRS_{AD} in All of Us cohort

We used an independent data set to replicate the association between PRS_{AD} and autoimmune diseases in disease-free individuals, using All of Us (AoU). The AoU is a diverse cohort of individuals with genomic data paired with electronic health records.[33] To perform our analysis, we included self-reported non-Hispanic white individuals with genetic information and who had been diagnosed with any autoimmune disease based on ICD codes or SNOMED codes (online supplemental table 2). Autoimmune disease was defined as a union of all the following traits: rheumatoid arthritis, systemic lupus erythematosus, type 1 diabetes, acute infective polyneuritis/Guillain-Barré syndrome, Addison's disease, ankylosing spondylitis, ulcerative colitis, Crohn's disease, multiple sclerosis, Grave's disease, Hashimoto thyroiditis, polymyalgia, vasculitis, psoriasis, Sjögren's syndrome/sicca syndrome, vitiligo, celiac disease, myasthenia gravis, autoimmune liver disease, alopecia areata, scleroderma, and Wegener's granulomatosis. Individuals with cancers and immunodeficiencies were excluded from the analysis. Using the version 7 controlled tier short-read whole-genome sequencing data, specifically the Allele Count/Allele Frequency (ACAF)-threshold genomic data (variants with population-specific allele frequency >1% or population-specific allele count >100)[34] and weights from Weissbrod *et al*,[31] we calculated the PRS_{AD} for 124,649 participants included in the analysis. Next, we standardized the PRS_{AD} and assessed the association between PRS_{AD} and our binary outcomes of autoimmune disease, adjusted for age at diagnosis/assessment, sex, and 10 principal components (PCs).

Statistical analysis

Using the weights from Weissbrod *et al*,[31] we computed a weighted PRS_{AD} for all patients in the GeRI study. We standardized the PRS_{AD} and also categorized PRS_{AD} into quintiles. To calculate cumulative incidence estimates by PRS_{AD}, quintiles were further categorized into low (Q1), average (Q2–Q4), and high genetic risk (Q5). Cumulative incidence curves were computed using Kaplan-Meier curves and log-rank testing. Cause-specific Cox proportional hazard models were employed to assess the

