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ORIGINAL ARTICLE

Improved survival with elevated BMI following immune checkpoint inhibition across various solid tumor cancer types

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Abstract

Introduction/Background: Obesity is a well-known risk factor for various cancers, yet emerging research demonstrates its association with improved survival outcomes in cancer treatment, labeled as "the obesity paradox." Studies investigating the clinical benefits of obesity across various cancer types after immune checkpoint inhibition (ICI) are limited.

Methods: Data were queried from the TriNetX database to identify patients with solid tumor malignancies of various organ systems (pulmonary/intrathoracic, cutaneous, head and neck, gastrointestinal, breast, genitourinary) who received ICI between 2012 and 2024. Propensity score matching was used to match cohorts for demographics, medical comorbidities, and oncologic staging. Primary outcome was overall survival (OS) up to 5 years and compared between obese body mass index (BMI; >30) and normal BMI (20–24.9) cohorts.

Results: After propensity score matching, there were a total of 18,434 patients, with 9217 patients in the obese BMI cohort and 9217 patients in the normal BMI cohort for all solid tumor malignancies. In the overall pan-cancer analysis, obese BMI was associated with significantly improved OS up to 5 years compared to the normal BMI cohort (hazard ratio [HR], 0.69 [0.66–0.72]). Subgroup analysis likewise demonstrated that obese BMI was associated with significantly improved OS up to 5 years for respiratory/intrathoracic (HR, 0.77 [0.72–0.83]), cutaneous (HR, 0.62 [0.63–0.78]), head and neck (HR, 0.67 [0.58–0.78]), gastrointestinal (HR, 0.67 [0.58–0.78]), breast (HR, 0.66 [0.55–0.79]), and genitourinary (HR, 0.57 [0.34–0.93]) malignancies (though not renal cell carcinoma specifically.)

Conclusions: Obesity was associated with improved 5-year OS after treatment with ICI across various solid tumor malignancies in this electronic health record–based

big data study. Further investigation is warranted to understand the mechanism of this association.

KEYWORDS
obesity, immune checkpoint inhibition, solid tumors, overall survival

INTRODUCTION

The advent of T-cell–directed immunotherapies has greatly advanced cancer management paradigms.[1,2] Immune checkpoint inhibition (ICI) has become a standard-of-care method for treating various solid tumor malignancies. However, only a fraction of patients responds to ICI, and the underlying factors that drive this heterogeneity in response to ICI have garnered tremendous research interest.[3,4] Generally, lack of response is thought to be driven by tumor- and patient-related mechanisms. Tumor related factors include T-cell exhaustion and physical obstruction in a fibrotic microenvironment.[5,6] Patient-related factors reflect the larger ecology of the tumor within the individual, such as physiologic reserve, immune phenotype, or immune suppression.[7,8] One recently described phenomenon, dubbed the “obesity paradox,” is the observation that patients with obesity may have improved outcomes with oncologic treatment; this phenomenon may represent a potential, under-investigated ecologic factor for patients receiving ICI.

Obesity is a well-known risk factor for various cancers and is associated with a chronic inflammatory state, increased PD-1 expression, increased T-cell exhaustion, and reduced T-cell proliferative capacity. It is suspected that αPD-1 T-cell exhaustion in the obese is associated with improved capacity for response to αPD-1 ICI via a leptin-driven signaling mechanism.[9] However, studies investigating this phenomenon are limited. Here, we leveraged population-level data from a multi-institutional health network, TriNetX, including data from 96 million individuals and 220 health care organizations across the United States. We sought to examine patients treated with ICI for solid tumor malignancies and compared overall survival (OS) in patients with obesity (body mass index [BMI] ≥30) versus normal BMI (BMI 20–24.9).

