JACC: CARDIOONCOLOGY VOL. 4, NO. 5, 2022

ORIGINAL RESEARCH

Burden of Cardiovascular Disease in Immune Checkpoint Inhibitor–Treated Patients

Reconciling Adjudicated and Coded Outcomes

Lavanya Kondapalli, MD,[a] Judith Hsia, MD,[a,b] Ronni Miller, PharmD,[c] Thomas W. Flaig, MD,[d] Marc P. Bonaca, MD, MPH[a,b]

ABSTRACT

BACKGROUND There is growing recognition of the risk of cardiovascular (CV) events, particularly myocarditis, in the context of immune checkpoint inhibitor (ICI) therapy; however, true event rates in real-world populations and in the background of CV disease remain uncertain.

OBJECTIVES The authors sought to determine CV event occurrence in ICI-treated patients and assess the accuracy of diagnosis by International Classification of Diseases (ICD) code compared with adjudication using established definitions and full-source documentation review.

METHODS Electronic medical record extraction identified potential CV events in ICI-treated patients in the University of Colorado Health system. Two cardiologists independently adjudicated events using standardized definitions. Agreement between ICD codes and adjudicated diagnoses was assessed using the kappa statistic.

RESULTS The cohort comprised 1,813 ICI-treated patients with a mean follow-up of 4.6 ± 3.4 years (3.2 ± 3.2 years pre-ICI and 1.4 ± 1.4 years post-ICI). Venous thromboembolic events (VTEs) were the most common event, occurring in 11.4% of patients pre-ICI and 11.3% post-ICI therapy. Post-ICI therapy, the crude rates of myocardial infarction (MI), heart failure, and stroke were 3.0%, 2.8%, and 1.6%, respectively. Six patients (0.3%) developed myocarditis post-ICI. Agreement between the ICD code and adjudication was greater for VTE ($\kappa = 0.82$; 95% CI: 0.79-0.85) and MI ($\kappa = 0.74$; 95% CI: 0.66-0.82) and worse for myocarditis ($\kappa = 0.50$; 95% CI: 0.20-0.80) and heart failure ($\kappa = 0.47$; 95% CI: 0.40-0.54).

CONCLUSIONS ICD codes correlated well with adjudicated events for VTE and MI, but correlation was worse for heart failure and myocarditis. Adjudication with standardized definitions can enhance the understanding of the incidence of CV events related to ICI therapy. (J Am Coll Cardiol CardioOnc 2022;4:649-656) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Division of Cardiology, University of Colorado School of Medicine, Aurora, Colorado, USA; [b]CPC Clinical Research, Aurora, Colorado, USA; [c]UCHealth Anschutz Medical Campus, Aurora, Colorado, USA; and the [d]Division of Medical Oncology, University of Colorado School of Medicine, Aurora, Colorado, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received April 22, 2022; revised manuscript received September 8, 2022, accepted September 15, 2022.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2022.09.003

JACC: CARDIOONCOLOGY, VOL. 4, NO. 5, 2022
DECEMBER 2022:649–656

ABBREVIATIONS AND ACRONYMS

CMR = cardiovascular magnetic resonance

CV = cardiovascular

EMR = electronic medical record

ICD = International Classification of Diseases

ICI = immune checkpoint inhibitor

MI = myocardial infarction

TIA = transient ischemic attack

VTE = venous thromboembolic event

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that block intrinsic down-regulators of immunity, such as cytotoxic T-lymphocyte antigen 4, programmed cell death 1, or programmed cell death ligand 1. By recent estimates, more than one-third of patients with cancer are eligible for ICI therapy.[1] Because the National Cancer Institute anticipates 1.8 million new cancer diagnoses annually in the United States, this translates into a large number of potential ICI recipients and underscores the importance of understanding cardiovascular (CV) risk in this patient population.[2]

Immune-related adverse events are observed in 70% to 90% of patients receiving ICI and can affect any organ.[3] The reported incidence of CV immune-related adverse events, including pericarditis, vasculitis, and myocarditis, is low.[4] Cardiotoxicity was reported in 10 of 5,347 patients in phase 3 trials, with only 1 having myocarditis.[5] In the World Health Organization database, 122 cases of myocarditis were identified among 31,321 adverse events in patients treated with ICIs.[4] Despite the relatively low frequency of CV events, the very high associated mortality rates ranging from 20% to 45% make myocarditis one of the most concerning complications of ICI therapy.

