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Cardiovascular Health and Outcomes in Cancer Patients Receiving Immune Checkpoint Inhibitors

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Whether cardiovascular (CV) disease is associated with clinical outcomes in cancer patients receiving immunotherapy is unknown. We reviewed the Mayo Clinic database for all cancer patients who received an immune checkpoint inhibitor (ICI). Multivariate logistic regression analysis, survival analyses, and Cox proportional-hazards models were formulated. Between March, 2010 and July, 2019, 3,326 patients received ICI. Mean patient age was 63.5 years (range: 16 to 96 years). In a Cox proportional-hazards model, obesity (hazard ratio [HR] 0.65, 95% confidence level [CI] 0.55 to 0.77, p < 0.001) and hypercholesterolemia (HR 0.80, 95% CI 0.72 to 0.89, p < 0.001) were associated with lower all-cause mortality while hypertension (HR 1.32, 95% CI 1.17 to 1.49, p < 0.001) and smoking (HR 1.17, 95% CI 1.06 to 1.29, p = 0.002) were associated with higher overall mortality. Among patients with lung cancer, multivariable-adjusted hazard ratios for death from any cause for beta blocker users, as compared with patients who had never used a beta blocker, were 1.39 (95% CI 1.10 to 1.76, p = 0.006). A total of 80 patients (2.4%) experienced CV immune-related adverse events. Event-related morality for ICI-induced myocarditis was 41.7% (5/12). Multivariable-adjusted hazard ratios for ICI-induced myocarditis were 5.2 (95% CI 1.4 to 18.7, p = 0.01) for history of heart failure, 4.06 (95% CI 1.15 to 14.3, p = 0.03) for history of acute coronary syndrome, and 1.07 (per each 1-year increase, 95% CI 1.01 to 1.14, p = 0.02) for age. In conclusion, our study shows that CV factors are associated with clinical outcomes in cancer patients receiving ICI and could be used to predict mortality. In patients with lung cancer, pretreatment beta blocker use is associated with higher all-cause mortality. Three clinical factors—history of heart failure, history of acute coronary syndrome, and age greater than 80 years—help identify patients at higher risk of ICI-induced myocarditis who might benefit from more intensive cardiac surveillance. **(Am J Cardiol 2020;125:1920−1926)**

Immune checkpoint inhibitors (ICIs) are revolutionizing the care of patients with refractory cancers.[1,2] Even though durable remissions are often seen, only a subset of patients achieves meaningful responses to ICI, highlighting the need for accurate predictors of clinical outcomes. Recently, several biologic determinants of response were described, including host genetic factors, programmed death 1 (PD-1) levels and gut microbiota.[3,4,5] Since multiple cardiovascular (CV) risk-enhancers and medications modulate key immune pathways, it is possible that they directly influence clinical outcomes in patients treated with ICI. In this study, we analyzed the associations of CV risk factors, disease states, and medications with clinical outcomes in a large cohort of immunotherapy-treated patients.

Methods

The Mayo Clinic Unified Data Platform Advanced Cohort Explorer (ACE) query tool was used to identify all patients who were treated at the Mayo Clinic with an ICI by 07/01/2019.[6] ICI agents included atezolizumab, avelumab, ipilimumab, nivolumab, and pembrolizumab. Demographic data were collected from ACE. Information about baseline CV health, pre-ICI CV medications, tumor type and stage (metastatic, nonmetastatic), and ICI agent was derived from ACE using an electronic search algorithm. Use of CV medications (aspirin, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta blocker, statins, and ezetimibe) was considered positive if there was at least 1 prescription prior to initiation of ICI. Hypercholesterolemia was defined as low-density lipoprotein-cholesterol (LDL-C) level greater than 70 mg/dl (at any time prior to ICI treatment) in the presence of an atherosclerotic cardiovascular disease (ASCVD), or greater than 100 mg/dl (at any time prior to ICI treatment) in the absence of established ASCVD.