Methods

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines. Our institutional review board exempted the study and waived informed consent because the study used only deidentified population-level records. Population-level data were obtained from the TriNetX Global Collaborative Network (TriNetX), a real-time multicenter global health network of health care organizations across the world. From this network, we queried patients in the United States. The TriNetX platform contains deidentified data of 96 million patients across 220 health care organizations from diverse demographic and socioeconomic backgrounds. Data from 2012 through 2024 were collected. Participant race information was collected from the database, which primarily obtains this information from institutional electronic health records (EHRs). The initial race categories included in the study were Asian, American Indian or Alaska Native, Black or African American, Native Hawaiian or Other Pacific Islander, White, and unknown. However, for post–propensity score matching (PSM) analysis, we included only White and Black or African American races because of low census in the other race categories that obviated a statistically meaningful comparison. In TriNetX, ethnicity is coded as "Hispanic or Latino," "Not Hispanic or Latino," or "Unknown/Not Reported," based on standardized health care data from EHRs, with missing data marked as "Unknown."

Study population

This epidemiologic investigation used codes from the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*), and the *Common Procedural Terminology* to define cohorts and outcomes. Our study period extends back to 2012. Please refer to the supplementary materials for ICD-9 conversion details (Supplementary Table 1); the TriNetX platform automatically converts ICD-10 codes to ICD-9 codes. Adult patients (≥18 years) with a solid tumor malignancy and treated with ICI (durvalumab, nivolumab, ipilimumab, or pembrolizumab) were identified per the ICD-10 codes listed in Supplementary Table 2.[10,11] Cohorts were distinguished by pre-treatment BMI, as defined by the following: obese BMI cohort with BMI ≥30 and normal BMI cohort with BMI 20–24.9.

Outcome variables

Cohorts were analyzed for survival outcomes and rates of immune-related adverse events (irAEs) and compared to the normal BMI cohort (which served as the study’s control). Overall survival was analyzed up to 5 years after starting ICI treatment. Multiple codes were used to capture irAEs after receiving ICI treatment (Supplementary Table 2) and measured up to 1 year after diagnosis.

Statistical analysis

Descriptive statistics were used to characterize the study population and summarize demographic characteristics. Data were reported as mean (range) for continuous variables and frequency (percentage) for

categorical variables. Patients were PSM between groups based on ICD-10 codes for age at diagnosis, sex, race, ethnicity, cardiovascular and respiratory diseases, tobacco use, alcohol use disorder, pathologic TNM staging, and other cancers (Table 1). PSM (1:1 using the nearest-neighbor greedy matching algorithm with a caliper size of 0.1 pooled SDs) was performed using the TriNetX Analytics platform and used when comparing cohorts with the normal BMI cohort. To assess balance in covariates after PSM, *p* values were calculated to determine whether significant differences remain between the treatment and control groups. Categorical covariates were assessed using chi-squared or Fisher exact tests to compare proportions. The hazard ratio (HR) was used to describe the relative risk based on comparison of time to event rates and was calculated using a proportional hazard model (a built-in function in TriNetX). The TriNetX platform calculates HRs and associated CIs using R's survival package, version 3.2-3, with the proportional hazard assumption tested using the generalized Schoenfeld approach. Results were reported using measures of effect size and 95% CIs to describe the magnitude of the difference between compared groups and precision of the estimates, respectively. HR, odds ratios (ORs), and 95% CIs were calculated through TriNetX Analytics. We employed Cox proportional hazards regression to estimate HRs (95% CI) and assess the differential effect of pretreatment BMI on OS.

Results

Cohort demographics

Data were collected on April 11, 2024, and analyzed between 2012 and 2024. Data from 64 health care organizations in the United States were included. Cohort demographics (pre- and post-PSM) are summarized in Table 1. After applying inclusion and exclusion criteria, the obese and normal BMI cohorts consisted of 15,642 patients and 9822 patients pre-PSM, respectively. After PSM, there were 9217 patients in the obese BMI cohort and 9470 patients in the normal BMI cohort with no significant differences in oncologic staging, demographics, or medical comorbidities between the two groups (Table 1).

TABLE 1 Cohort baseline characteristics – all cancers.