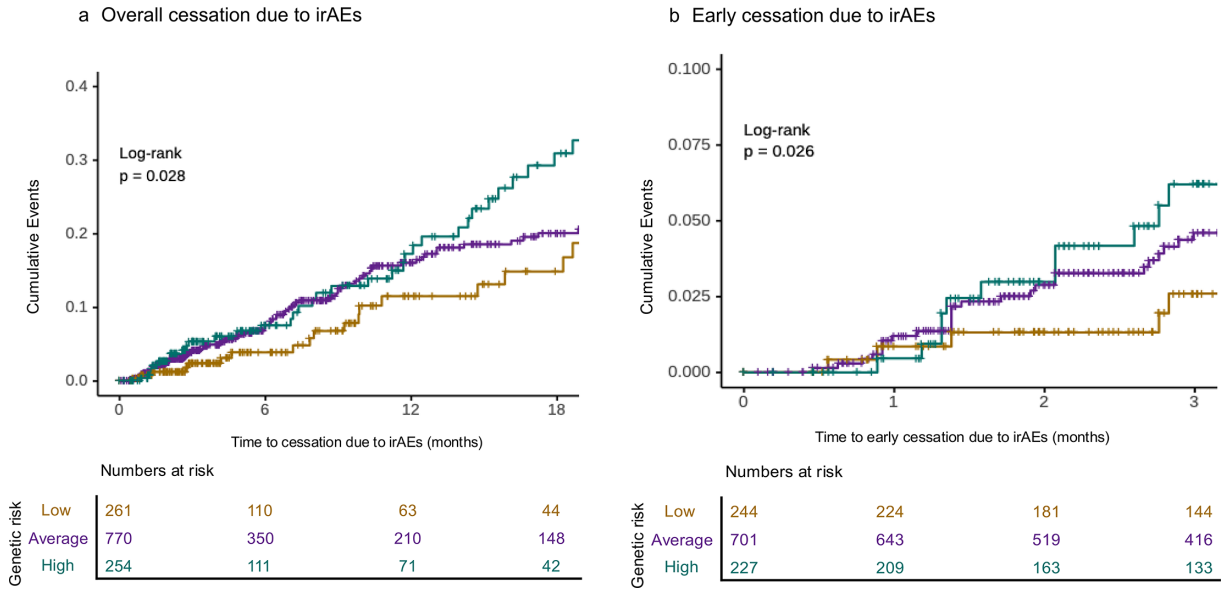

Figure 2 Cumulative incidence curves for (a) overall discontinuation of immune checkpoint inhibitor (ICI) therapy due to immune-related adverse events (irAEs) and (b) early discontinuation of ICI therapy due to irAEs (≤3 months) across categories of polygenic risk score of autoimmune disease (PRS_{AD}) in the Genetics of immune-related adverse events and Response to Immunotherapy (GeRI) study. PRS_{AD} quintiles were categorized into low (Q1), average (Q2–Q4), and high genetic risk (Q5). The p values included on each plot are the results of a log-rank test for the difference between the curves (two-sided). Due to few individuals having cessation after the first dose due to irAEs, the numbers at risk (at time 0) do not match the total number in the study.

HR of the continuous (per SD) and categorical PRS_{AD} on overall, early, and late cessation of ICIs due to irAEs. Early ICI discontinuation due to irAEs was defined as discontinuation of ICI therapy within 3 months of the start of therapy due to irAEs; late discontinuation was defined as discontinuation of ICI due to irAEs at or after 3 months of therapy.[11 19 35–38] To address competing risks, such as discontinuation of ICI for reasons other than the event of interest, such as death from any cause and disease progression, we performed a Fine-Gray subdistribution hazard analysis. Additionally, we tested the PRS_{AD} for association with individual irAE subtypes. All models were adjusted for age at diagnosis, sex, lung cancer histology, type of therapy, recruiting center, and the first five PCs. For a subset of patients who had therapy cessation due to irAEs (N=67), data on the toxicity grade were available. To further assess the association between the PRS_{AD} and irAE grade, we performed a Fine-Gray subdistribution hazard model. Next, we conducted stratified analyses by type of ICI therapy, disease stage, lung cancer histology, sex, and smoking status using a competing risk model. We also conducted stratified analysis by line of therapy in a subset of patients with available line of therapy information (N=677). All stratified analyses were adjusted for age at diagnosis, sex, lung cancer histology, recruiting center, and five PCs, except when conducting subgroup analyses by lung cancer histology and sex, respectively. Analyses were conducted using PLINK, R V.4.2.3 (R Foundation for Statistical Computing), and all p values were two-sided.

RESULTS

GeRI study characteristics

We analyzed data from a total of 1,302 patients with NSCLC treated with ICIs (online supplemental table 1). In this study, the median age at lung cancer diagnosis was 66 years (IQR: 59–73). Nearly half (48%) of the patients were women, and 83% of the patients were either current or former smokers. Adenocarcinoma was the most common histology, accounting for 72% of the cases, and 79% of patients had stage IV disease. 92% of patients received PD-1/PD-L1 inhibitor monotherapy, and 8% received combination therapy. Among the 1,302 patients overall, 171 (13%) experienced ICI cessation due to irAEs, with 58 (4.6%) experiencing ICI cessation due to irAEs less than 3 months from the start of therapy (defined as early ICI cessation). The median time to ICI cessation due to irAEs was 6.9 (1.9–13.1) months.

PRS_{AD} is associated with autoimmune diseases in the AoU cohort

First, we validated PRS_{AD} in the general population using the AoU cohort, including 124,649 participants, of whom 22,036 (17.7%) individuals had an autoimmune disease (online supplemental table 3). The cohort comprised 74,625 (59.9%) women and 50,024 (40.1%) men. The mean age of diagnosis was 56.09 years (SD=15.62), whereas the mean age at assessment was 55.09 years (SD=17.21). We found an association between PRS_{AD} and autoimmune disease with an OR per SD of 1.18 (95% CI=1.16 to 1.19, $p=5.9\times10^{-106}$). As shown in online supplemental table 4, the PRS_{AD} demonstrated an increased risk

in individuals in the highest quintile (Q5) with an OR of 1.55 (95% CI=1.49 to 1.63, p=2.3×10^{-77}).