CV adverse events associated with new cancer therapeutics are often not identified until the drugs are in widespread use, and ICIs are no exception. Cancer trials are not powered or generally designed with formal CV event adjudication to ascertain differences in CV events and often exclude patients with underlying CV disease.[6] Initial trials of cancer therapeutics often occur in late-stage patients with a short follow-up because of their disease course, and CV endpoints are generally captured through adverse event reporting systems that include nonspecific terms, symptoms, and testing findings, making assessment for imbalances in infrequent events difficult. Evaluating CV events with ICI use in a real-world setting may provide clinically relevant insight, particularly if CV events are adjudicated. On-trial CV events identified by adverse event coding performed by oncologists may lack fidelity. CV event definitions and adjudication procedures are well established for CV outcomes trials but can be expensive.[7,8] To address these knowledge gaps, we evaluated CV events before and after ICI administration in a real-world population and assessed the adequacy of International Classification of Diseases (ICD) coding compared with adjudication for specific types of CV events.

METHODS

STUDY POPULATION AND PROCEDURES. This retrospective observational study was approved by the Colorado Multiple Institutions Review Board. The University of Colorado enterprise health data warehouse, Health Data Compass, integrated data from the electronic medical record (EMR), provider billing, and state and public data sources for all patients ≥18 years of age who received ICI within the University of Colorado Health System from January 2011 to April 2019. This is a regional health system serving Colorado, southern Wyoming, and western Nebraska with a large academic medical center, 12 community-based hospitals, and a network of outpatient clinics. To comply with institutional privacy requirements, patients over the age of 89 years or who received ICI therapy when they were over the age of 89 were excluded from the data set. Patients for whom ICI was prescribed but not administered were excluded from the analysis. During the time span queried, ICD code versions 9 and 10 were in use.

Medical history was collected by surveying International Classification of Diseases-9th Revision and -10th Revision codes. All ICD provenances were used in this search (billing diagnosis, encounter diagnosis, medical history, and problem list) and were reported at most once per individual. ICI use was gathered from a prescription database and identified through the Medication Epic Identifier. ICIs were reported at most once per individual, but individuals may be prescribed more than 1 type of ICI. ICD codes identifying potential CV events were prespecified in the statistical analysis plan. CV events were defined as prior if they occurred before the first dose of ICI and as subsequent if they occurred on or after the day of the first dose of ICI. Events are reported as proportions. The cancer diagnosis for which ICI therapy was administered was determined by chart review.

ADJUDICATION OF CV EVENTS. CV events of interest included cardiac ischemic events such as myocardial infarction (MI), hospitalization for unstable angina, hospitalization for heart failure or heart failure exacerbation requiring treatment, transient ischemic attack (TIA), stroke, hypertensive emergency, noncoronary (peripheral) vascular events, and venous thromboembolism (VTE) defined as either deep vein thrombosis and/or pulmonary embolism and ICI myocarditis. For patients with potential CV events identified by ICD code, all EMR data including encounter notes, specialist assessments, diagnostic testing, and medications were independently reviewed by 2 cardiologists, and events were

adjudicated using prespecified definitions.[8,9] Discrepancies were resolved by consensus.

STATISTICAL METHODS. Continuous variables are presented as mean ± SD, and categoric variables are reported as counts (percentages). Kappa coefficients and 95% CIs were determined for the comparison of CV events identified by ICD code and those adjudicated through chart review. Event rates are reported using both crude percentages in the absence of time-to-event analyses that incorporate competing risks and censoring. Here, patients could have multiple events, and these were included in the total count. SAS version 9.4 (SAS Institute, Inc) was used for all data manipulation and analysis.

RESULTS

The analysis population included 1,813 patients treated with ICI from January 2011 to April 2019. Patients were followed within the University of Colorado Health System for 4.6 ± 3.4 years. The duration of any medical care in the health system before ICI initiation was 3.2 ± 3.2 years, and post-ICI it was 1.4 ± 1.4 years. At the conclusion of this analysis, 859 (47%) patients were alive, and their average post-ICI follow-up was 2.2 ± 1.5 years. For the 954 patients who died, follow-up post-ICI was 0.7 ± 0.8 years. Of the CV events, 94 events were deemed related to the cause of death, and 21 were fatal events.

The baseline characteristics of the cohort are summarized in **Table 1**. Demographics were generally consistent with the population in the state of Colorado.[10] CV risk factor prevalence at baseline included 48.2% with hypertension, 16.1% with diabetes, and 11.3% current smokers. A wide range of malignancies were treated with ICIs, either in clinical trials or as standard of care, including both solid tumors and hematologic malignancies (**Table 2**). The most common types of cancer were melanoma, lung, and kidney/urinary tract cancers. Pembrolizumab was the most common ICI prescribed followed by nivolumab and ipilimumab (**Table 2**).

