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Association between serum lactate dehydrogenase and cutaneous immune-related adverse events among patients on immune checkpoint inhibitors for advanced melanoma

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Keywords

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To the Editor: Immune checkpoint inhibitors (ICIs) represent a major breakthrough in the treatment of advanced malignancies. Although prior studies have sought to identify predictive biomarkers for ICI treatment response and the development of immune-related adverse events (irAEs),[1] there is limited research regarding the relationship between clinical biomarkers such as tumor burden and cutaneous immune-related adverse events (cirAEs), which are among the most prevalent irAEs.[2] We thus evaluated the association between cirAE incidence or severity and tumor burden using serum lactate dehydrogenase (LDH)[3] as a surrogate marker.

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We reviewed the records of patients with stage IV melanoma who received ICI therapy at Massachusetts General Hospital between January 1, 2016 and March 8, 2019 and who developed a cirAE. Demographics, clinical history, and cirAE-related variables were abstracted. LDH values at baseline and at greater than 3 months post-ICI initiation were obtained and categorized as high (>210 U/L) or low (≤210 U/L), based on the upper limit of the laboratory normal range at our institution. Patients without baseline or greater than 3-month LDH values were excluded. The same variables were collected for a group of patients with stage IV melanoma without cirAEs who received ICIs between 2014 and 2019. Differences in baseline characteristics by cirAE status were assessed using Fisher's exact and Mann-Whitney U tests. Binomial logistic regression was used to examine differences in cirAE incidence, severity, and morphologic patterns based on LDH levels at each timepoint. Multivariate models included age, sex, and covariates significant to $P < .10$.

Among patients who developed cirAEs (n = 63), 18 (28.9%) and 14 (22.2%) had a high LDH at baseline and greater than 3 months post-ICI, respectively. In the non-cirAE group (n = 46), 24 (52.2%) had a high LDH at baseline and 26 (56.5%) had an elevated value greater than 3 months post-ICI (Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/98c99dcvtt/1). Multivariate analysis demonstrated that high LDH prior to starting ICI therapy was significantly associated with a lower odds of developing a cirAE (odds ratio, 0.37; 95% CI, 0.14–0.92; $P<.033$). This relationship persisted greater than 3 months after ICI initiation, with a significant inverse association between high LDH and cirAE development (odds ratio, 0.30; 95% CI 0.12–0.77; $P<.013$). The severity and subtype of cirAE did not differ significantly based on LDH value at either of the examined time points (Table I). Additional results on the association between LDH levels and progression-free/overall survival are included in the Mendeley Supplement (Supplemental Material, available via Mendeley at https://data.mendeley.com/datasets/98c99dcvtt/1).

These results suggest that elevated LDH is a marker for ICI response and may reflect later risk of cirAE development. As cirAEs are thought to represent bystander effects from activated T cells,[4] we hypothesize that, mechanistically, patients with an increased tumor burden have decreased anti-tumor T-cell activity at baseline and after ICI initiation, thus experiencing less severe cirAEs. Although the relationship between tumor/neoantigen burden and ICI-induced T-cell responses is not fully understood, study results suggest that tumor degree present at the time of immunotherapy influences the magnitude of immune responses.[5]

Study limitations include its retrospective design, small sample size, and reliance on medical records, which provided variable detail regarding comorbidities that may have impacted LDH levels. Nonetheless, our findings represent a relatively novel association between elevated LDH and the development of cirAEs. Further research is needed to explore the predictive role of tumor burden on clinical prognosis and the development of immunologic toxicities during ICI therapy for melanoma as well as other tumor types.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of interest

Dr Chen has received honoraria from Pfizer and Novartis for serving on an advisory board for digital media. Authors Asdourian, Otto, Jacoby, Shah, Thompson, Blum, Reynolds, Semenov, Lawrence, Sullivan, Boland, amd Villani have no conflicts of interest to declare.

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Table I.

Multivariate outcomes of cirAE incidence and severity by LDH category

Outcome*	OR‡ (95% CI)	*P* value¶
Development of cirAE (any type)		
High LDH† at pre-ICI baseline	0.37 (0.14–0.92)	**.033**
High LDH at >3 months post-ICI	0.30 (0.12–0.77)	**.013**
Development of cirAE (subtypes)		
Macular and papular rash		
High LDH at pre-ICI baseline	0.19 (0.02–1.93)	NS
High LDH at >3 months post-ICI	1.15 (0.24–5.59)	NS
Pruritus		
High LDH at pre-ICI baseline	1.43 (0.35–5.84)	NS
High LDH at >3 months post-ICI	0.51 (0.09–2.85)	NS
Rash NOS		
High LDH at pre-ICI baseline	1.83 (0.52–6.48)	NS
High LDH at >3 months post-ICI	0.97 (0.25–3.77)	NS
Other		
High LDH at pre-ICI baseline	0.82 (0.18–3.78)	NS
High LDH at >3 months post-ICI	1.63 (0.38–7.03)	NS
Low cirAE severity among all patients§		
High LDH at pre-ICI baseline	1.43 (0.47–4.29)	NS
High LDH at >3 months post-ICI	3.80 (0.78–10.03)	NS
High cirAE severity among all patients§		
High LDH at pre-ICI baseline	0.70 (0.23–2.11)	NS
High LDH at >3 months post-ICI	0.36 (0.10–1.28)	NS
Low cirAE severity among cirAE patients‖		
High LDH at pre-ICI baseline	0.70 (0.20–2.51)	NS
High LDH at >3 months post-ICI	1.80 (0.45–7.18)	NS
High cirAE severity among cirAE patients‖		
High LDH at pre-ICI baseline	1.42 (0.40–5.05)	NS

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Outcome*	OR‡ (95% CI)	*P* value¶
High LDH at >3 months post-ICI	0.56 (0.14–2.23)	NS

CI, Confidence interval; *cirAE*, cutaneous immune-related adverse event; *ICI*, immune checkpoint inhibitor; *LDH*, lactate dehydrogenase; *NOS*, not otherwise specified; *NS*, not significant; *OR*, odds ratio.

*Binomial logistic regression was used for all models. All models included age at the start of ICI regimen, sex, and additional clinical features significant to $P<.10$ as covariates, with details as follows for each model:Development of cirAE (any type): age, sex, Eastern Cooperative Oncology Group (ECOG) status, history of kidney disease, any irAE.Development of cirAE (subtypes): age, sex, ECOG status, history of kidney disease, any irAE.Low or high cirAE severity among all patients: age, sex, ECOG status, history of kidney disease, any irAE.Low or high cirAE severity among cirAE patients: age, sex, ECOG status, history of kidney disease, any irAE.

†LDH values were categorized into “high” (>210 U/L) and “low” (≤210 U/L) based on our institution’s laboratory reference range, with 210 U/L being the upper limit of normal.

‡Reference LDH category for all models is LDH value of “low” (≤210 U/L).

§cirAE severity was categorized based on peak CTCAE v5.0 grade as determined by any evaluating physician. Category of “high” includes grades 2, 3, or 4 and “low” includes grade 1. Reference cirAE category for models is having no history of cirAE.

‖cirAE severity was categorized based on peak CTCAE v5.0 grade as determined by any evaluating physician. Category of “high” includes grades 2, 3, or 4 and “low” includes grade 1. Reference cirAE category for low cirAE severity models is having no history of grade 1 cirAE. Reference cirAE category for high cirAE severity models is having no history of grades 2–4 cirAE.

¶Bolded *P* values represent statistical significance to $P<.05$.

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