Description	Obese BMI (≥30) Before PSM *N* (% of cohort) *N* = 15,642	Normal BMI (20–24.9) Before PSM *N* (% of cohort) *N* = 9822	Standard difference before PSM*	Obese BMI (≥30) After PSM *N* (% of cohort) *N* = 9217	Normal BMI (20–24.9) After PSM *N* (% of cohort) *N* = 9217	Standard difference after PSM*
Sex						
Male	7132 (45.6%)	4995 (50.9%)	0.105	4559 (49.5%)	4609 (50.0%)	0.011
Female	6637 (42.4%)	3253 (33.1%)	0.193	3188 (34.6%)	3167 (34.4%)	0.005
Race						
White	11,225 (71.8%)	6446 (65.6%)	0.133	6250 (67.8%)	6196 (67.2%)	0.0125
Black or African American	1598 (10.2%)	846 (8.6%)	0.055	751 (8.1%)	815 (8.8%)	0.025
Ethnicity						
Hispanic or Latino	844 (5.4%)	446 (4.5%)	0.039	428 (4.6%)	420 (4.6%)	0.004
Comorbidities						
Diseases of the circulatory system	14,356 (91.8%)	8735 (88.9%)	0.097	8280 (89.8%)	8251 (89.5%)	0.010
Ischemic heart diseases	5816 (37.2%)	3651 (37.2%)	0.0002	3411 (37.0%)	3406 (37.0%)	0.001
Type 2 diabetes mellitus	6743 (43.1%0	2665 (27.1%)	0.340	2604 (28.3%)	2655 (28.8%)	0.012
Tobacco use	3426 (21.9%)	2634 (26.8%)	0.115	2351 (25.5%)	2348 (25.5%)	0.001
Alcohol-related disorders	1976 (12.66%)	1816 (18.5%)	0.162	1482 (16.1%)	1521 (16.5%)	0.012
TNM stage						
T	3127 (20.0%)	2039 (20.8%)	0.019	1845 (20.0%)	1896 (20.6%)	0.014
N	3129 (20.0%)	2057 (20.9%)	0.023	1864 (20.2%)	1911 (20.7%)	0.013
M	2788 (17.8%)	1876 (19.1%)	0.033	1718 (18.6%)	1,40 (18.9%)	0.006

All cancers

In the overall pan-cancer analysis of solid tumor malignancies, obese BMI was associated with significantly improved OS at all measured time points compared to the normal BMI cohort (1-year OS 67.5% vs. 55.5%, $p < .001$; 3-year OS 44.9% vs. 33.7%, $p < .001$; 5-year OS 36.2% vs. 25.5%, $p < .001$; HR, 0.70 [0.67–0.73]) (Figure 1, Table 2). Obese BMI was associated with higher rates of irAEs at 1 year compared to normal BMI (risk difference 3.62%; OR, 1.16 [1.10–1.24], Table 2).

Pulmonary/intrathoracic malignancies

Post-PSM, the obese and normal BMI cohorts each included 3997 patients with a malignancy of the respiratory/intrathoracic organs (Supplementary Table 3). Obese BMI was associated with significantly improved OS at all measured time points compared to the normal BMI cohort (1-year OS 70.7% vs. 61.9%, $p < .001$; 3-year OS 47.5% vs. 41.9%, $p < .001$; 5-year OS 38.7% vs. 32.7%, $p < .001$; HR, 0.77 [0.72–0.83]) (Figure 1). Obese BMI was associated with higher rates of irAEs at 1 year compared to normal BMI (risk difference 4.28%; OR, 1.20 [1.09–1.31]).

Non–small cell lung cancer

In patients with non–small cell lung cancer (NSCLC; Supplementary Table 4), obese BMI ($n = 1319$) was associated with significantly improved OS at all measured time points compared to the normal BM ($n = 1319$) cohort (1-year OS 69.4% vs. 59.1%, $p < .001$; 3-year OS 47.1% vs. 38.6%, $p < .001$; 5-year OS 40.3% vs. 31.0%, $p < .001$; HR, 0.74 [0.66–0.83]).

