Risk Factors for Immune Checkpoint Inhibitor–Related Myocarditis: An Integrative Review

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Abstract

Purpose: The purpose of this integrative literature review was to determine factors that increase the risk of immune checkpoint inhibitor (ICI)–related myocarditis in the cancer patient population. **Methods:** A literature review was conducted using the following databases: PubMed, Scopus, and Cochrane Review. Dates searched were from inception through March 1, 2022. Inclusion criteria included English language, cancer patients receiving ICI treatment, and risk factors for myocarditis. Articles were excluded if they were a non-human study, duplicate, had an irrelevant title or content, or were a review or commentary. **Results:** Patients with cancer who receive ICIs have an associated increased risk of myocarditis if they are older than 64 years, have a body mass index (BMI) greater than 28, and have a history of cardiovascular medication use. **Conclusions:** Myocarditis remains a rare cardiovascular adverse effect of ICIs. However, the mortality risk among this subset of patients remains high. Additional prospective randomized-controlled trials would be beneficial to further determine a causal relationship between risk factors for ICI-related myocarditis. Risk stratification tools may allow oncology medical providers to identify patients at a higher risk of ICI-related myocarditis to increase earlier surveillance.

With the expanding use of immune checkpoint inhibitors (ICIs) to treat malignancy, side effects including myocarditis are commonly reported, further increasing the need for education on the prevention, diagnosis, and management of such toxicities. In 2011, the US Food and Drug Administration (FDA) approved the use of ipilimumab (Yervoy) as the first ICI for the treatment of advanced melanoma (FDA, 2011). Since then, clinical trials have paved the way for the approval of additional ICI-based therapy to improve clinical outcomes and, ultimately, eradicate cancer.

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BACKGROUND

Cancer cells evade the immune system and proliferate unchecked through a variety of mechanisms, including binding to and suppressing T-lymphocyte surface proteins that would otherwise allow killer T cells to recognize and destroy tumor cells (Ho et al., 2021). Immune checkpoint inhibitors are monoclonal antibodies that target cancer cells "blocking intrinsic downregulators of immunity, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) or its ligand, programmed cell death ligand 1 (PD-L1)" (Postow et al., 2018). Removing this immune blockade restores the activation and response of T cells to recognize and attack cancer cells. This nonspecific immune activation can lead to the immune-mediated adverse reactions that result in the immune system attacking healthy cells along with tumor cells. Any system or organ can be negatively impacted, resulting in toxicities such as colitis, hepatitis, nephritis, myocarditis, pneumonitis, dermatitis, or endocrinopathies (Martins et al., 2019).

As noted, ICI-related myocarditis (ICIrM) is among the list of potential toxicities. "Myocarditis is a form of heart disease that results from inflammation of the heart muscles that compromise the heart" (CDC, 2021). The reported prevalence of ICIrM ranges from 1.14% to 3.2%, and the mortality rate ranges between 22% and 50% (Ma et al., 2021; Mahmood et al., 2018; Oren et al., 2020; Salem et al., 2018). Following the initiation of ICI therapy, myocarditis has a reported median onset of 23 days and has been reported over 180 days following initial drug administration (Fan et al., 2019; Mahmood et al., 2018). While the exact mechanism of ICIrM is still under investigation, an oral abstract presented by Steven M. Blum, MD, at the American Society of Clinical Oncology (ASCO) 2022 Annual Meeting reported "increased intramyocardial T cells and the activation of interferon response gene networks" as a potential pathological pathway (Blum et al., 2022).

Patients with ICIrM may present with cardiovascular (CV) symptoms such as chest pain, fatigue, dyspnea, arrhythmias, heart failure, or acute coronary artery syndrome that can lead clinicians toward an incorrect root cause diagnosis (Neilan et al., 2018; Turker & Jahangir, 2020). Troponin and brain natriuretic peptide (BNP) levels may be elevated along with nonspecific ST-T changes observed on electrocardiograms (Turker & Jahangir, 2020).

Studies evaluating risk factors for ICIrM are limited but growing. This review focuses on two nonmodifiable clinical characteristics (age and gender) and two modifiable risk factors (body mass index and CV medications) at the time of ICI initiation. With a high mortality rate, identifying which patients are at increased risk for ICIrM is critical. This review examined clinical characteristics that may lead to increased risk of ICIrM in the setting of cancer.

