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The positive effect of immune checkpoint inhibitor-induced thyroiditis on overall survival accounting for immortal time bias: a retrospective cohort study of 6596 patients

S. Street[1], **D. Chute**[2], **I. Strohbehn**[2], **S. Zhao**[2], **M. Rengarajan**[3], **A. Faje**[3], **H. Seethapathy**[2], **M. Lee**[2], **R. Seethapathy**[2], **Z. Drobni**[4,5], **O. Rahma**[6], **T. G. Neilan**[7], **R. J. Sullivan**[7], **A. C. Villani**[8], **L. Zubiri**[9], **M. J. Mooradian**[9], **K. L. Reynolds**[9], **M. E. Sise**[2,*]

[1]Department of Medicine;

[2]Division of Nephrology, Department of Medicine;

[3]Division of Endocrinology, Department of Medicine;

[4]Cardiovascular Imaging Research Center (CIRC), Department of Radiology and Division of Cardiology, Massachusetts General Hospital, Boston, USA;

[5]Heart and Vascular Center, Semmelweis University, Budapest, Hungary;

[6]Division of Hematology and Oncology, Dana Farber Cancer Institute, Boston;

[7]Cardio-Oncology Program, Division of Cardiology Department of Medicine;

[8]Division of Rheumatology, Allergy, and Immunology;

[9]Division of Hematology and Oncology, Massachusetts General Hospital, Boston, USA.

It has been hypothesized that immune-related adverse events (irAEs) are a biomarker for treatment effect and a positive prognostic indicator in patients receiving immune checkpoint inhibitors (ICIs). ICI-induced thyroiditis is a common irAE that has been associated with improved survival.[1–3] We investigated whether the prolonged survival associated with ICI-induced thyroiditis was merely a product of immortal time bias using time-varying Cox proportional hazard modeling and conditional landmark analysis in a retrospective cohort study of consecutive adults who received ICIs between 2010 and 2019. Immortal time bias can occur when a cohort study is designed so that follow-up includes a period of time where participants in the exposed group cannot experience the outcome.

The follow-up period began with the first ICI exposure; patients were followed until death or to June 2020. Patients were excluded if they had a history of thyroid disease determined by ICD9/10 codes or were prescribed thyroid replacement therapy at baseline. We defined ICI-induced hypothyroidism as the initiation of thyroid replacement therapy after day 14 of ICI therapy.[4] Thyrotoxicosis was defined by concurrent thyroid stimulating hormone <0.5 ug/dl and free T4 >1.9 ng/dl. We carried out time-independent and time-varying Cox proportional hazards models and survival analysis with and without a conditional

* msise@partners.org.

landmark to demonstrate the effect of immortal time bias on the estimate of the effect[5,6] (Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2021.05.357).

We identified 9419 patients receiving ICIs; after exclusions, 6596 were included. Mean age was 64 years (standard deviation 13), 57% male, and 89% white, non-Hispanic. Patients were followed for a median of 9.6 months (interquartile range 3.6–19.9 months) (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.05.357). Thyroiditis developed in 1155 (17%). Median time to thyroiditis was 3.1 months (interquartile range 1.5–6.2 months).

Multivariable models were adjusted for age, sex, race, cancer type, ICI class, pre-existing rheumatologic disease, and Charlson comorbidity score. ICI-induced thyroiditis was independently associated with a large improvement in overall survival in the time-independent model [adjusted hazard ratio (aHR) 0.47, 95% confidence interval (CI) 0.44–0.53, $P < 0.001$]. The association with improved survival remained consistent, albeit with a lower effect estimate with time-varying Cox models (aHR 0.80, 95% CI 0.71–0.89, $P < 0.001$) (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2021.05.357).

In the survival analysis, without applying a conditional landmark, thyroiditis was associated with a large reduction in death: HR 0.44 (0.39–0.49, $P < 0.001$). When a 6-month landmark was applied, a weaker, but statistically significant improvement in overall survival was found: HR for death 0.76 (95% CI 0.65–0.88, $P < 0.001$) (Figure 1). Applying a 3-month landmark yielded a very similar result: HR 0.78 (95% CI 0.67–0.92, $P = 0.002$). A 6-month landmark analysis was used to determine the association between thyroid dysfunction and overall survival in each malignancy subgroup (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2021.05.357). Patients with lung cancer demonstrated the strongest relationship between thyroiditis and overall survival (HR for death 0.56 [95% CI 0.40–0.79], $P < 0.001$). The relationship was least in breast, melanoma, and genitourinary tumors.