The most common CV events were venous thromboembolic events (**Central Illustration,** Supplemental Figure 1). Adjudicated VTE occurred in 206 patients (11.4%) pre-ICI and 205 patients (11.3%) post-ICI. Pulmonary embolism was identified in 89 patients (4.9%) pre-ICI and 97 patients (5.4%) post-ICI and deep vein thrombosis in 146 patients (8.1%) pre-ICI and 148 patients (8.2%) post-ICI. MI, heart failure, and stroke were more commonly identified than myocarditis. Adjudicated MI was identified in 33 of 1,813 patients (1.8%) pre-ICI and 54 patients (3.0%) post-ICI, heart failure in 40 patients (2.2%) pre-ICI and 50 patients (2.8%) post-ICI, and stroke in 33 patients (1.8%) pre-ICI and 29 patients (1.6%) post-ICI. One adjudicated myocarditis event was identified before ICI initiation, and 6 patients (0.3%) had

TABLE 1 Baseline Characteristics (N = 1,813)

Age, y	62.5 ± 13.5
≤65	990 (54.6)
>65	823 (45.4)
Female	751 (41.4)
Race/ethnicity	
White	1627 (89.7)
Hispanic	106 (5.8)
Black or African American	40 (2.2)
Asian	26 (1.4)
American Indian and Alaska Native	3 (0.2)
Native Hawaiian and Other Pacific Islander	3 (0.2)
Other, including multiple races	90 (5.0)
Hypertension	874 (48.2)
Diabetes mellitus	291 (16.1)
Current smoker	204 (11.3)
Chronic kidney disease (eGFR ≤60)	207 (11.4)
Coronary revascularization	309 (17.0)

Values are mean ± SD or n (%). Chronic kidney disease was defined by the most recent eGFR rate before the first ICI administration. Other disease states at baseline were determined by International Classification of Diseases codes present before the first ICI administration.

eGFR = estimated glomerular filtration rate; ICI = immune checkpoint inhibitor.

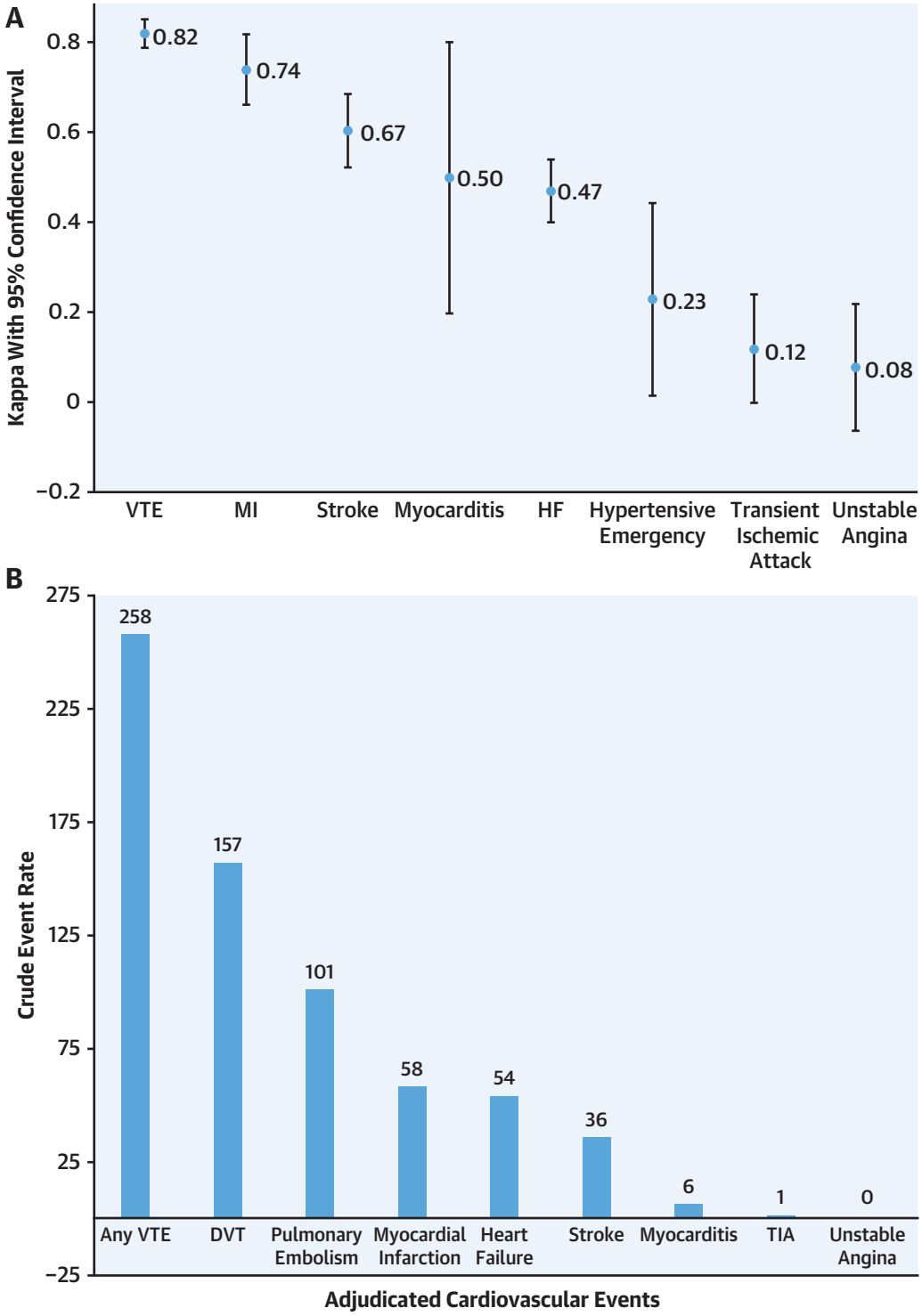
TABLE 2 Cancer Types Treated With ICIs and Frequency of Use