ASCVD was defined as any of the following events: stroke, transient ischemic attack (TIA), acute coronary syndromes (ACS), coronary artery disease (CAD) with stable angina, coronary or other arterial revascularization, and peripheral vascular disease. Elevated triglyceride level was defined as greater than 200 mg/dl. The last day of clinical follow up was considered the last day of contact with

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patients who have not been reported as deceased by the end of the study. Data regarding CV events during follow-up was collected using ICD diagnosis codes. CV-immune-related adverse events (IRAE), including myocarditis, takotsubu syndrome, pericarditis, pericardial effusion, and vasculitis, were extracted using ACE. Events were documented as drug-related when the medical chart stated high suspicion for CV-IRAE. Information about deaths was collected from the death registry of ACE and additional chart review was performed for patients who experienced a CV-IRAE. The Institutional Review Board deemed the study exempt from informed consent procedures because no data was directly collected from patients. Patients who did not provide research authorization were excluded.

Descriptive statistics were generated for the complete cohort and for the tumor subgroups. Multivariable logistic regression analyses were conducted to determine factors associated with being a recipient of a CV medication, while adjusting for traditional CV risk factors and diseases (age, hypertension, diabetes mellitus, obesity, atrial fibrillation, nicotine use, history of acute coronary syndrome, history of stroke, history of peripheral arterial disease, history of carotid artery stenosis, history of aortic aneurysm, history of heart failure, history of any ASCVD, hypercholesterolemia (LDL-C>70 mg/dl in the presence of ASCVD or >100 mg/dl in its absence), pre-ICI use of statins, aspirin, beta blockers, ACE inhibitors, ARBs, or ezetimibe, as well as the type of cancer (lung cancer, melanoma, renal cancer, and other) and ICI. Cox proportional-hazards models were formulated to assess for factors associated with all-cause mortality or CV events during follow-up, considering demographics, the above-mentioned baseline CV risk factors and diseases and use of CV medications. Univariable survival analyzes were set and Kaplan-Meier curves were created to illustrate survival trends associated with the individual parameters. Overall survival was measured as the time from initiation of ICI until death from any cause or last documented follow-up for patients who did not die.

Time to CV-IRAE was defined as the interval of time from ICI initiation to a clinical event (myocarditis, takotsubu syndrome, pericarditis, pericardial effusion, or vasculitis), if one occurred. For this endpoint, patients who were free of a clinical CV-IRAE, regardless of survival status, were censored at the time of their last follow-up. Cox proportional-hazards models were fitted for the entire cohort as well as the individual tumor types evaluating for associations between disease states and medications with outcome variables (all-cause mortality, CV-IRAE). Data analysis was performed using JMP.

Results

A total of 3,326 patients were treated with ICI between 03/01/2010 and 07/01/2019. The demographic and baseline clinical characteristics of the cohort are presented in Table 1. The mean age was 63.5 (range 16 to 96) and 1,296

Table 1
Demographic and baseline clinical characteristics of cancer patients treated with immune checkpoint inhibitors (n = 3,326)

Variable	Total (n = 3,326)	Male (n = 2,030)	Female (n = 1,296)
Age (mean, range) (years)	63.5 (16 to 96)	64.5 (16 to 96)	61.9 (17 to 94)
White	3,095 (93%)	1,910 (94%)	1,185 (91%)
Cancer type			
Lung cancer	632 (19%)	394 (19%)	238 (18%)
Melanoma	687 (21%)	420 (21%)	266 (21%)
Renal cancer	207 (6%)	136 (7%)	71 (5%)
Other	1800 (54%)	1080 (53%)	721 (55%)
Immune checkpoint inhibitor			
Atezolizumab	251 (8%)	137 (7%)	63 (5%)
Avelumab	18 (1%)	10 (1%)	8 (1%)
Ipilimumab	474 (14%)	314 (15%)	160 (12%)
Nivolumab	1,070 (32%)	655 (32%)	414 (32%)
Pembrolizumab	1,513 (45%)	881 (43%)	633 (49%)
Cardiovascular conditions			
Hypertension	1,218 (37%)	819 (40%)	400 (31%)
Diabetes mellitus	928 (28%)	605 (30%)	323 (25%)
Obesity	333 (10%)	219 (11%)	114 (9%)
Body mass index (Kg/m^2)	27	28	26
Hypercholesterolemia	1,088 (33%)	659 (32%)	429 (33%)
Prior atherosclerotic cardiovascular disease	591 (18%)	407 (20%)	184 (14%)
History of atrial fibrillation	397 (12%)	282 (14%)	115 (9%)
Prior smoker	1,382 (42%)	923 (45%)	459 (35%)
Prior acute coronary syndrome	582 (17%)	393 (19%)	189 (15%)
Prior stroke	242 (7%)	188 (9%)	54 (4%)
Prior peripheral arterial disease	100 (3%)	76 (4%)	24 (2%)
Prior aortic aneurysm	618 (19%)	424 (21%)	194 (15%)
Prior carotid artery stenosis	57 (2%)	43 (2%)	14 (1%)
Prior heart failure	383 (12%)	260 (13%)	123 (9%)

