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Malignancy Risk in Autoimmune Blistering Disorders: A Retrospective Cohort Study

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To the Editor,

Autoimmune blistering disorders (AIBD) are chronic, antibody-mediated diseases of the skin and mucous membranes that carry substantial morbidity and mortality.[1,2] Previous studies have suggested an association with malignancy, particularly squamous cell carcinoma and lymphoma, but have been limited by small sample sizes and subtype-specific cohorts.[3] We conducted a population-based analysis using the TriNetX Research Network, a federated electronic health record database, to better define malignancy risk in this population.

We conducted a retrospective cohort study using the TriNetX Research Network, a de-identified EHR database with longitudinal patient-level data from over 100 healthcare organizations. We identified adults with ICD-10 codes for pemphigus (L10), pemphigoid (L12), or other bullous disorders (L13) and excluded those with prior malignancy. The index date was the diagnosis of bullous disorder for our exposure cohort and a general exam encounter for controls; events >20 years prior were excluded. Patients were matched 1:1 to controls by demographics (age, sex, race), comorbidities (hypertension, diabetes, chronic respiratory disease, obesity, ischemic heart disease, chronic kidney disease, liver disease, heart failure, and nicotine dependence), family history of malignancy, and immunosuppression use, yielding 30,218 patients per group. Outcomes were assessed from one day post-index through 1, 5, and 10 years of follow up. Covariate balance was assessed via standardized mean differences, with all covariates achieving SMD <0.1. Absolute risks, risk differences (RD), Kaplan-Meier

TABLE 1.

Hazard Ratios With 95% Confidence Intervals For Malignancies In Aibd Vs Controls at 1, 5, and 10 Years.

Malignancy	1 Year HR (95% CI)	5 Year HR (95% CI)	10 Year HR (95% CI)
Any neoplasm	5.607 (5.093, 6.174)	3.595 (3.416, 3.784)	3.275 (3.13, 3.426)
Any malignant cancer	4.478 (3.768, 5.322)	3.066 (2.808, 3.348)	2.734 (2.531, 2.953)
Any lymphoma	15.851 (5.736, 43.8)	4.376 (2.979, 6.428)	3.472 (2.51, 4.804)
Non-Hodgkin lymphoma	19.897 (6.205, 63.8)	4.314 (2.882, 6.457)	3.344 (2.389, 4.681)
Squamous cell carcinoma of skin (SCC)	16.727 (8.156, 34.304)	7.565 (5.659, 10.112)	6.523 (5.081, 8.373)
Basal cell carcinoma of skin (BCC)	12.958 (7.167, 23.427)	4.95 (3.972, 6.167)	4.909 (4.04, 5.964)
Any melanoma	15.596 (4.814, 50.529)	4.134 (2.805, 6.094)	3.793 (2.684, 5.362)
Melanoma in situ	--*	5.374 (2.925, 9.874)	4.1 (2.498, 6.727)
Malignant melanoma	11.784 (3.589, 38.691)	5.027 (3.102, 8.147)	3.905 (2.623, 5.814)
Lung cancer	2.073 (1.266, 3.394)	1.709 (1.323, 2.208)	1.586 (1.267, 1.986)
Breast cancer	3.415 (2.12, 5.5)	2.108 (1.65, 2.693)	2.035 (1.643, 2.521)
Prostate cancer	2.34 (1.494, 3.665)	1.739 (1.364, 2.218)	1.562 (1.26, 1.937)
Colorectal cancer	2.966 (1.557, 5.653)	2.358 (1.663, 3.343)	2.269 (1.677, 3.071)
Kidney cancer	6.01 (2.3, 15.706)	3.684 (2.207, 6.149)	2.886 (1.916, 4.345)
Bladder cancer	4.729 (1.925, 11.62)	2.282 (1.5, 3.473)	2.475 (1.679, 3.648)
Leukemia	6.21 (2.59, 14.889)	4.187 (2.665, 6.578)	3.024 (2.069, 4.42)
Pancreatic cancer	1.609 (0.599, 4.322)	1.246 (0.754, 2.061)	1.441 (0.916, 2.267)
Benign neoplasms (except benign neuroendocrine tumors)	4.559 (4.018, 5.172)	3.613 (3.382, 3.859)	3.186 (3.006, 3.377)