METHODS

A comprehensive literature search was conducted with the assistance of a research librarian to identify peer-reviewed evidence on the clinical characteristics that may contribute to an increased risk of ICIrM in the cancer patient population. In March 2022, electronic databases searched were PubMed, Scopus, and Cochrane Review with the following search terms applied: "immune checkpoint inhibitor" AND "myocarditis" OR "cardiovascular" OR "cardiotoxic*" AND "risk." Dates searched were from inception through March 1, 2022.

Initially, 601 articles were identified using the search terms. A secondary review of literature for additional primary sources revealed one additional resource. Inclusion criteria required that each article be in English and describe and evaluate the intervention of an ICI with myocarditis as an immune-related adverse event (irAE) in humans. Studies addressing related risk factors or clinical characteristics were included.

Articles that reported on ICIrM as part of a larger group of CV toxicities and events were excluded. Articles that reported on myocarditis incidence without included extractable data classified as clinical characteristics or risk factors were excluded. Review articles, case reports, abstracts, editorials, and opinion articles were excluded. Studies were excluded if the number of participants with myocarditis was ≤ 1.

A total of 177 full-text articles remained after initial screening for duplicates and relevance. Of those, 163 were excluded based on inclusion and exclusion criteria. Thirteen articles met the

inclusion and exclusion criteria and are a part of this review (Figure 1; Page et al., 2021).

RESULTS

This integrative review focused on studies that reported on or evaluated factors including age, sex, body mass index, and use of CV medications that may place patients at increased risk for ICIrM. The clinical characteristics of the population group included in the 13 studies are summarized in Table 1. All studies were retrospective; five utilized cases with either matched or unmatched controls. Data were drawn from the FDA Adverse Event Reporting System (FAERS) database for four of the studies (Fan et al., 2019; Lal et al., 2021; Ma et al., 2021; Zamami et al. 2019). Another three (Noseda et al., 2020; Salem et al., 2018; Shah et al., 2020) used data from VigiBase, the World Health Organization's global database of individual case safety reports, to compare CV adverse event reporting in patients who received ICIs. Ma and colleagues (2021) also included ICIrM cases from EudraVigilance (EV), a pharmacovigilance database of collated suspected adverse drug reactions in the European Economic Area (Postigo et al., 2018). Participant samples from the studies evaluated in this literature review ranged from 28 to 90,740. Within these studies, the number of participants reported to have ICIrM ranged from 12 to 1,235. The results are organized into categories of clinical characteristics that may place a patient at an increased risk for myocarditis.