Melanoma	716 (39.5)
Lung	468 (25.8)
Kidney and urinary tract	225 (12.4)
Gastric, colon, and esophageal	71 (3.9)
Head and neck	65 (3.6)
Reproductive tract	59 (3.3)
Hepatocellular, pancreas, spleen, gallbladder, and biliary	51 (2.8)
Lymphoma, leukemia, and myeloma	40 (2.2)
Breast	34 (1.9)
Sarcoma	29 (1.6)
Endocrine	20 (1.1%)
Prostate	18 (1.0)
Mesothelioma	14 (0.8)
Other	6 (0.3)
Specific ICI therapy types	
Pembrolizumab	851 (46.9)
Nivolumab	769 (42.4)
Ipilimumab	474 (26.1)
Azetolizumab	104 (5.7)
Durvalumab	21 (1.2)
Cemiplimab	6 (0.3)
Avelumab	6 (0.3)

Values are n (%). Three patients had more than 1 cancer diagnosis. The cancer diagnosis associated with immune checkpoint inhibitors (ICIs) administration in pharmacy records is shown. Patients were counted once for each type of ICI received; they could receive more than 1 type of ICI.

JACC: CARDIOONCOLOGY, VOL. 4, NO. 5, 2022
DECEMBER 2022:649–656

CENTRAL ILLUSTRATION **Adjudicated Cardiovascular Events and Agreement With International Classification of Diseases Coding**



Kondapalli L, et al. J Am Coll Cardiol CardioOnc. 2022;4(5):649–656.

Continued on the next page

myocarditis after ICI initiation. Hypertensive emergency was infrequent (1 patient pre-ICI and 3 post-ICI) as were noncoronary vascular events (5 patients pre-ICI and 2 patients post-ICI). The rates of adjudicated arrhythmia and pericardial disease events are presented in Supplemental Table 1.

The accuracy of ICD coding for the identification of CV events relative to adjudication varied by clinical event type (**Central Illustration**). For VTE and MI, ICD codes correlated well with events determined by adjudication ($\kappa = 0.82$ [95% CI: 0.79-0.85] and 0.74 [95% CI: 0.66-0.82], respectively). For heart failure and myocarditis, the kappa statistic was 0.47 (95% CI: 0.40-0.54) and 0.50 (95% CI: 0.20-0.80), respectively. Agreement between ICD codes and adjudication was particularly poor for hypertensive emergency ($\kappa = 0.23$ [95% CI: 0.01-0.44]), TIA ($\kappa = 0.12$ [95% CI: −0.00 to 0.24]), and unstable angina ($\kappa = 0.08$ [95% CI: −0.06 to 0.22]). As shown in **Table 3**, in the 6 cases in which an ICD code for myocarditis was present after ICI initiation but myocarditis was not confirmed by adjudication, the reasons for reclassification included a prior diagnosis of viral myocarditis that was coded, non-ST-segment elevation MI, and age-related complete heart block. Chart review indicated that the ICD codes were used for initial suspicion of myocarditis that was not confirmed on subsequent testing (eg, cardiovascular magnetic resonance [CMR]) or when an alternative diagnosis was subsequently identified (eg, acute coronary syndrome or heart failure). An additional 2 cases of adjudicated myocarditis resulted from adjudicating for a different event (eg, MI) and determining the event was actually ICI myocarditis. **Table 4** provides the rates of ICD-coded versus adjudicated CV events by patient in this study. With the exception of MI, ICD coding overestimated the number of CV events.