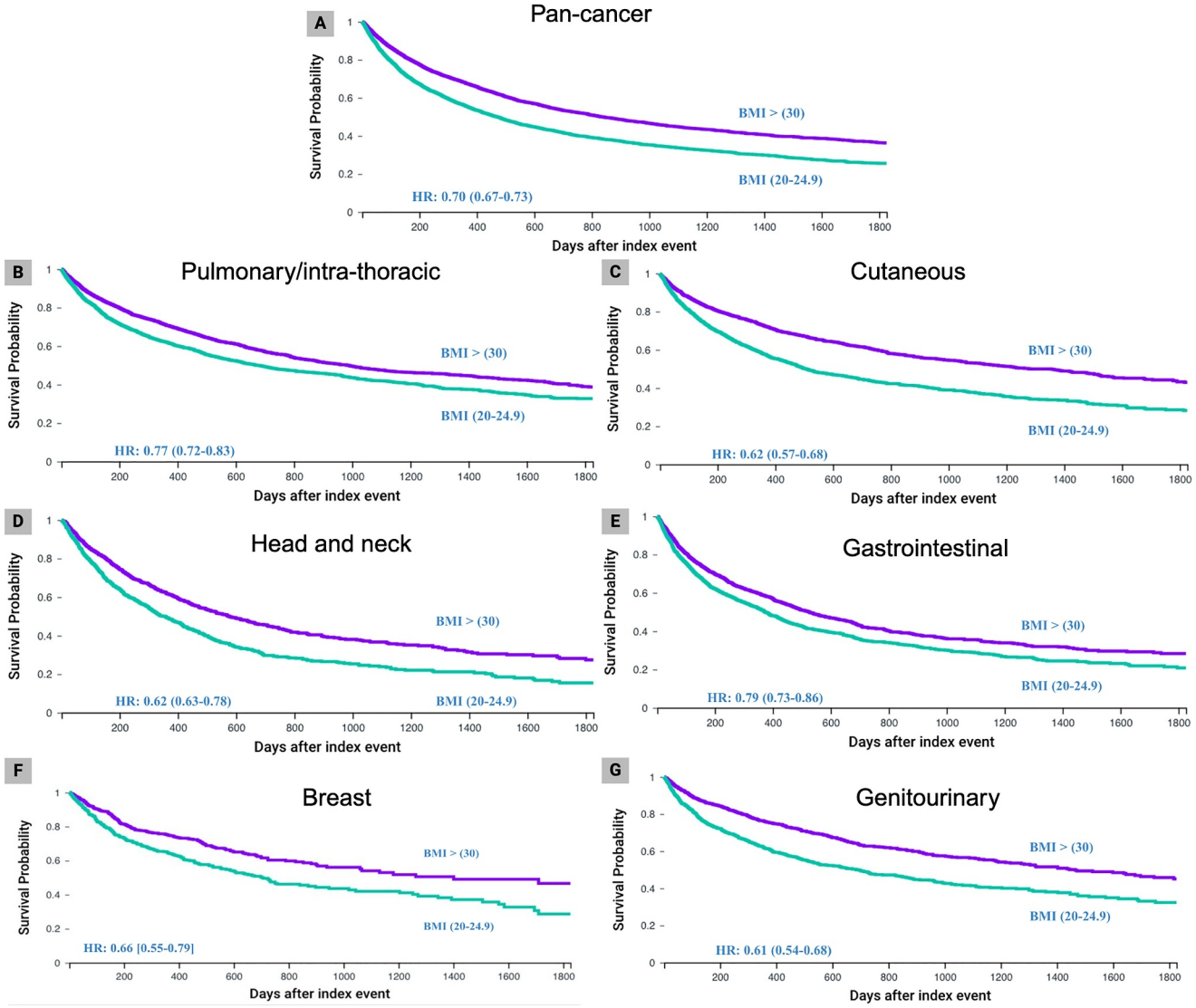

FIGURE 1 Kaplan-Meier survival curves depicting overall survival up to 5 years posttreatment with immune checkpoint inhibition between the obese (purple) and normal (green) BMI cohorts for the (A) overall pan-cancer analysis and malignancies of the following organ systems; (B) pulmonary/intrathoracic; (C) cutaneous; (D) head and neck; (E) gastrointestinal; (F) breast; and (G) genitourinary.