In conclusion, after accounting for immortal time bias, we showed a 20% reduction in the aHR for death in patients who develop ICI-induced thyroiditis. The association between thyroiditis and overall survival varied by tumor type, but was strongest in patients with lung cancer, possibly related to the shared developmental origin of thyroid and lung epithelia. Our study demonstrates the large effect of immortal time bias. Future studies with large cohorts are needed to examine the association of other irAEs with survival and must utilize methods that account for mmortal time bias.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DISCLOSURE

LZ serves as a consultant for Merck and reports a grant from SEOM to study immune-related toxicities. TGN has been a consultant to and received fees from Parexel Imaging, Intrinsic Imaging, H3-Biomedicine, and AbbVie, outside of the current work. TGN also reports consultant fees from Bristol-Myers Squibb (BMS) for a Scientific Advisory Board focused on myocarditis related to immune checkpoint inhibitors and an unrestricted grant from AstraZeneca to study atherosclerosis related to immune checkpoint inhibitors. OR reports research support from Merck. Speaker for activities supported by educational grants from BMS and Merck. Consultant for Merck, Celgene, Five Prime, GlaxoSmithKline, Bayer, Roche/Genentech, Puretech, Imvax, Sobi. In addition, he has a patent 'Methods of using pembrolizumab and trebananib' pending. MJM has served as a consultant and/or received honorarium from AstraZeneca, Nektar Therapeutics, Catalysis Pharmaceuticals, Immunai. RJS has been a consultant/served on advisory boards for AstraZeneca, Eisai, Merck, Novartis, Oncosec, Pfizer, Replimune and received research funding from Merck. All other authors have declared no conflicts of interest.

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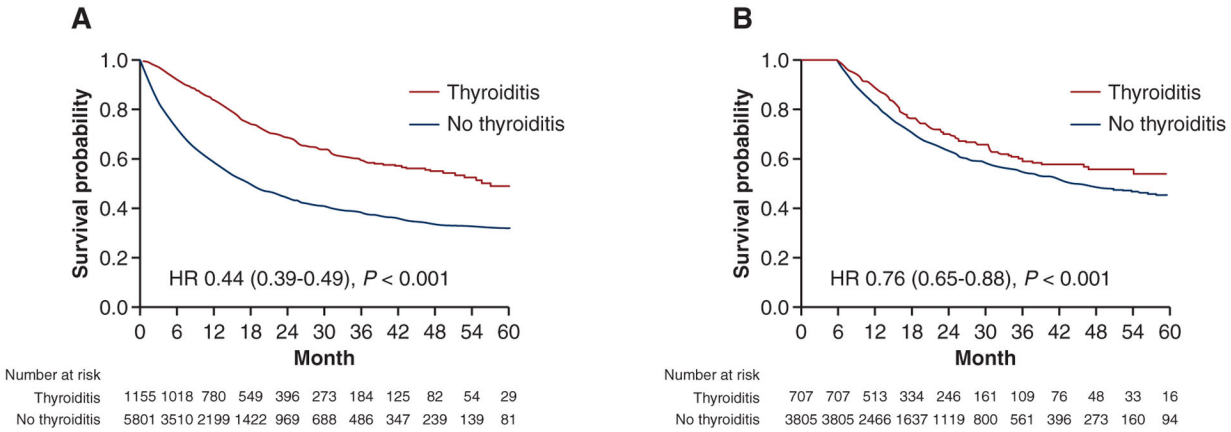

Figure 1.

Kaplan–Meier survival curves without a landmark (1A) and using a 6-month landmark analysis (1B). For the conditional landmark analysis, 2444 patients did not survive until the 6-month landmark and were excluded. Of the 4512 remaining patients, 707 developed thyroiditis within 6 months, whereas 3805 patients either never developed thyroiditis or developed it after the 6-month landmark. Most patients received programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors (87%), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors (5%), and 8% received combined PD-1/CTLA-4.

HR, hazard ratio.