Hypercholesterolemia was defined as LDL-C level greater than 70 mg/dl in the presence of an ASCVD, or greater than 100 mg/dl in the absence of ASCVD. Obesity was defined as BMI ≥ 30.

(39%) patients were female. The most common cancer diagnosis was melanoma (687, 21%), followed by lung cancer (632, 19%) and renal cancers (207, 6%).

Hypertension and diabetes mellitus were present in 1,218 (37%) and 928 (28%) of the patients, respectively. History of acute coronary syndrome and history of stroke were documented in 582 (17%) and 242 (7%) of the patients. There were no significant differences in the prevalence of CV risk factors and diseases among the 3 most common tumor groups except for hypercholesterolemia being less frequent in patients with renal cancers compared with lung cancers and melanoma (renal: 28%, lung: 39%, melanoma 35%, p = 0.02).

The use of cardio-preventive medications is outlined in Table 2. More than a third of the patients were treated with statins prior to ICI and 1,792 (54%) patients had a documented use of a beta blocker. Aspirin and statins were less frequently used in patients with renal cancers compared with those with lung cancers or melanomas (aspirin: lung: 50%, melanoma: 50%, renal: 40%, p = 0.03; statin: lung: 22.2%, melanoma: 19.4%, renal: 13.6%, p = 0.02). There were no significant differences in the utilization of other cardioprotective medications between the different tumor groups.

Table 2
Baseline use of cardioprotective medications among cancer patients receiving immune checkpoint inhibitors

Medication	Number, %
Any statin use	1,249 (38%)
High-intensity statin use	177 (5%)
Ezetimibe	102 (3%)
Aspirin	1,515 (46%)
Beta blockers	1,792 (54%)
Angiotensin-converting enzyme inhibitors	1,003 (30%)
Angiotensin receptor blockers	464 (14%)

At a mean follow-up of 16 months, 1,790 (54%) patients died. Myocardial infarction and stroke occurred in 213 (7%) and 227 (7%) patients. Incident heart failure was present in 354 (11%) patients. Cancer type and stage were not associated with overall mortality in a survival analysis (log-rank test, p = 0.95, p = 0.28).

In a multi-variable Cox proportional-hazards model also adjusting for smoking history, use of aspirin, beta blocker, ACE-inhibitor and ARB, hypertension (HR 1.32, 95% CI 1.17 to 1.49, p < 0.001), history of stroke (HR 1.26, 95% CI 1.06 to 1.50, p = 0.009), and history of heart failure (HR 1.26, 95% CI 1.09 to 1.46, P=0.002) were associated with higher all-cause mortality. In contrast, obesity (HR 0.65, 95% CI 0.55 to 0.77, p < 0.001) and hypercholesterolemia (HR 0.80, 95% CI 0.72 to 0.89, p < 0.001) were associated with lower overall mortality rates. Higher preimmunotherapy body-mass index (BMI) value was associated with lower all-cause mortality (risk ratio: 0.96, per each 1-unit increase, 95% CI, 0.95 to 0.98, p < 0.001) and was consistent among the 3 most common tumor types (risk ratio: lung: 0.96, melanoma: 0.96, renal: 0.94). Ezetimibe was marginally associated with more favorable survival (HR 0.75, 95% CI 0.57 to 0.99, p = 0.04). There was no association between the use of aspirin, statins, ACE-inhibitors, or ARBs prior to diagnosis and overall survival. A Forest plot demonstrating the association between CV health and all-cause mortality in ICI-treated patients is presented in Figure 1. A cancer-specific representation of multivariable Cox proportional-hazards ratios is shown in Table 3.