TABLE 2 Overall survival compared to patients with normal BMI (20–24.9).

Obese BMI (>30) vs normal BMI (20–24.9): all cancers			
Overall survival			
Outcome and time point	**HR (95% CI)**	**Survival probability**	**Log rank test *p* value**
1-year	-	67.5% vs. 55.5%	<.0001
3-year	-	44.9% vs. 33.7%	<.0001
5-year	0.70 (0.67–0.73)	36.2% vs. 25.5%	<.0001
Immune-related adverse events			
1-year	1.16 (1.10–1.24)	-	-

Cutaneous malignancies

Post-PSM, the obese and normal BMI cohorts each included 2417 patients with cutaneous malignancy (Supplementary Table 5). Obese BMI was associated with significantly improved OS at all measured time points compared to the normal BMI cohort (1-year OS 71.3% vs. 57.6%, $p < .001$; 3-year OS 53.0% vs. 37.4%, $p < .001$; 5-year OS 42.9% vs. 28.2%, $p < .001$; HR, 0.62 [0.57–0.68]) (Figure 1). There was no difference in rates of irAEs a 1 year between the obese and normal BMI cohorts (risk difference 0.496%, OR 1.02 [0.91–1.15]).

Melanoma

In patients with melanoma (Supplementary Table 6), obese BMI ($n = 1196$) was associated with significantly improved OS at all measured time points compared to the normal BMI ($n = 1196$) cohort (1-year OS 79.4% vs. 66.7%, $p < .001$; 3-year OS 63.9% vs. 49.9%, $p < .001$; 5-year OS 53.5% vs. 39.0%, $p < .001$; HR, 0.62 [0.54–0.71]).

Head and neck malignancies

Post-PSM, the obese and normal BMI cohorts each included 995 patients with a malignancy of the head and neck (Supplementary Table 7). Obese BMI was associated with significantly improved OS at all measured time points compared to the normal BMI cohort (1-year OS 61.6% vs. 49.1%, $p < .001$; 3-year OS 36.6% vs. 23.9%, $p < .001$; 5-year OS 27.4% vs.15.5%, $p < .001$; HR, 0.68 [0.60–0.77]) (Figure 1). There was no difference in rates of irAEs at 1 year between the obese and normal BMI cohorts (risk difference, 1.71%; OR, 1.08 [0.96–1.10].

Gastrointestinal malignancies

Post-PSM, the obese and normal BMI cohorts each included 2477 patients with gastrointestinal malignancy (Supplementary Table 8). Obese BMI was associated with significantly improved OS at all measured time points compared to the normal BMI cohort (1-year OS 58.9% vs. 50.9%, $p < .001$; 3-year OS 35.5% vs. 28.7%, $p < .001$; 5-year OS 28.3% vs. 20.8%, $p < .001$; HR, 0.79 [0.73–0.86]). Obese BMI was associated with higher rates of irAEs at 1 year compared to normal BMI (risk difference, 5.935%; OR, 1.29 [1.15–1.44]).

Breast malignancies

Post-PSM, the obese and normal BMI cohorts each included 719 patients with breast malignancy (Supplementary Table 9). Obese BMI was associated with significantly improved OS at all measured time points compared to the normal BMI cohort (1-year OS 74.6% vs. 64.8%, $p < .001$; 3-year OS 54.9% vs. 42.0%, $p < .001$; 5-year OS 46.6% vs. 28.6%, $p < .001$; HR, 0.66 [0.55–0.79]). Obese BMI was associated with higher rates of irAEs at 1 year compared to normal BMI (risk difference, 5.15%; OR, 1.24 [1.01–1.54]).

Triple-negative breast cancer

In patients with triple-negative breast cancer (TNBC), obese BMI ($n = 717$) was associated with significantly improved OS compared to normal BMI ($n = 717$) cohorts at all measured time points (1-year OS 74.7% vs. 64.5%, $p < .001$; 3-year OS 54.6% vs. 41.7%, $p < .001$; 5-year OS 48.3% vs. 27.5%, $p < .001$; HR, 0.65 [0.54–0.77]) (Supplementary Table 10).