TABLE 3 Description of Cases With International Classification of Diseases (ICD) Codes For Myocarditis When Adjudication Revealed Alternate Diagnoses

Case	ICD Diagnoses	Eventual Diagnosis Through Adjudication
1	Infective myocarditis; myocarditis, unspecified; acute myocarditis, unspecified	Diagnosed with viral myocarditis 5 years before cancer diagnosis
2	Isolated myocarditis	Ventricular bigeminy noted while on pembrolizumab; troponin and LVEF by echo were normal, CMR without myocarditis; 40% PVC burden on Holter decreased to 5% with metoprolol.
3	Acute myocarditis, unspecified	In the setting of pembrolizumab had chest pain that resolved with thoracentesis; inpatient serial troponin monitoring revealed NSTEMI. CMR showed LAD infarct and no myocarditis.
4	Myocarditis, unspecified	After the first infusion of ipilimumab, admitted with diagnosis of *Clostridioides difficile* colitis and developed a NSTEMI treated with a drug-eluting stent to the RCA.
5	Myocarditis, unspecified	Patient had dyspnea and fluid retention when diuretic agents were held while on ipilimumab and nivolumab; CXR was ordered with myocarditis as the suspected diagnosis and was unremarkable. Symptoms improved within 1 week of restarting diuretics.
6	Myocarditis, unspecified	Presented with complete heart block in the setting of receiving ipilimumab/nivolumab. Troponin and LVEF by echo were normal, and heart block was thought to be age related. Underwent emergent dual-chamber pacemaker placement.

CMR = cardiovascular magnetic resonance; CXR = chest X-ray; echo = echocardiography; LAD = left anterior descending; LVEF = left ventricular ejection fraction; NSTEMI = non-ST-segment elevation myocardial infarction; PVC = premature ventricular contraction; RCA = right coronary artery.

DISCUSSION

In a large, real-world data set of patients treated with ICIs, VTE, MI, heart failure, and stroke were much more frequent than myocarditis (**Central Illustration**). The former (VTE, MI, heart failure, and stroke) occurred before and after ICI administration, whereas myocarditis was primarily detected post-ICI. For some types of CV events (VTE and MI), ICD coding and adjudication correlated well, whereas the correlation was worse for events such as myocarditis and heart failure.

An important finding from this analysis is that common CV events, likely related to an underlying CV disease or malignancy, are much more frequent among patients treated with ICI than myocarditis, which is consistent with the aphorism about hoofbeats and zebras. In contrast to cancer clinical trials in which patients with comorbidities may be excluded, the prevalence of hypertension, diabetes, smoking, and renal impairment among patients in this real-world data set was generally in-line with national rates.[11-14]

CENTRAL ILLUSTRATION Continued

(A) Agreement between cardiovascular events identified by International Classification of Diseases (ICD) code and adjudication. Kappa statistics with 95% CIs are shown. ICD coding and adjudication correlation was strongest for venous thromboembolic event (VTE) and myocardial infarction (MI). VTE included pulmonary embolism and deep vein thrombosis (DVT). **(B)** Crude event rates of adjudicated CV events after the initiation of immune checkpoint inhibitor (ICI) therapy. Patients could have multiple events, and recurrent events were included in the total count. The mean duration of follow-up was 1.4 ± 1.4 years post-ICI.

JACC: CARDIOONCOLOGY, VOL. 4, NO. 5, 2022
DECEMBER 2022:649–656

TABLE 4 Frequency of ICD Coded Versus Adjudicated Cardiovascular Events

Cardiovascular Event	ICD Coded	Adjudicated
VTE	476	381
MI	74	86
Stroke	93	59
Myocarditis[a]	10	6
Heart failure	215	86
Hypertensive emergency	22	4
TIA	47	3
UA	25	1

Cardiovascular events were reported at most once per individual. [a]An additional 2 cases of adjudicated myocarditis resulted from adjudicating for a different event (eg, MI) and determining the event was actually immune checkpoint inhibitor myocarditis.

ICD = International Classification of Diseases; MI = myocardial infarction; TIA = transient ischemic attack; UA = unstable angina; VTE = venous thromboembolism.