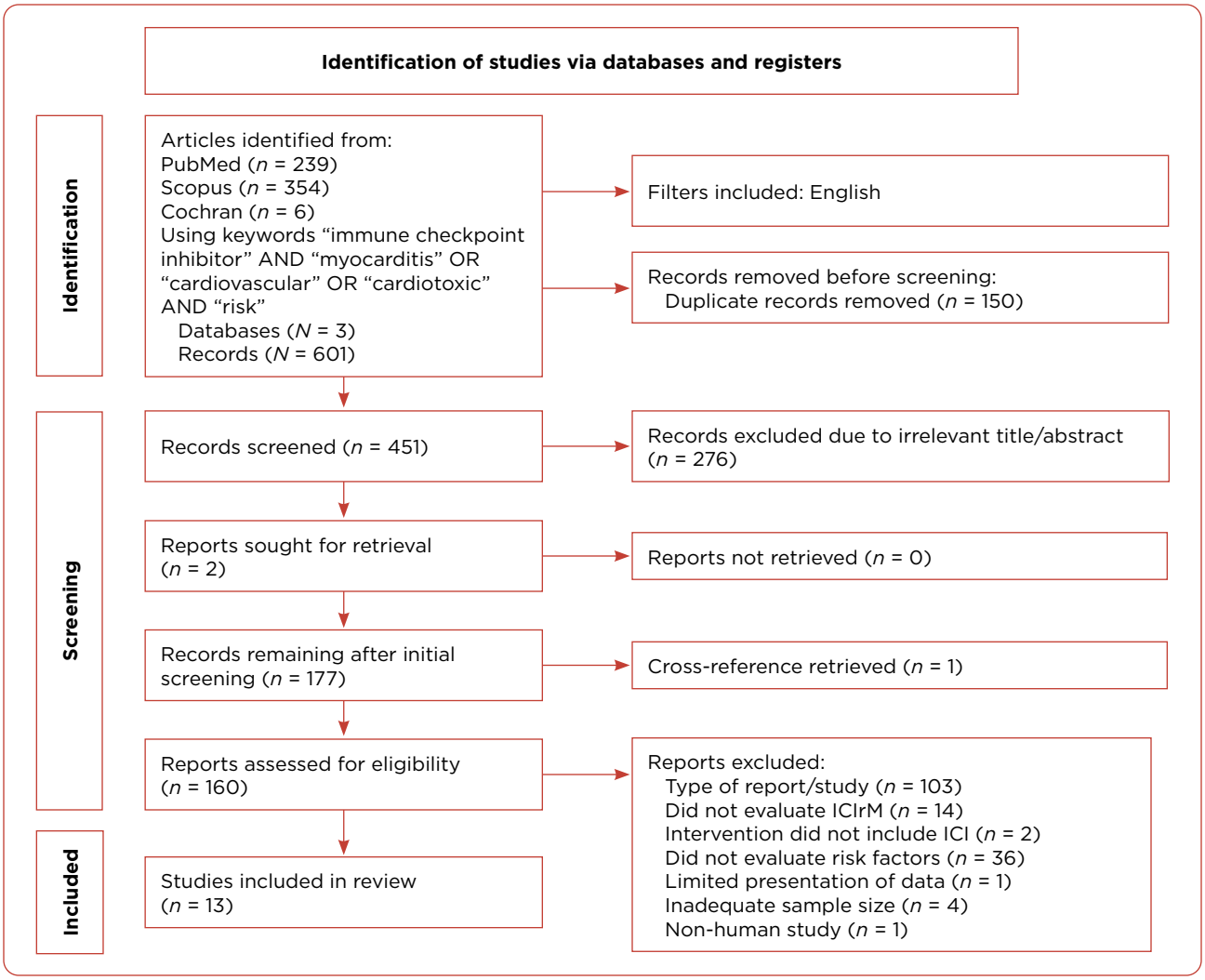

Figure 1. PRISMA flow diagram. ICIrM = immune checkpoint inhibitor–related myocarditis; ICI = immune checkpoint inhibitor.

Table 1. Summary of Primary Sources of Evidence Showing Risk Factors for ICI-Related Myocarditis

Author	Study design/ Level of evidence	Sample, sample size, setting, country of origin	Intervention	Findings	Limitations
Awadalla et al. (2019)	Retrospective, case-control study Level of evidence: III	Sample: Study arm: 16-center institutional registry of ICIrM cases Controls: Single-center registry of ICI treated participants without ICIrM Sample size: 101 ICIrM participants, 201 ICI participants without ICIrM Setting: 16-center institutional registries Country: USA	ICI therapy Flu vaccination within 6 months of ICI therapy	Age: 67 ± 18 years, $p = 0.15$ Sex: Males: 72%, $p = 0.16$ BMI: 28 ± 7 kg/m^2, $p = .01$ CV medications: Statin: $p = .02$ ACE-I/ARB: $p = .07$	Study arm participants are from 16 institutions, whereas control arm is from single institution Limited generalization with no report of participant race and smaller female participant inclusion No report of female myocarditis rates Control arm single-center region bias
Fan et al. (2019)	Retrospective Level of evidence: III	Sample: FAERS database Sample size: 43,147 ICIrAEs, of which 315 ICIrM cases analyzed Setting: Not specified Countries: Europe, Americas, Asia, Australia, and Africa	ICI therapy	Age: 51.11% ≥ 65 years vs. 27.94% < 65 years Sex: Males: 72%, $p = .16$	SR database system can lead to inherent reporting bias including "underreporting, false reporting, incomplete reporting, inaccurate reporting, and arbitrariness" 21% of adverse events were reported by nonhealth-care professionals Difficult to control for confounding factors with FAERS database that might impact myocarditis risk FAERS reports are not verified No cohort group for comparison
Lal et al. (2021)	Retrospective Level of evidence: III	Sample: FAERS database Sample size: 90,740 AE reports, of which 345 ICIrM cases analyzed Setting: Not specified Countries: Not specified if reports outside USA were excluded	ICI therapy and/or conventional chemotherapy	Sex: Males: $q < .001$	SR database system can lead to inherent reporting bias FAERS reports are not verified Difficult to control for confounding factors No cohort group for comparison

Note. ACE = angiotensin-converting enzyme; ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CV = cardiovascular; EMB = endomyocardial biopsy; EU = European Union; EV = EudraVigilance; FAERS = Food & Drug Administration adverse event reporting system; ICI = immune checkpoint inhibitor; ICIrAE = immune checkpoint inhibitor–related adverse event; ICIrM = immune checkpoint inhibitor–related myocarditis; irAE = immune-related adverse event; MGH = Massachusetts General Hospital; MDACC = MD Anderson Cancer Center; SR = spontaneous reporting; RPCCC = Roswell Park Comprehensive Cancer Center; UK = United Kingdom; USA = United States of America.