In the subgroup of patients with lung cancer (n = 632, 19%), comparison of survival curves using log-rank test showed higher mortality in beta blocker users compared to nonusers (p = 0.012). Multivariable-adjusted hazard ratios for death from any cause were 1.39 (95% CI 1.10 to 1.76, p = 0.006) for beta blocker use, in a model also adjusting for hypertension, obesity, hypercholesterolemia, smoking history, history of stroke, history of heart failure, and

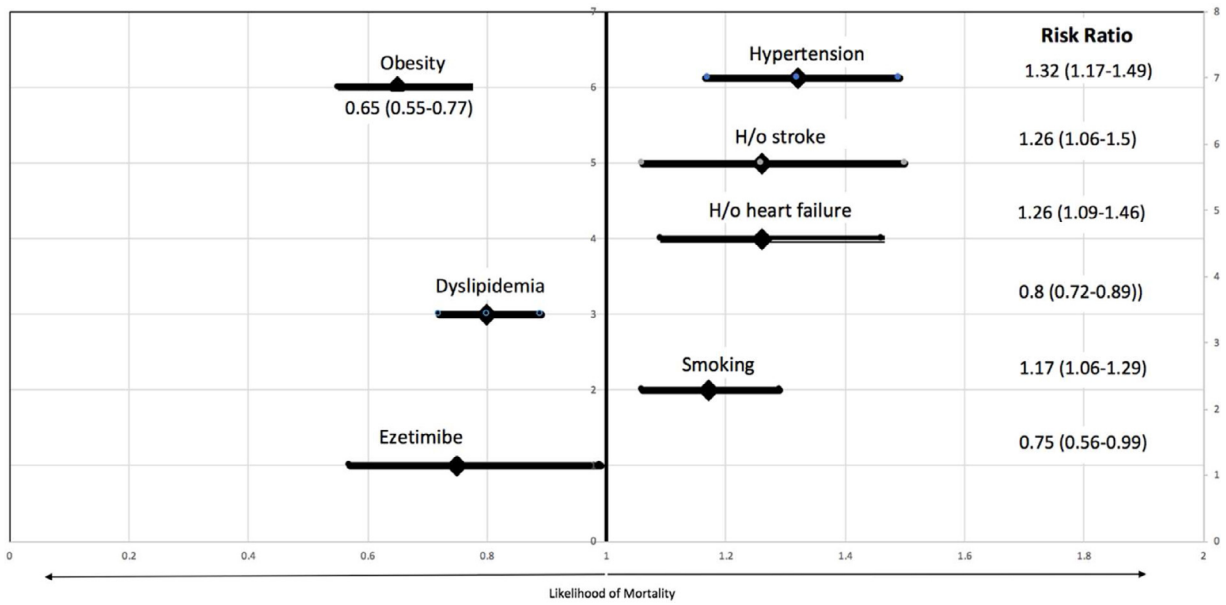


Figure 1. Forest plot of mortality of ICI-treated patients according to cardiovascular parameters.

Table 3
Cancer-specific multivariable adjusted hazard ratios and confidence intervals for all-cause mortality in patients receiving immune checkpoint inhibitors

Variable	Lung cancer	Melanoma	Renal cancer
Hypercholesterolemia	0.77 (95% CI 0.61 to 0.97)	0.79 (95% CI 0.63 to 1.00)	
Obesity	0.67 (95% CI 0.46 to 0.94)	0.61 (95% CI 0.42 to 0.89)	
Prior smoking	1.28 (95% CI 1.03 to 1.60)		
Hypertension			1.70 (95% CI 1.09 to 2.62)
Prior heart failure			2.27 (95% CI 1.22 to 4.0)
Prior beta blocker use	1.39 (95% CI 1.10 to 1.76)		