PRS$_{AD}$ is associated with early ICI cessation due to irAEs

Individuals in the top quintile (Q5) of the PRS$_{AD}$ experienced increased cumulative ICI cessation events due to irAEs, with 14.9% in the high genetic risk group compared with 8.4% in the low genetic risk group (Q1) (log-rank p=0.03, figure 2a). This was particularly evident in early ICI cessation due to irAEs, with 4.8% early discontinuation among those with high genetic risk (Q5) and 2% early discontinuation among those with low genetic risk (Q1) within 3 months of initiation of ICI therapy (log-rank p=0.03, figure 2b).

Our cause-specific Cox proportional hazards model demonstrated an association between PRS$_{AD}$ and ICI cessation due to irAEs (HR per SD=1.17, 95% CI=1.01 to 1.36, p=0.04). This association was stronger in individuals at high genetic risk (Q5), where the risk was doubled compared with those individuals at low genetic risk (Q1) (HR=2.03, 95% CI=1.19 to 3.46, p=0.009). In our competing risk model, we observed a subdistribution HR per SD of 1.24 (95% CI=1.07 to 1.44, p=0.004). Similar to the cause-specific hazards model, we also observed a stronger association for individuals at high genetic risk (HR=2.25, 95% CI=1.33 to 3.83, p=0.003) when compared with the low genetic risk group.

The association between PRS$_{AD}$ and ICI discontinuation due to irAEs was stronger in individuals who had early ICI cessation as a result of irAEs (cause-specific HR per SD=1.38, 95% CI=1.08 to 1.78, p=0.01; subdistribution HR per SD=1.40, 95% CI=1.11 to 1.78, p=0.005). Moreover, individuals with high genetic risk (Q5) exhibited nearly a fourfold higher likelihood of discontinuing ICI treatment due to irAEs within the first 3 months compared with those in the low genetic risk group (cause-specific HR=4.38, 95% CI=1.46 to 13.09, p=0.008 and subdistribution HR=4.53, 95% CI=1.51 to 13.6, p=0.007). We did not observe a statistically significant association between PRS$_{AD}$ and late ICI cessation due to irAEs (table 1). In a subset of patients who had cessation of ICI therapy due to irAEs (N=67), we observed that PRS$_{AD}$ was strongly associated with grade 3 and 4 irAEs (HR=1.88, 95% CI=1.23 to 2.67, p=0.004, online supplemental table 5).

Additionally, we examined the association between PRS$_{AD}$ and each irAE subtype leading to ICI discontinuation (online supplemental table 6). Information regarding the type of irAE leading to discontinuation was available for 126 patients. Among 126 patients who had discontinuation of ICI therapy due to irAEs, the top irAEs were colitis (19.3%), pneumonitis (16.4%), and hepatitis (6.25%). Online supplemental table 6 reports the association for each irAE subtype. We observed a statistically significant association between PRS$_{AD}$ and ICI cessation

Table 1 Association of standardized polygenic risk score (PRS) of autoimmune disease (mean 0 and SD of 1) and PRS quintiles (Q1 to Q5) on overall, early and late time to immune checkpoint inhibitor (ICI) therapy cessation due to immune-related adverse events (irAEs) in the Genetics of immune-related adverse events and Response to Immunotherapy (GeRI) study, using cause-specific Cox proportional hazards model and Fine-Gray subdistribution hazards model