As such, heart failure and acute coronary and cerebrovascular syndromes are to be expected because of the background comorbidities of the population. Our observation that myocarditis was observed in 1 patient before ICI and 6 patients after ICI is consistent with reports of ICI-associated inflammation.[15] The incidence of myocarditis in this study of 0.3% is lower than the reported incidence of myocarditis (1.14%-1.40%) in more recent prospective studies.[16,17] The lower incidence of myocarditis cases in our study may reflect the reliance of ICD coding triggered predominantly by oncology providers for the detection of signs and symptoms of myocardial injury in contrast to prospective studies that screened for suspected cases. However, the incidence of myocarditis (0.3%) in this study is similar to the incidence of myocarditis (0.39%) reported in a retrospective pharmacovigilance study of the World Health Organization's VigiBase database, which adds validity to our work.[4] We note that routine screening with biomarkers would increase the ascertainment of potential myocarditis events; however, it would not be expected to modify the number of myocarditis events that result in clinically overt cases that would then be expected to translate into a clinical encounter and a diagnosis code. The relative rarity of myocarditis relative to other CV events underscores the importance of appropriate evaluation and management of patients presenting with cardiac symptoms, particularly as ICI therapy evolves to earlier and broader use. Given the observational nature of this study and the overall small number of CV events, we are not able to draw connections between whether the use of ICIs led to CV events like VTE and ischemia. Interestingly, through analysis of the World Health Organization pharmacovigilance database, Allouchery et al[18] found that ICIs did not correlate with higher reporting of VTEs compared with other anticancer drugs. In contrast, Drobni et al[19] showed that atherosclerotic cardiovascular events increased after ICI initiation as did atherosclerosis on imaging.

The major contribution of this work is that these findings suggest that the use of ICD codes alone may be sufficient to assess the occurrence of specific CV events (eg, VTE and MI), whereas adjudication may be more useful for the following types of CV events in which codes are less specific: unstable angina (ICD n = 25 vs adjudication n = 1), transient ischemic attack (n = 47 vs n = 3), heart failure (n = 215 vs n = 86), and noncoronary vascular events (n = 59 vs n = 6) (Table 4). Myocarditis was identified by ICD coding in 1 patient pre-ICI and 9 patients post-ICI; adjudication identified 1 patient with myocarditis pre-ICI and 6 post-ICI. The reason for this difference was generally initial misclassification of patients presenting with myocardial injury as myocarditis, which was subsequently recognized as being caused by an alternative etiology. This observation underscores the difficulty of diagnosing conditions like ICI myocarditis, unstable angina, and TIA in the clinical setting and a limitation to ICD-based analyses, which may not capture changes in diagnosis with evolution of the clinical picture over time. For example, as shown in Table 3, for someone presenting with chest pain and elevated troponin, the initial clinical diagnosis may be myocarditis. However, additional work-up (eg, serial troponins, angiogram, and CMR) may show an alternative diagnosis such as non-ST-segment elevation MI with findings of left anterior descending infarct on CMR and no myocarditis. Code-based analyses generally look for the presence of the code and not for changes, and in this case, the event would be misclassified as myocarditis. Also, most of the coding for CV events in this study was performed by oncology providers, so there may be significant variability in the coding of CV events. Developing harmonized definitions of CV events with integration into standard oncology adverse event reporting, educating oncology providers, and a move toward more multidisciplinary team management may lead to more precise coding of CV events. In the meantime, adjudication of potential CV events may be useful and may increase specificity for true diagnoses relative to ICD codes alone. Because VTE and MI comprise the bulk of the identified events, selective application of event adjudication (eg, restricting to subsets with poor agreement) should substantially mitigate the resourcing of adjudicating other types of events.

This analysis supports the need for evidence-based CV management in patients with cancer, including those receiving ICIs. Patients can be on ICIs for years and switch from 1 ICI or combination to another. Although ICI myocarditis can be fatal and warrants proper evaluation, this analysis and the work of others show that ICI myocarditis is rare in contrast to VTE, ischemic CV events, and heart failure, all of which can benefit from evidence-based treatments. In fact, the overwhelming majority of deaths related to CV causes in this cohort were related to events other than myocarditis. A multidisciplinary team-based approach may facilitate the evaluation of ICI-treated patients with CV symptoms for acute coronary syndromes and heart failure as well as myocarditis/pericarditis. Evidence-based efforts to formalize the identification of CV events will also help oncologists rapidly diagnose cardiac side effects and improve patient care. The management of CV risk factors will be an ongoing topic for provider-patient discussion and will evolve as cancer outcomes continue to improve. This analysis contributes to cardio-oncologic care by raising awareness of the relative frequency of CV events among patients treated with ICI and identifying the types of CV events for which ICD coding is sufficiently accurate for clinical research purposes.