*Only significant values are included in the table.

ezetimibe use (Figure 2). Obesity (HR 0.67, 95% CI 0.46 to 0.94, p = 0.03) and hypercholesterolemia (HR 0.77, 95% CI 0.61 to 0.97, p = 0.03) were associated with a reduced risk of all-cause death in the lung cancer cohort. To further elucidate the association between pre-ICI beta blocker use and all-cause mortality in lung cancer patients, a univariable Cox proportional-hazards model was fit to evaluate the interaction between the strength of the CV indication for beta blockers (history of heart failure or atrial fibrillation, or history of acute coronary syndrome up to 3 years prior to beta blocker use = "compelling indication" vs other indications) and all-cause mortality. No association between beta blocker use and excess mortality was found in patients with a "compelling indication" for beta blocker (p = 0.53). Beta blocker users had a higher incidence of sepsis after initiation of ICI compared with nonusers, in a multivariable logistic regression analysis (8.1% vs 4.5%, p = 0.03). The incidence of hypotension, bradycardia, and syncope were not statistically different in beta blocker users compared with nonusers. No association between the use of pre-ICI beta blocker and myocardial infarction, stroke, or heart failure during follow up was demonstrated in a multivariable Cox proportional-hazards model.

In patients with melanoma (n = 687, 21%), obesity (HR 0.61, 95% CI 0.42 to 0.89, p = 0.01) was associated with a lower likelihood of death. In addition, ezetimibe use showed a trend towards lower all-cause mortality (HR 0.55, 95% CI 0.30 to 1.01). In patients with renal cancers (n = 207, 6%), hypertension (HR 1.70, 95% CI 1.09 to 2.62, p = 0.02) and history of heart failure (HR 2.27, 95% CI 1.22 to 4.0, p = 0.01) were associated with higher overall mortality. In the remaining group of cancer patients (nonlung, nonmelanoma, nonrenal cancers; n = 1,800), hypertension (HR 1.41, 95% CI 1.21 to 1.64, p < 0.0001), and history of heart failure (HR 1.26, 95% CI 1.03 to 1.54, p = 0.02) were associated with higher all-cause death, while obesity (HR 0.64, 95% CI 0.51 to 0.80, p < 0.0001) and hypercholesterolemia (HR 0.83, 95% CI 0.72 to 0.96, p=0.01) were associated with lower overall mortality rates. Use of beta blockers prior to ICI was not associated with all-cause mortality among patients with nonpulmonary malignancies.

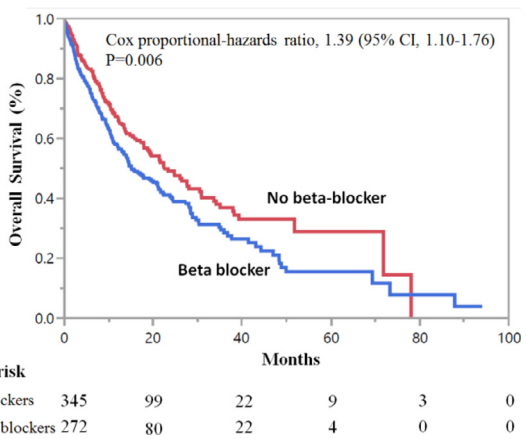


Figure 2. Overall survival in lung cancer patients receiving immune checkpoint inhibitors according to beta blocker use.

A total of 80 patients (2.4%) experienced any type of CV-IRAE (Table 4). In summary, ICI-induced myocarditis occurred in 12 (0.36%) patients, pericarditis/pericardial effusion in 58 (1.74%) patients, and vasculitis in 9 (0.27%) patients. Of all CV-IRAE events, myocarditis was associated with the highest event-related mortality (5/12, 42%) and vasculitis with the lowest (0/9, 0%).