Genitourinary malignancies

Post-PSM, the obese and normal BMI cohorts each included 1725 patients with genitourinary malignancy (Supplementary Table 11). Obese BMI was associated with significantly improved OS at all measured time points years (1-year OS 69.7% vs. 56.9%, $p < .001$; 3-year OS 56.3% vs. 41.3%, $p < .001$; 5-year OS 45.0% vs. 32.3%, $p < .001$; HR, 0.61 [0.54–0.68]) (Figure 1). Obese BMI was associated with higher rates of irAEs at 1 year compared to normal BMI (risk difference, 4.29%; OR, 1.21 [1.05–1.40].

Renal cell carcinoma

In patients with renal cell carcinoma (RCC), there was no statistically significant difference in OS between obese BMI ($n = 40$) and normal BMI ($n = 40$) cohorts at any measured time points (1-year OS 78.4% vs. 73.2%, $p = .5722$; 3-year OS 53.2% vs. 36.8%, $p = .3756$; 5-year OS 44.3% vs. 36.8%, $p = .4519$; HR, 0.76 [0.38–1.55]) (Supplementary Table 12).

Discussion

This EHR-based big data study is the largest to date to investigate the association between obesity and survival outcomes after ICI for various solid tumor malignancies. Study results indicate that obesity is associated with improved OS after ICI in the pan-solid tumor malignancy analysis. Subgroup analyses of specific tumor sites or histologic subtypes commonly treated with ICI (such as melanoma and NSCLC) similarly demonstrated an improved OS in all groups besides RCC. An et al.'s meta-analysis of 13 studies with >5000 patients treated with ICIs corroborates our study's findings of associations between obese BMI and improved survival.[12] In a cohort of 250 humans with a variety of cancers treated with anti–PD-(L)1 checkpoint inhibition, Wang et al.[8] found that obese patients had significantly better progression-free survival (PFS) and OS compared to nonobese patients. To better understand the immunologic mechanisms of these findings, this same group studied diet-induced obese mice with B16 melanoma and found that obesity was associated with PD-1–mediated T-cell dysfunction, possibly due to leptin signaling pathways which increased PD-1 expression yet promoted T-cell dysfunction. Though much is yet to be investigated, these underlying mechanisms may be related to obesity's altering of baseline host and tumor metabolism, immune cell function, and tumor microenvironment immune cell composition.[13]

Study findings suggest that obesity (BMI ≥ 30) is associated with improved OS for NSCLC. In a pooled analysis of four clinical trials with more than 2200 patients with advanced NSCLC treated with atezolizumab, Kichenadasse et al. likewise found that high BMI (including overweight [25–29.9] and obese [≥30] BMIs) was independently associated with improved OS.[14] This association has also been highlighted by numerous meta-analyses and large retrospective cohort studies (even when considering differences between visceral fat mass versus skeletal mass) and has also been associated with improved PFS.[15–17] Interestingly, BMI's association with improved survival is not necessarily linear and has not been universally demonstrated.[18,19]

In melanoma, obesity's association with improved survival after ICI has also been previously demonstrated. McQuade et al. performed a pooled analysis of two cohorts with 538 patients with metastatic melanoma treated with various ICI regimens and found that obesity was independently associated with both improved PFS and OS.[13] Analysis of the cancer genome analysis by Wang et al. revealed that obesity was associated with a 1.57-fold increase in mean PD-1 expression.[9] To dive deeper beyond the crude BMI metric, Lee et al. performed a retrospective analysis of 266 patients treated with ICI for unresectable/metastatic melanoma and implemented additional adiposity metrics, such as skeletal muscle index and visceral fat index, in their analysis. In their study, they found that the protective effect of obesity was linked with increases in a patient's visceral fat index.[18]