Table 1. Summary of Primary Sources of Evidence Showing Risk Factors for ICI-Related Myocarditis (cont.)

Author	Study design/ Level of evidence	Sample, sample size, setting, country of origin	Intervention	Findings	Limitations
Ma et al. (2021)	Retrospective Level of evidence: III	Sample: EV database and FAERS database Sample size: 1,235 ICIrM of 13,399 participants Setting: Not specified Country: Not specified	Intervention: ICI therapy	Age: > 65 years Sex: Males: 60%	SR database system can lead to inherent reporting bias FAERS reports are not verified Difficult to control for confounding factors No cohort group for comparison Fewer reports from Asia or Africa, limiting generalization Large-scale clinical trials need to be conducted to conclude causation
Mahmood et al. (2018)	Retrospective Level of evidence: III	Sample: Study arm: Multi-center registry with 8 sites Control arm: Single-center registry Sample size: 35 with ICIrM, 105 ICI-treated without ICIrM Setting: Study arm: not specified Control arm: MGH Country: USA	ICI therapy	Age: 65 ± 13 years, $p = .85$ Sex: Males: 71%, Females: $p = .83$ BMI: 29.0 ± 8.4 kg/m^2, $p = .02$ CV medications: ACE/ARB: $p = .007$ Statin: $p = .51$	Control cohort did not undergo testing to exclude myocarditis Underestimation of incidence rate if ICI-treated participants presented to another hospital for treatment of ICIrM Control arm single-center region bias
Noseda et al. (2020)	Retrospective matched case-control Level of evidence: III	Sample: VigiBase Sample size: 108 ICIrM cases, 108 cases of ICIrAE other than ICIrM Setting: VigiBase Countries: USA, Japan, EU, Australia, UK, Switzerland, Canada, Turkey, and Montenegro	ICI therapy	CV medications: $p = .026$	VigiBase does not systematically collect preexisting and/or comorbidities. Inherent reporting bias may be present if preexisting CVD determination based on drug names and related prescribing indications Matched case-control based on sex and age limited evaluation of those risk factors

Note. ACE = angiotensin-converting enzyme; ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CV = cardiovascular; EMB = endomyocardial biopsy; EU = European Union; EV = EudraVigilance; FAERS = Food & Drug Administration adverse event reporting system; ICI = immune checkpoint inhibitor; ICIrAE = immune checkpoint inhibitor–related adverse event; ICIrM = immune checkpoint inhibitor–related myocarditis; irAE = immune-related adverse event; MGH = Massachusetts General Hospital; MDACC = MD Anderson Cancer Center; SR = spontaneous reporting; RPCCC = Roswell Park Comprehensive Cancer Center; UK = United Kingdom; USA = United States of America.

Table 1. Summary of Primary Sources of Evidence Showing Risk Factors for ICI-Related Myocarditis (cont.)

Author	Study design/ Level of evidence	Sample, sample size, setting, country of origin	Intervention	Findings	Limitations
Oren et al. (2020)	Retrospective Level of evidence: III	Sample: Mayo Clinic Unified Data Platform ACE Database Sample size: 3,326 received ICI therapy, 12 ICIrM cases Setting: Mayo database Country: USA	ICI therapy	Age: > 80 years, HR: 1.07 (per each 1-year increase), $p = .02$ Sex: Males: 66% BMI: Obese: 25%	Small ICIrM sample size Underestimation of incidence rate if ICI-treated participants presented to another hospital outside Mayo database for treatment of ICIrM Cancer-specific mortality data unavailable and difficult to control for confounding CV risk factors ICI dose and therapy duration therapy not included in evaluation for possible increased risk of ICIrM
Palaskas et al. (2021)	Retrospective Level of evidence: III	Sample: Suspected ICIrM cases who underwent EMB Sample size: 28 cases underwent EMB for suspected ICIrM, 18 positive for ICIrM/inflammation Setting: MDACC Country: USA	ICI therapy with EMB biopsy	Age: EMB positive: 76 years, median Sex: EMB positive males: 78% BMI > 25 kg/m^2: EMB positive 61%	Single-center region bias No report of how many patients screened for ICIrM Small sample size
Puzanov et al. (2021)	Retrospective Level of evidence: III	Sample: Single-center Sample size: 1,001 received ICI therapy, 15 ICIrM cases analyzed (11 severe ICIrM, 4 subclinical ICIrM) Setting: RPCCC, an NCI Comprehensive Cancer Center Country: USA	ICI therapy	Age: 73.3 years, median Sex: Males: 63.6%	Single-center region bias No control arm to compare clinical characteristics Small ICIrM sample size
Salem et al. (2018)	Retrospective Level of evidence: III	Sample: VigiBase Sample size: 5,515 irAE cases of which 122 ICIrM cases analyzed Setting: VigiBase Countries: Global	ICI therapy	Age: 66.4 years, mean Sex: Males: 67%, Females: 33%	SR database system can lead to inherent reporting bias Difficult to control for confounding factors