	Overall		Early*		Late*	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Cause-specific hazards model†						
Per 1 SD	1.17 (1.01 to 1.36)	0.04	1.38 (1.08 to 1.78)	**0.01**	1.10 (0.91 to 1.33)	0.33
Q1	1.00	1.00	1.00	1.00	1.00	
Q2	1.69 (0.97 to 2.98)	0.07	3.31 (1.07 to 10.37)	**0.04**	1.31 (0.67 to 2.56)	0.43
Q3	1.49 (0.85 to 2.61)	0.16	2.96 (0.93 to 9.41)	0.07	1.17 (0.61 to 2.26)	0.63
Q4	1.52 (0.87 to 2.65)	0.14	3.60 (1.16 to 11.14)	**0.03**	1.10 (0.57 to 2.11)	0.78
Q5	2.03 (1.19 to 3.46)	0.009	4.38 (1.46 to 13.09)	**0.008**	1.53 (0.82 to 2.87)	0.18
Fine-Gray subdistribution hazards model†						
Per 1 SD	1.24 (1.07 to 1.44)	0.004	1.40 (1.11 to 1.78)	**0.005**	1.18 (0.98 to 1.42)	0.08
Q1	1.00	1.00	1.00	1.00	1.00	
Q2	1.68 (0.96 to 2.96)	0.07	3.20 (1.02 to 10.1)	**0.04**	1.31 (0.67 to 2.56)	0.4
Q3	1.73 (0.99 to 3.03)	0.05	3.07 (0.96 to 9.82)	0.06	1.42 (0.75 to 2.72)	0.3
Q4	1.81 (1.04 to 3.16)	0.04	3.63 (1.16 to 11.4)	**0.03**	1.40 (0.72 to 2.70)	0.3
Q5	2.25 (1.33 to 3.83)	0.003	4.53 (1.51 to 13.6)	**0.007**	1.77 (0.95 to 3.28)	0.07

Bold represents p<0.05.
*Early ICI cessation is defined as ICI cessation due to irAEs within 3 months of ICI therapy initiation, whereas late ICI cessation is defined as discontinuation of ICI therapy after 3 months from the start of the ICI therapy.
†All models are adjusted for age at diagnosis, sex, type of ICI therapy, lung cancer histology, recruiting center, and five principal components.
CI, Confidence Intervals; HR, Hazards ratio; SD, Standard Deviation.

Table 2 Stratified Fine-Gray subdistribution hazard analyses assessing the association between polygenic risk score of autoimmune disease and immune checkpoint inhibitor cessation due to immune-related adverse events in the Genetics of immune-related adverse events and Response to Immunotherapy (GeRI) study, by type of therapy, disease stage, lung cancer histology, sex, and smoking status

Variable	N	HR per SD*	95% CI	P value
Type of ICI therapy†				
Anti PD-1/PD-L1 monotherapy	1212	1.21	1.04 to 1.41	**0.02**
Anti PD-1/PD-L1 inhibitor+anti-CTLA-4 inhibitor	90	1.76	0.90 to 3.45	0.1
Lung cancer stage†				
I	55	4.68	0.31 to 70.9	0.3
II	47	1.16	0.47 to 2.86	0.7
III	161	1.04	0.72 to 1.50	0.8
IV	963	1.35	1.11 to 1.64	**0.003**
Lung cancer histology‡				
Adenocarcinoma	933	1.22	1.03 to 1.45	**0.02**
Squamous cell carcinoma	220	1.55	1.04 to 2.33	**0.03**
NOS	59	1.25	0.65 to 2.39	0.50
Other	52	0.64	0.34 to 1.24	0.19
Sex§				
Male	671	1.44	1.17 to 1.77	**0.0005**
Female	631	1.06	0.86 to 1.31	0.58
Smoking status†				
Ever	901	1.21	1.01 to 1.44	**0.03**
Never	181	1.32	0.81 to 2.16	0.27

Bold represents p<0.05.
*PRS was standardized to have a mean of 0 and SD of 1
†Models are adjusted for age at diagnosis, sex, lung cancer histology, recruiting center, and five principal components.
‡Models are adjusted for age at diagnosis, sex, recruiting center, and five principal components.
§Models are adjusted for age at diagnosis, lung cancer histology, recruiting center, and five principal components.
CI, Confidence Interval; CTLA-4, cytotoxic T-lymphocyte associated protein 4; HR, Hazard ratio; ICI, Immune checkpoint inhibitor therapy; NOS, Not Otherwise Specified; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; SD, Standard Deviation.

due to hepatitis irAE (HR per SD=2.16, 95% CI=1.08 to 4.32, p=0.03).