Studies investigating obesity's association with survival outcomes after ICI treatment for head and neck malignancies are limited but rapidly evolving. In support of this study's findings, Kang et al.'s meta-analysis of 50 studies in patients with head and neck squamous cell carcinoma (HNSCC) treated with ICI found that high BMI was associated with both improved OS and PFS.[20] Zhang et al.'s retrospective review of 49 patients who received pembrolizumab for recurrent/metastatic HNSCC likewise demonstrated obesity's survival benefit.[21] Their results, however, are difficult to translate given the low numbers (11 patients with either obese or overweight BMI). Our group previously leveraged the TriNetX database to analyze this association in HNSCC on a population scale, and our previous findings corroborated the presented survival benefits.[9] Regarding treatment modalities outside of ICI, sarcopenia was likewise found to be associated with worse OS and disease-specific survival in patients with HNSCC.[22,23]

Obesity tends to be a negative prognostic factor for surgical procedures for gastrointestinal tumors because of risk of increased blood loss, poor lymph node dissection, and postoperative complications.[24,25] However, in terms of oncologic outcomes after ICI, Deng et al. found that higher BMI was associated with improved PFS and OS after ICI for gastric cancers.[26] Similar findings were demonstrated by Chen et al.'s analysis of 1340 patients with advanced esophageal cancer.[27] Our study results reinforce these findings by demonstrating improved OS in gastrointestinal malignancies in a cohort of nearly 5000 patients. However, these findings are not universal and likewise require further investigation.[28]

TNBC is the primary subtype of breast cancer treated with anti–PD-(L)1 therapy, as demonstrated by near-identical numbers in subgroup analysis.[29] TNBC generally has a poor prognosis and resistance to conventional therapy because of its high proliferative activity, growth rate, aggressive clinical course, and early rates of metastases.[30] Harborg et al. performed a systematic review and meta-analysis of 13 studies of 8944 patients with TNBC and found that obesity was associated with both shorter PFS and OS when treated with traditional systemic therapies.[29] However, to our knowledge, there are no published studies investigating the effects obesity on TNBC response to ICI. Previous reports suggest that TNBC may be more primed to response to ICI due to its greater presence of tumor infiltrating lymphocytes, higher PD-1 expression, and higher tumor mutation burden relative to other breast cancer subtypes.[31] Pingili et al. investigated mice models and demonstrated that although breast cancer exacerbates obesity-driven immunosuppression, anti–PD-1 therapy reinvigorates antitumor immunity in the tumor microenvironment, mammary fat pad, and periphery.[32] To our knowledge, our study is the first to investigate the association of obesity with ICI response in TNBC and demonstrate an increased OS in patients with obesity.

ICI for genitourinary cancers has been largely centered around metastatic RCC. De Giorgi et al.'s prospective trial of 313 patients with RCC found that elevated BMI was an independent predictor for improved OS after ICI treatment.[33] Lalani et al. performed a retrospective analysis of 735 patients with metastatic RCC treated with anti–PD-(L)1 therapy and likewise found that the high BMI cohort demonstrated significantly improved OS, had a higher objective response rate, and increased time to treatment failure.[34] Interestingly, our subanalysis of patients with RCC did not demonstrate a survival benefit associated with obesity but may be explained by our small cohort ($n = 32$).

Additional investigations have demonstrated that sarcopenia is associated with worse outcomes after ICI. In a systematic review and meta-analysis of 1284 patients from 14 studies, Lee et al. found that sarcopenia was associated with worse OS and PFS after ICI.[35] Li et al.'s meta-analysis of 519 patients from eight studies suggests, however, that sarcopenia is not associated with an increase in irAEs.[36]

Previous literature supports the link between obesity and increased rates of irAEs after treatment with ICI.[37] Guzman-Prado highlighted this association in their meta-analysis with 1937 patients, and Gülave et al.[38] likewise confirmed this association in their review of more than 5000 patients from 15 studies across five solid tumor indications (NSCLC, melanoma, urothelial cell carcinoma, HNSCC, and RCC).[37] Interestingly, although our study demonstrated this association between pulmonary/intrathoracic, gastrointestinal, breast, and genitourinary malignancies, there was no significant association found in cutaneous and head and neck malignancies. Obesity is thought to be associated with increased rates of irAEs for reasons similar to improved ICI efficacy: chronic inflammatory state, increased PD-1 expression, increased T-cell exhaustion, and reduced T-cell proliferative capacity, but this relationship and mechanism require further investigation.[8]