Note. ACE = angiotensin-converting enzyme; ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CV = cardiovascular; EMB = endomyocardial biopsy; EU = European Union; EV = EudraVigilance; FAERS = Food & Drug Administration adverse event reporting system; ICI = immune checkpoint inhibitor; ICIrAE = immune checkpoint inhibitor–related adverse event; ICIrM = immune checkpoint inhibitor–related myocarditis; irAE = immune-related adverse event; MGH = Massachusetts General Hospital; MDACC = MD Anderson Cancer Center; SR = spontaneous reporting; RPCCC = Roswell Park Comprehensive Cancer Center; UK = United Kingdom; USA = United States of America.

Table 1. Summary of Primary Sources of Evidence Showing Risk Factors for ICI-Related Myocarditis (cont.)

Author	Study design/ Level of evidence	Sample, sample size, setting, country of origin	Intervention	Findings	Limitations
Shah et al. (2020)	Retrospective Level of evidence: III	Sample: Single-center and VigiBase Database Sample size: 455 treated with ICI, of which 194 ICIrM cases analyzed VigiBase: Not specified Setting: Vanderbilt University, VigiBase Database Countries: USA, global	ICI therapy	Sex: 69 years, median $p < .001$ in setting of combination ipilimumab and nivolumab and ipilimumab monotherapy	Single-center region bias SR database system can lead to inherent reporting bias Difficult to control for confounding factors
Zamami et al. (2019)	Retrospective Level of evidence: III	Sample: FAERS database Sample size: 13,096 ICI treated or which 105 ICIrM cases analyzed Setting: FAERS database Countries: Global	ICI therapy	Age: ≥ 75 years, $p < .001$ Sex: Females, $p = .004$	SR database system can lead to inherent reporting bias Difficult to control for confounding factors
Zlotoff et al. (2021)	Retrospective Level of evidence: III	Sample: 23-center international registry and single-center MGH registry Sample size: Study arm: 140 ICIrM cases Control arm: 179 Setting: Not specified Countries: USA and international (countries not specified)	ICI therapy during same time interval for whom ECG data were available	Age: 65.9 ± 14.7 years, $p = .02$ Sex: Males: 70.7% BMI 27.8 ± 6.1 kg/m^2, $p = .002$	Clinical data collection from medical records at each participating center was not protocolized leading to some incomplete data Control group single-center region bias

Note. ACE = angiotensin-converting enzyme; ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CV = cardiovascular; EMB = endomyocardial biopsy; EU = European Union; EV = EudraVigilance; FAERS = Food & Drug Administration adverse event reporting system; ICI = immune checkpoint inhibitor; ICIrAE = immune checkpoint inhibitor–related adverse event; ICIrM = immune checkpoint inhibitor–related myocarditis; irAE = immune-related adverse event; MGH = Massachusetts General Hospital; MDACC = MD Anderson Cancer Center; SR = spontaneous reporting; RPCCC = Roswell Park Comprehensive Cancer Center; UK = United Kingdom; USA = United States of America.