STUDY LIMITATIONS. Although the cohort is a good representation of residents in a large regional center, as the only National Cancer Institute–designated center in the state of Colorado, it attracts patients who may only interface with the health system during their cancer treatment. It is not feasible in the data set to discriminate whether patients are responding to ICI therapy and correlate this to CV events (ie, to determine if events such as new VTE correlate with the progression of underlying malignancy). Because the EMR reflects an incomplete health care record, we are cautious about inferring CV event rates within our cohort. The initial patient screening was performed using ICD codes, which carries the risk of reduced sensitivity of identifying events because it is dependent on the entry of billing codes. A number of the patients received ICI in clinical trials, which may have excluded individuals with active CV disease. Additional limitations are that it does not include time-to-event analysis, and the data set does not include cardiac biomarker data (eg, troponin). Moreover, we observed a low frequency of some events and consequent wide CIs.

The strengths of the analysis include the fact that it represents all ICI-treated patients during an 8-year period and that CV events were independently adjudicated by 2 cardiologists. Another strength of this work is that it offers a model for identifying CV events retrospectively that can be applied to any new cancer therapeutic.

CONCLUSIONS

ICI therapy is becoming a mainstay of contemporary cancer therapy with an incompletely understood CV impact. In this analysis of real-world patients, common CV events such as VTE, MI, heart failure, and stroke were also those most frequently identified in patients post-ICI therapy, whereas myocarditis was rare. This work shows that ICD codes can be used to determine the incidence of MI and VTE; however, this method lacks the fidelity needed to accurately identify other CV events. Adjudication, which is typical of CV trials, is an effective approach to determine the rates of CV events in patients treated with ICIs.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Electronic medical record data extraction was supported by the Health Data Compass Data Warehouse project (healthdatacompass.org). Dr Hsia has received salary support from CPC, a nonprofit academic research organization affiliated with the University of Colorado that receives research grant/consulting funding from Abbott, Agios, Alexion Pharma, Alnylam, Amgen, Angionetics, Anthos, ARCA Biopharma, Array, AstraZeneca, Atentiv, Audentes, Bayer, Better Therapeutics, Brigham and Women's Hospital, Bristol-Myers Squibb, Cardiol Therapeutics, CellResearch, Cook Medical, Cook, Cook Regentec, CSL Behring, Eidos Therapeutics, EP Trading Co, Esperion Therapeutics, EverlyHealth, Faraday, Fortress Biotech, HDL Therapeutics, Heartflow, Hummingbird Bioscience, Insmed, Janssen, Kowa Research, Lexicon, Merck, Medtronic, Moderna, Novate Medical, NovoNordisk, Pfizer, PhaseBio, PPD Development, Prairie Education and Research, Prothena Biosciences, Regeneron, Regio Biosciences, Sanifit Therapeutics, Sanofi, Smith and Nephew, Stealth BioTherapeutics, University of Colorado, University of Pittsburgh, Worldwide Clinical Trials, Wraser, and Yale Cardiovascular Research Group; and reports owning AstraZeneca stock. Dr Miller has received salary support from Janssen Oncology. Dr Flaig has received research funding/clinical research contracts in which he serves as the principal investigator with Janssen Oncology, Medivation, Sanofi, Pfizer, Bristol-Myers Squibb, Roche/Genetech, Exelixis, Aragon Pharmaceuticals, Sotio, Tokai Pharmaceuticals, AstraZeneca/Medimmune, Lilly, Astellas Pharma, Agensys, Seattle Genetics, La Roche-Posay, and Merck; and is a founder and owns stock in Aurora Oncology. The University of Colorado has filed 2 patents in which Dr Flaig is an inventor related to early-stage bladder cancer treatment detection; neither is currently commercialized or licensed. Dr Bonaca has received salary support from CPC and from an AHA SFRN under award numbers 18SFRN3390085 (BWH-DH SFRN Center) and 18SFRN33960262 (BWH-DH Clinical Project); has stock in Medtronic and Pfizer; and has received consulting fees from Audentes. Dr Kondapalli has reported that she has no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Lavanya Kondapalli, Division of Cardiology, University of Colorado School of Medicine, 12631 East 17th Avenue, Mail Stop B130, Aurora, Colorado 80045, USA. E-mail: lavanya.kondapalli@cuanschutz.edu. Twitter: @CardioOncCO, @cpcresearch.