Limitations

Accurately capturing cancer diagnoses, treatment, adverse events, and outcomes are dependent on accurate documentation and inclusion and exclusion ICD-10 codes during the TriNetX cohort building and analysis. The platform is also unable to define or capture PFS. Furthermore, given limitations within the TriNetX platform, we were unable to differentiate ICI treatment setting (e.g., neoadjuvant, recurrent/metastatic disease). Other clinical factors that could not be matched for (either because of limitations within TriNetX platform or insufficient numbers for stratification) include histologic tumor grade, severity of each medical comorbidity (e.g., stratifying degree of hemoglobin A1c), diet, lifestyle, degree of physical activity, and socioeconomic status, which all have been demonstrated to influence health outcomes.[39,40]

As an additional point of caution, this study identifies a patient's BMI at a time prior to treatment (which may vary) and cannot account for progressive weight loss secondary to either the malignancy itself or ICI. Although this is an important consideration given the risk of reverse causality, we attempted to mitigate this risk with PSM for key clinical characteristics. Collider stratification bias is an additional factor that must be considered and could not be adequately tested for within the platform. BMI is a crude and therefore inadequate measure of adiposity because it cannot differentiate between lean mass like skeletal muscle versus visceral adipose tissue. Furthermore, it cannot account for variations in body composition associated with age, sex, and even ethnicity.[41] We attempted to mitigate these variations via propensity score matching. Imaging techniques (e.g., computed tomography, magnetic resonance imaging) have been used to distinguish visceral from subcutaneous fat and how this can affect overall clinical outcomes in gastrointestinal or colorectal cancers but are outside the scope of this study.[42]

Conclusions

This large population-based study provides evidence demonstrating an improved OS in obese patients up to 5 years after treatment with ICI across various solid tumor malignancies. Furthermore, study is necessary to understand the mechanism of this relationship.

AUTHOR CONTRIBUTIONS

Eric V. Mastrolonardo: Conceptualization; data curation; formal analysis; visualization; writing—original draft; methodology; investigation; project administration; writing—review & editing; validation; and resources. **Pablo Llerena**: Conceptualization; formal analysis; data curation; visualization; writing—original draft; methodology; investigation; project administration; and writing—review & editing. **Emma De Ravin**: Conceptualization; data curation; visualization; formal analysis; writing—original draft; methodology; and investigation. **Kathryn Nunes**: Data curation; formal analysis; visualization; writing—original draft; methodology; investigation; and project administration. **Praneet C. Kaki**: Data curation; formal analysis; writing—review & editing; methodology; and software. **Kelly M. Bridgham**: Data curation; formal analysis; visualization; methodology; investigation; validation; and writing—review & editing. **Dev R. Amin**: Data curation; visualization; formal analysis; investigation; writing—review & editing; and validation. **Daniel J. Campbell**: Formal analysis; visualization; investigation; writing—review & editing; and validation. **Ramez Philips**: Formal analysis; visualization; investigation; writing—review & editing; and validation. **Scott H. Koeneman**: Supervision; validation; methodology; investigation; and writing—review & editing. **David M. Cognetti**: Supervision; writing—review & editing; validation; and investigation. **Adam J. Luginbuhl**: Investigation; supervision; writing—review & editing; and validation. **Nicole L. Simone**: Investigation; supervision; writing—review & editing; and validation. **Jennifer M. Johnson**: Investigation; supervision; writing—review & editing; and validation. **Joseph M. Curry**: Conceptualization; data curation; formal analysis; visualization; writing—review & editing; supervision; project administration; investigation; validation; methodology; and resources.

CONFLICT OF INTEREST STATEMENT

Joseph Curry, MD, is a consultant for Rakuten Medical.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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