To further characterize the differential association between PRS_{AD} and ICI cessation, we performed stratified analyses by type of ICI therapy, disease stage, lung cancer histology, sex, and smoking status (table 2). Early ICI discontinuation for irAEs occurred in 4 of the 13 patients (30.8%) with high PRS_{AD} genetic risk (Q5) who received combination PD-1/PD-L1 inhibitors and CTLA-4 inhibitors, versus 3 of 21 patients (14.3%) with low PRS_{AD} genetic risk (Q1) who received combination PD-1/PD-L1 and CTLA-4 inhibitors. Patients who received PD-1/PD-L1 monotherapy had an HR per SD of 1.21 (95% CI=1.04 to 1.41, p=0.02), whereas those who received a combination of PD-1/PD-L1 inhibitors and CTLA-4 inhibitors showed an HR per SD of 1.76 (95% CI=0.90 to 3.45, p=0.1). We examined the interaction between PRS_{AD} and type of ICI therapy and observed no statistically significant interaction, but a trend towards a stronger effect in the combination Anti-PD-1/PD-L1+anti-CTLA-4 group with an interaction HR per SD of 1.27 (95% CI=0.77 to 2.09, p=0.35). Future studies with larger sample sizes of patients treated with combination therapy should be performed to determine whether the combination therapy magnifies the effect of PRS_{AD}.

The association between PRS_{AD} and cessation of ICI therapy was stronger in men with an HR per SD of 1.44 (95% CI=1.17 to 1.77, $p=5\times10^{-4}$) than in women with an HR per SD of 1.06 (95% CI=0.86 to 1.31, p=0.58). We observed a consistent association between PRS_{AD} and cessation of ICI therapy in patients with stage IV NSCLC (HR per SD=1.35, 95% CI=1.11 to 1.64, $p=3\times10^{-3}$), as well as in ever smokers (HR per SD=1.21, 95% CI=1.01 to 1.44, p=0.03). When stratified by lung cancer histology, we observed an HR per SD of 1.22 (95% CI=1.03 to 1.45, p=0.02) in patients with adenocarcinomas and an HR per SD of 1.55 (95% CI=1.04 to 2.33, p=0.03) in patients with squamous cell carcinomas. Among a subset of patients (N=677), we evaluated the relationship between PRS_{AD} and the discontinuation of ICI therapy, stratified by line of therapy (online supplemental table 5). In patients who received ICIs as a first-line treatment (N=263), we observed an HR per SD of 1.64 (95% CI=1.14 to 2.35, p=0.008).

DISCUSSION

Here, using a multicenter, clinically annotated cohort of patients with NSCLC treated with ICIs, we demonstrate that a composite PRS for autoimmune disease predicts the cessation of ICIs due to irAEs. Our results suggest that PRS_{AD} may broadly predict clinically significant irAEs (grades 3 and above) that lead to therapy discontinuation. Further, PRS_{AD} is more strongly associated with early ICI discontinuation due to irAEs. Early discontinuation is often due to severe irAEs and may limit potential efficacy. On the other hand, late ICI discontinuation may be more likely to occur due to lower-grade toxicity after a prolonged period of disease control. Our results continue to build on a body of recent work[25–27 37] describing the association of germline genetic variation on the risk of irAE development in patients with solid tumors treated with ICIs and represent further proof of principle that continued investigation of germline predictors of ICI toxicity is warranted.