In a Cox Proportional-Hazards Model, history of ACS (HR 4.06, 95% CI 1.15 to 14.3, p = 0.03), history of heart failure (HR 5.2, 95% CI 1.4 to 18.7, p = 0.01), Hashimoto's Thyroiditis (HR 15.9, 95% CI 1.9 to 132.9, p = 0.01), and advanced age (HR 1.07 with each unit increase in age, 95% CI 1.01 to 1.14; p = 0.02) were associated with higher incidence of myocarditis. A risk prediction model was formulated utilizing 3 pre-ICI clinical factors: history of ACS, history of heart failure, and age older than 80 years. Hashimoto's Thyroiditis was not included in the model due to very low number of patients with this diagnosis. The incidence of ICI-mediated myocarditis in patients with any of the 3 factors was elevated to the same extent, and so was its incidence in patients with any combination of 2 clinical factors, allowing the creation of a point-based risk prediction calculator (Figure 3).

Discussion

Our study reports several important findings including an association between obesity and improved overall survival in immunotherapy-treated cancer patients. This observation is consistent with a recent retrospective study in which obesity was associated with a 26% improvement in overall survival in patients with metastatic melanoma who were treated with ICI.[7] The protective association between obesity and clinical outcomes could be mediated by excess leptin, a driver of proinflammatory T helper 1 (T_H1) immune responses which may augment antitumor immunity.[8] Polarization of the immune system towards a T_H1 phenotype has been suggested as an explanation. However, the exact

Table 4
Clinical descriptors of cardiovascular immune-related adverse events

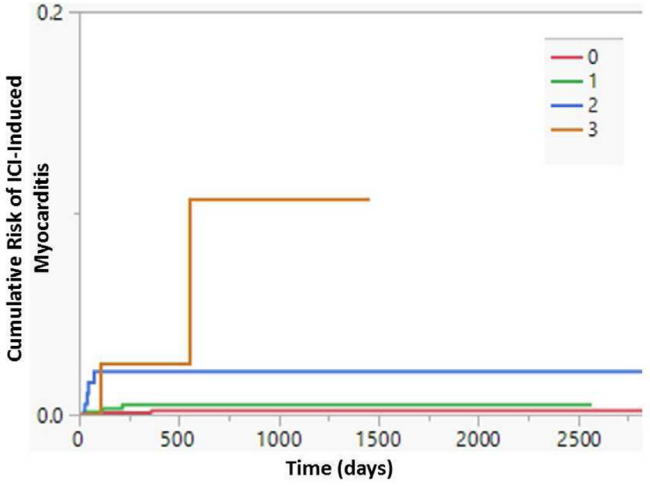
Variable	Pericarditis/Pericardial effusion (n = 58)	Vasculitis (n = 9)	Myocarditis (n = 12)
Mean age (years)	61.8	59.9	74.5
Men	40 (69%)	6 (67%)	8 (66%)
Caucasian	54 (93%)	8 (89%)	11 (91%)
Lung cancer	12 (21%)	4 (44%)	4 (33%)
Melanoma	9 (16%)	1 (11%)	4 (33%)
Renal cancer	5 (9%)	1 (11%)	0
Hypertension	16 (28%)	3 (33%)	5 (42%)
Diabetes mellitus	11 (19%)	4 (44%)	7 (58%)
Obesity	7 (12%)	2 (22%)	3 (25%)
History of atrial fibrillation	7 (12%)	1 (11%)	3 (25%)
Smoking history	27 (47%)	3 (33%)	7 (58%)
History of ACS	12 (21%)	1 (11%)	7 (58%)
Heart failure	4 (7%)	0	6 (50%)
Hypercholesterolemia	20 (35%)	3 (33%)	8 (67%)
History of stroke	2 (4%)	0	0
Mean duration from ICI initiation to IRAE (months)	6.3 (range: 0.1-38.1)	8.1 (range: 0.2-34.2)	4.6 (range: 0.6-4.6)
Event-related mortality	15 (26%)	0	5 (42%)

mechanism by which obesity is associated with better outcomes in immunotherapy-treated patients remains unknown. It is also possible that the paradoxical obesity association is captured due to confounding factors such as the suboptimal nature of BMI as a marker of visceral adiposity as well as the energy reserves available within adipose tissue. Further studies of the obesity-outcome association will be needed to determine the appropriate surveillance strategy in patients who are obese who are treated with ICI.