JACC: CARDIOONCOLOGY, VOL. 4, NO. 5, 2022
DECEMBER 2022:649–656

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: CV disease is common among patients receiving ICI. The most common cardiovascular events after ICI initiation were VTE, MI, heart failure, and stroke, whereas myocarditis was rare. Determining the incidence of CV events related to ICI therapy remains challenging because using ICD codes proved relatively reliable for MI and VTE but less accurate for other CV events. More in-depth analysis with techniques like adjudication are needed to accurately assess the rates of most CV events.

TRANSLATIONAL OUTLOOK: Future studies should focus on identifying predictors of CV events in patients receiving ICIs and on determining effective strategies to mitigate their CV risk. It is of critical importance to continue to clarify the incidence of CV rates from ICI therapy to help patients and providers understand CV risk associated with ICI therapy and curtail a "one-size-fits-all" approach of elaborate cardiac evaluations for rare events.

REFERENCES

1. Haslam A, Gill J, Prasad V. Estimation of the percentage of US patients with cancer who are eligible for immune checkpoint inhibitor drugs. *JAMA Netw Open*. 2020:e200423.

2. National Cancer Institute Cancer Statistics. Accessed June 27, 2021. https://www.cancer.gov/about-cancer/understanding/statistics

3. Zhang LRKL, Lyon AR, Palaskas N, Neilan TG. The evolving immunotherapy landscape and the epidemiology, diagnosis, and management of cardiotoxicity. *J Am Coll Cardiol CardioOnc*. 2021;3(1):35–47.

4. Salem JE, Manouchehri A, Moey M, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. *Lancet Oncol*. 2018;19:1579–1589.

5. Ederhy S, Voisin AL, Champiat S. Myocarditis with immune checkpoint blockade. *N Engl J Med*. 2017;376:290–291.

6. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: race-, sex-, and age-based disparities. *JAMA*. 2004;291:2720–2726.

7. Bonaca MP. Adjudicating cardiovascular events in immuno-oncology trials. Accessed March 23, 2022. https://www.fda.gov/media/110321/download

8. Hicks KA, Mahaffey KW, Mehran R, et al. 2017 cardiovascular and stroke endpoint definitions for clinical trials. *J Am Coll Cardiol*. 2018;71:1021–1034.

9. Bonaca MP, Olenchock BA, Salem JE, et al. Myocarditis in the setting of cancer therapeutics: proposed case definitions for emerging clinical syndromes in cardio-oncology. *Circulation*. 2019;140:80–91.

10. United States Census Bureau. Accessed June 27, 2021. census.gov/quickfacts/CO

11. Centers for Disease Control and Prevention. *National Diabetes Statistics Report, 2020*. Centers for Disease Control and Prevention, US Department of Health and Human Services; 2020.

12. Centers for Disease Control and Prevention. Smoking and tobacco use. Accessed June 28, 2021. https://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/index.htm

13. Grams ME, Juraschek SP, Selvin E, et al. Trends in the prevalence of reduced GFR in the United States: a comparison of creatinine- and cystin C-based estimates. *Am J Kidney Dis*. 2013;62:253–260.

14. Ostchega Y, Fryar CD, Nwankwo T, Nguyen DT. *Hypertension Prevalence Among Adults Aged 18 and Over: United States, 2017-2018*. NCHS data brief no. 364. National Center for Health Statistics; 2020. https://www.cdc.gov/nchs/data/databriefs/db364-h.pdf

15. Ramos-Casals M, Brahmer JR, Callahan MK, et al. Immune-related adverse events of checkpoint inhibitors. *Nat Rev Dis Primers*. 2020;6:38.

16. Mahmood SS, Fradley MG, Cohen JV, et al. Myocarditis in patients treated with immune checkpoint inhibitors. *J Am Coll Cardiol*. 2018;71:1755–1764.

17. Waliany S, Neal JW, Reddy S, et al. Myocarditis surveillance with high-sensitivity troponin I during cancer treatment with immune checkpoint inhibitors. *J Am Coll Cardiol CardioOnc*. 2021;3:137–139.

18. Allouchery M, Beuvon C, Perault-Pochat MC, Roblot P, Puyade M, Martin M. Immune checkpoint inhibitors and venous thromboembolism: an analysis of the WHO pharmacovigilance database. *Clin Pharmacol Ther*. 2022;112:164–170.

19. Drobni ZD, Alvi RM, Taron J, et al. Association between immune checkpoint inhibitors with cardiovascular events and atherosclerotic plaque. *Circulation*. 2020;142:2299–2311.

KEY WORDS cardiac immune-related adverse events, checkpoint myocarditis, immunotherapy

APPENDIX For supplemental table and figure, please see the online version of this paper.