Our findings provide valuable insights into the biological mechanisms underlying irAEs and hold the potential to influence the clinical management of patients undergoing ICI therapy. Specifically, we demonstrate a clear overlap between genetic predisposition to autoimmunity and the development of irAEs that result in the cessation of ICI treatment. This relationship is particularly pronounced in cases of ICI-mediated hepatitis. The association between genetic susceptibility to autoimmunity and ICI-mediated hepatitis points to the involvement of immune mechanisms, including liver-specific T-cell activation and cytokine dysregulation, in driving this subtype of irAE.[39–41] The observed overlap with autoimmune pathways reinforces the importance of investigating immune-genetic interactions in greater depth. Targeted studies at the individual variant and gene levels are necessary to elucidate the biological basis of this relationship.

Our study also has important clinical implications that could influence the management and treatment of patients with cancer receiving ICIs, particularly in early-stage cancers where there are other treatment modalities available. Currently, for multiple indications across solid tumor oncology, including advanced melanoma,[4 5] renal cell carcinoma[42 43 44], hepatocellular carcinoma,[45] and others, clinical equipoise exists around the decision to treat with either combination ICI therapy or ICI monotherapy with or without other therapies. Our stratified analysis demonstrates the association of PRS_{AD} with ICI discontinuation across types of ICI therapy (monotherapy vs combination therapy), with a stronger, although not significant association in the combination anti-PD-1/PD-L-1 and anti-CTLA-4 therapy group, where the risk of ICI toxicity is highest.[4 16] The lack of statistical significance may be attributed to the smaller sample size of patients receiving anti-PD-1/PD-L-1 and anti-CTLA-4 therapy in our study. Additionally, while we conducted stratified analyses based on ICI therapy, the small size of the groups that also received chemotherapy limited our ability to investigate these subgroups in greater detail. If prospectively validated as a predictive marker of severe ICI toxicity and early cessation, PRS_{AD} may emerge as a useful adjunctive tool to help guide treatment decisions in these and related scenarios. In addition, given the emerging landscape of clinical trials investigating the use of prophylactic immunosuppressants to help maximize exposure to combination ICI therapy in advanced melanoma and other solid tumors,[46 47] individuals with high PRS_{AD} genetic risk may represent a subpopulation of patients who could particularly benefit from such approaches.

Despite the association of PRS_{AD} with early ICI discontinuation for irAEs demonstrated in our study, it is likely that additional features also contribute to the risk of severe irAE development in patients treated with ICIs. In addition to refining predictive germline genetic signatures, future efforts could include the development of multimodal platforms incorporating tumor-intrinsic features,[22] host T-cell[22] or B-cell repertoires,[24] features of host-microbiome[23] and other components, which have been suggested to additionally predict for irAE development. The declining cost of germline sequencing may suggest that PRS_{AD} could be more easily incorporated into routine practice if prospectively validated as a marker of severe ICI toxicity.[48]

Our study has several limitations. First, a subset of patients (N=176) included in our study lacked lung cancer staging information, limiting our ability to fully describe the impact of our analyses across different disease stages. Furthermore, we were only able to assess the association between PRS_{AD} and the severity of irAEs in a limited subset of patients (N=67). Similarly, we were only able to examine the impact of the line of therapy on a small subset of patients. Therefore, future studies with more comprehensive and granular data on the line of therapy, disease stage, irAE type, and severity are warranted. Additionally, our analyses did not account for immune-specific confounding factors that might influence the risk of irAEs, including baseline immune status and concomitant medications, which can modulate immune responses, highlighting the need for future studies that incorporate these factors to provide a more robust understanding of irAE risk. While our study cohort largely mirrors the genetic diversity of the population used to develop PRS_{AD}, further research involving more ethnically diverse groups will be important to assess the broader applicability of these findings. Despite these limitations, it is important to recognize that our study stands as one of the largest studies of germline genetics and irAEs in patients with NSCLC treated with ICIs, providing valuable insights into predictors of toxicity in this patient population.

In summary, we describe the utility of a germline PRS for autoimmune disease to help identify patients at high risk for early ICI cessation due to severe irAEs. Future efforts to continue to refine germline PRSs to predict severe ICI toxicity could further develop our understanding of irAE pathogenesis and assist with treatment decisions, especially in clinical scenarios in which the risk of severe irAE development is high.

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