A second predictive factor for favorable clinical outcomes was hypercholesterolemia. Emerging animal model evidence suggests that LDL-C stimulates adaptive immune responses and may augment inflammatory pathways.[9,10] It is possible that elevated circulating LDL-C levels are either a marker of or directly culminate in heightened T cell immunity that is associated with improved clinical responses in patients who receive immunotherapy. Nevertheless, the relationship between circulating lipid levels and clinical outcomes is compounded by the effects of different cancers and their treatments on lipid synthesis and metabolism and may thus be influenced by unadjusted factors that are difficult to measure.

We also demonstrate an association between the use of beta blockers prior to ICI and higher all-cause mortality in patients with lung cancer. Despite a growing body of evidence suggesting that adrenergic stimuli reprogram T cell pathways, the nature and extent to which beta blockers affect immunosuppression remain unclear.[11,12] We suspect that, even if beta blockers have an impact on the adaptive immune system, it is likely to be modest relative to its potential hazards in ICI-treated lung cancer patients. Our analysis supports this hypothesis with no mortality increase seen in the subgroup of patients who had a strong CV indication for beta blockade. In addition, since CV endpoints were not affected by beta blocker use in our Cox proportional-hazards model, it is possible that beta blocker-mediated adverse effects or increased cancer-related death were responsible for the higher mortality in patients who used beta blockers.

We also provide data on CV-IRAE. Although rare, these events are significantly under-diagnosed making their clinical



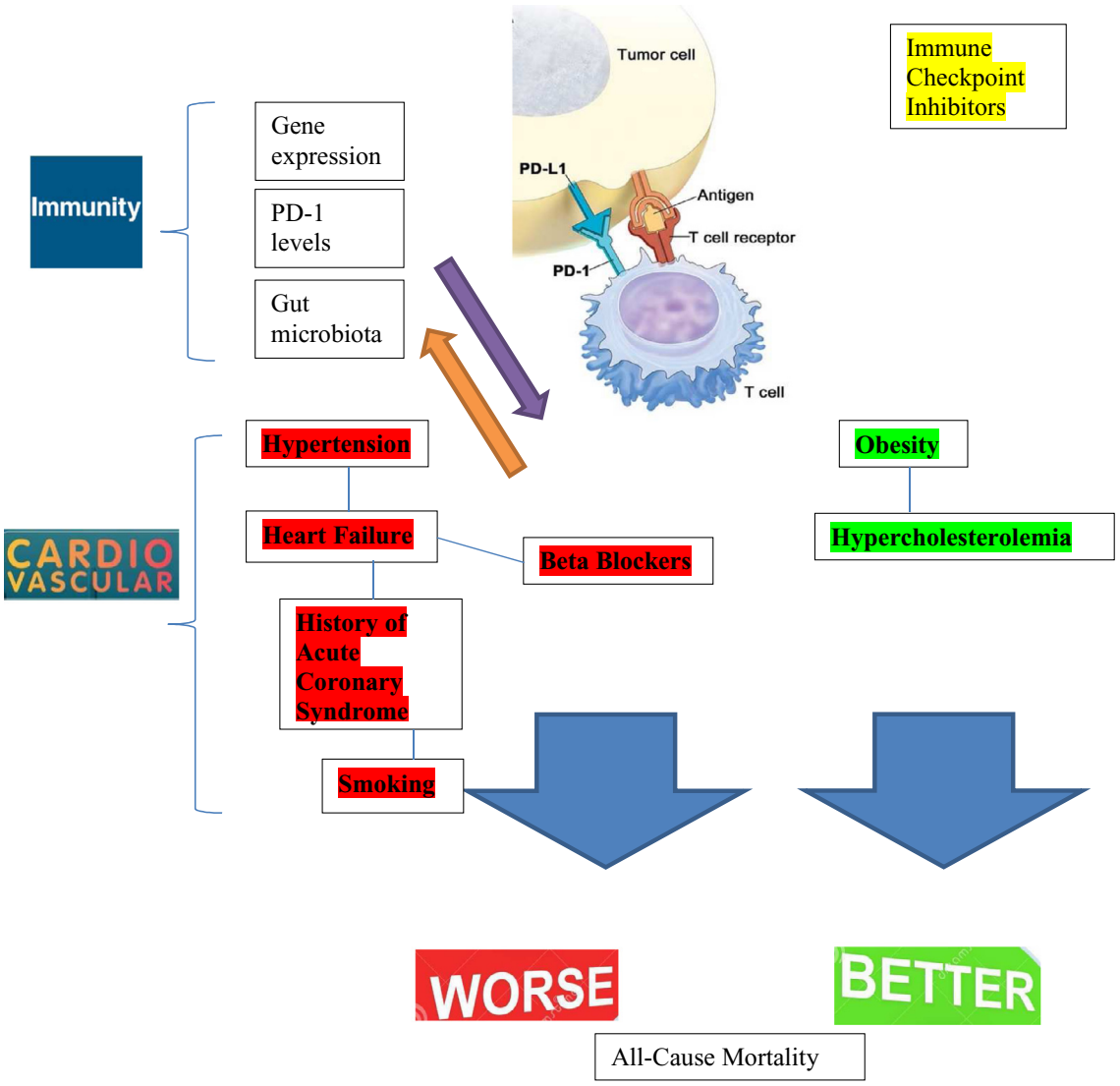
Risk Factors	Points
History of ACS	1
History of HF	1
Age≥80	1