*Censored due to low patient outcome volume

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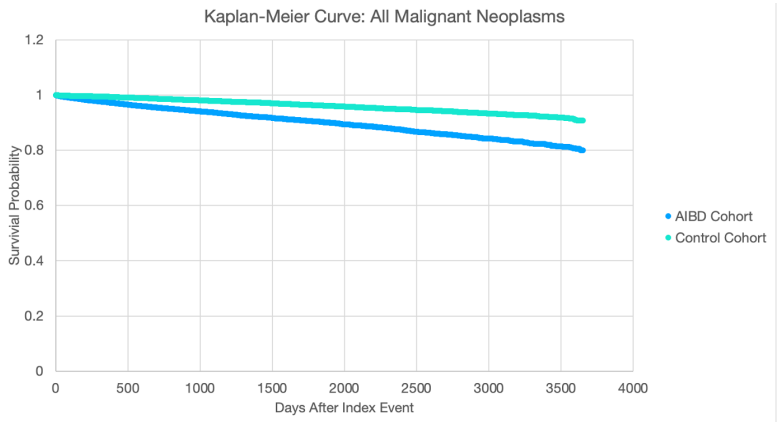
FIGURE 1. Kaplan-Meier survival curves for malignant cancer in AIBD vs controls.



Kaplan-Meier survival analysis for any malignant cancer in patients with autoimmune blistering disorders (AIBD) compared with matched controls over 10 years of follow-up. Patients with AIBD demonstrated significantly reduced survival probability, with curves diverging within the first year and remaining separated throughout the observation period.

curves, log-rank tests, and Cox proportional hazards models were used to estimate hazard ratios with 95% confidence intervals, with non-overlapping confidence intervals considered significant.

At 1 year follow-up, patients with AIBD had a significantly higher incidence of any neoplasm (including benign tumors; RD 5.95%, HR 5.61, CI 5.09-6.17) and, more importantly, any malignant cancer (RD 1.47%, HR 4.48, 95% CI 3.77-5.32) compared with controls. Elevated risks persisted at 5 (RD 9.59%, HR 3.60, 95% CI 3.42-3.78) and 10 years (RD 9.57%, HR 3.28, 95% CI 3.13-3.43). Site-specific analyses at 1 year also showed especially high risks for cutaneous cancers, including melanoma (RD 0.064%, HR 11.78, 95% CI 3.59-38.69), squamous cell carcinoma (RD 0.33%, HR 16.73, 95% CI 8.16-34.3), and basal cell carcinoma (RD 0.39%, HR 12.96, 95% CI 7.17-23.43), as well as hematologic cancers such as lymphoma (RD 0.15%, HR 15.85, 95% CI 5.74-43.8) and non-Hodgkin lymphoma (RD 0.14%, HR 19.90, CI 6.21-63.8) at one year. Risks at 1 year were modestly increased for kidney, bladder, colorectal, breast, and prostate cancers, while pancreatic cancer was not significantly associated. Results at 5 and 10 years preserved the directionality of findings (Table 1). Across malignancy types, HR was highest at 1 year follow-up and attenuated over time, but significantly elevated at 5- and 10-year follow-up, demonstrating persistently elevated malignancy risk in patients with AIBD (Table 1). Survival was lower among patients with AIBD compared to matched controls (Figure 1).

Subtype analyses revealed that pemphigoid was the major driver of malignancy risk, with consistently elevated hazards across cutaneous and hematologic cancers.[3] Pemphigus and other bullous disorders also demonstrated increased risks, particularly for skin cancers, though estimates were less precise given smaller sample sizes.

Taken together, these findings show that adults with AIBD face a persistently elevated risk of malignancies for up to a decade after diagnosis. The strongest associations were observed for cutaneous and hematologic cancers, and pemphigoid contributed most prominently to the signal. These results reinforce prior single-center observations and underscore the importance of cancer surveillance in AIBD, particularly vigilant screening for skin cancers and hematologic malignancies.[1,2,3] Limitations of this study include reliance on ICD coding, absence of treatment-level data, and potential residual confounding. Nonetheless, the large-matched cohort and long-term follow-up strengthen the validity of these findings.

DISCLOSURES

The authors have no conflicts of interest to disclose.

Ethics Statement: This study was exempt from informed consent as it involved the secondary analysis of aggregate de-identified data and does not involve interaction with human subjects. All data were de-identified in accordance with the HIPAA Privacy Rule (Section §164.514(a)), with the process attested to through a formal determination by a qualified expert as defined in Section §164.514(b)(1). This formal determination was refreshed in December 2020.

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