# Risk Factors / Points	Absolute incidence	Incidence per 1,000 person years
0	0.13%	1
1	1.4%	4
2	2.8%	12
3	4.5%	42

Figure 3. Cumulative incidence of immune checkpoint inhibitor-induced myocarditis stratified by number of risk factors.

characterization very challenging. Nevertheless, some of these entities carry high mortality rates (myocarditis, 42%) and with increasing dissemination of ICI in clinical oncology and continued aging of the population, immune-mediated CV processes are likely to increase in prevalence. In the largest study of immunotherapy-related myocarditis to date, an event rate of 1.4% was reported, which is higher than our rate possibly due to the tertiary care nature of our center and consequent missing of CV events.[13] The same recent report has shown that the presence of diabetes mellitus, obstructive sleep apnea, and obesity increases the risk of myocarditis secondary to ICI.[13] We further identify history of ACS or heart failure, advanced age, and history of Hashimoto Thyroiditis as additional important risk factors and present a risk prediction formula that, although limited by the retrospective basis of the registry and the small event rate, provides preliminary insights to practicing clinicians about the high-risk patient. We suggest that special vigilance is applied in cases of individuals with 1 of more of the above-mentioned risk factors, including a lower threshold for measuring troponin and obtaining 12-lead electrocardiogram with any new cardiorespiratory symptom, to increase the likelihood of early diagnosis and timely intervention in this highly fatal condition. Prospective studies are needed to accurately determine and validate the clinically important risk factors for ICI-related myocarditis

Our study has several limitations. First, it is retrospective and based on a hospital registry with its inherent inaccuracy. Secondly, CV events might have been missed if they occurred outside the Mayo system. In addition, no data on cancer-specific mortality was available and it remains possible that unadjusted factors accounted for the different outcomes among patients with various CV risk factors. Lastly, the dose and duration of immunotherapy medications, as well as prior anti-cancer therapies, are not included in our analysis.



PD-1=programmed death 1.

Figure 4. Interaction between immunity and cardiovascular disease—associations demonstrated in our study.

In CV conditions are independently associated with overall survival in cancer patients receiving ICI. This novel finding hopefully will encourage further studies to evaluate the predictive impact of noncancer disease states in patients treated with immunotherapy. Understanding the complex cross talk between CV health and adaptive immunity may allow the incorporation of such factors as obesity, heart failure, smoking, and hypercholesterolemia into outcome-prediction algorithms and may enable more precise prognostication in ICI-treated patients (Figure 4). In addition, prospective trials that would investigate the association between beta blocker use and overall mortality in lung cancer patients are needed.

CRediT author statement

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