Age

The increasing age of a patient receiving ICI therapy was implicated in association with a higher risk for ICIrM. Four of the studies demonstrated that advanced age was significantly associated with the development of myocarditis (Oren et al., 2020; Shah et al., 2020; Zamami et al., 2019; Zlotoff et al., 2021). In the Oren and colleagues (2020) study, 12 of 3,326 participants who received ICI treatment at Mayo Clinic between March 2010 and July 2019 developed ICIrM with a mean age of 74.5. They reported participants with advanced age had a higher incidence of ICIrM with each 1-year unit increase in age (hazard ratio [HR], 1.07, $p = .02$). Eighty years of age or older with a history of acute coronary syndrome (ACS) and a history of heart failure (HF) were noted to be cumulative risk factors of ICIrM. Using VigiBase, Shah and colleagues (2020) identified a significant association between age and myocarditis in 194 patients with ICIrM with a mean age of 66.4 ($p < .001$). Furthermore, participants receiving a combination therapy of ipilimumab and nivolumab (Opdivo) had a higher incidence of fatal myocarditis with a mean age of 70.9 years compared with participants with nonfatal myocarditis with a mean age of 60.7 years ($p = .03$). The Zamami and colleagues (2021) study involved 105 cases of ICIrM that occurred between October 2013 and June 2018, as identified in the FDA FAERS database. Zamami and colleagues reported a significant association of age ≥ 75 years with the development of myocarditis ($p \leq .001$). A mean age of 65.9 years, as reported by Zlotoff and colleagues (2021), was significantly associated with the development of ICIrM in the comparison of 140 myocarditis cases to 179 non-matched controls identified in a 23-center registry ($p = .02$).

Conversely, three studies showed no significant association between age and the development of ICIrM (Awadalla et al., 2019; Palaskas et al., 2020; Puzanov et al., 2021). In the Awadalla and colleagues (2019) study from a 16-center registry, designed to collate cases of ICIrM, 101 participants with a mean age of 67 (± 18) at the start of ICI therapy were diagnosed with myocarditis. The mean age of participants at the start of ICI therapy in the Mahmood and colleagues (2018) study was 65 for both reported cases of myocarditis ($n = 35$) and the control study group ($n = 105$). The Palaskas and colleagues (2020) study analyzed a positive endomyocardial biopsy (EMB) study group ($n = 18$) compared with an EMB-negative group ($n = 10$). Palaskas and colleagues reported a wide age range from 24 to 95 years for all participants at initiation of ICI and suspected of myocarditis. A median age of 76 years for participants with an EMB positive for myocarditis was compared with the EMB-negative group with a median age of 70. Among the 15 participants with an elevated troponin level and diagnosed with ICIrM, Puzanov and colleagues (2021) found the median age to be 73 for the severe myocarditis group ($n = 11$) and 73.5 for the subclinical myocarditis group ($n = 4$).

While no statistical analysis was completed, Fan and colleagues (2019) evaluated data from FDA FAERS from 2014 through 2018 and reported the majority of ICIrM cases ($n = 161$) occurred in patients aged 65 years and older (51.1%). The remaining four studies did not have statistical testing performed (Lal et al., 2021; Ma et al., 2021; Noseda et al., 2020; Salem et al., 2018). Noseda and colleagues (2020) reported no differences related to age in cases compared with controls, as age was used as a matching criterion. In this study of 108 myocarditis cases with 108 matched controls, the median age for both groups was 68 years. The Ma and colleagues (2021) study included participants younger than 18 years old to those older than 85 years. Ma and colleagues reported participants older than 64 years of age had a higher incidence of ICIrM ($n = 583$), especially those of ages between 65 and 85 years ($n = 563$). Salem and colleagues (2018) evaluated data submitted to VigiBase between January 2008 and January 2018, identifying 99 patients with ICIrM and known ages. The reported mean age at onset was 66.4. No age-specific data related to ICIrM was provided in the Lal and colleagues (2021) study.

Sex

Lal and colleagues (2021) used the FDA FAERS database to retrospectively investigate cardiac adverse events in patients who received immunotherapy compared with the reference group who received treatment with conventional chemotherapy. Of the 345 total myocarditis cases reported

between January 2010 and March 2020, Lal and colleagues noted that males were at significant increased risk for ICIrM ($q < .001$). Zamami and colleagues (2019) used the FDA FAERS database to retrospectively evaluate 105 myocarditis cases between October 2013 and June 2018. The authors identified significant sex-specificity of females experiencing myocarditis only in the setting of ICI therapy use ($p = .004$). No level of significance was reached for the number of female myocarditis cases outside the setting of ICIs.

In a case-control study evaluating ICI-treated participants, Awadalla and colleagues (2019) reported 72% of males ($n = 73$) diagnosed with myocarditis without a statistically significant association of sex when compared with the control group. Shah and colleagues (2020) also reported no significant association between sex and an increased rate of developing myocarditis or any other associated irAE even when controlling for treatment type, seasonality, age, and performance status (p value not reported).

In 2019, Fan and colleagues published a retrospective pharmacovigilance study that retrieved reports from the FDA FAERS database between January 2004 and June 2018. Of the 43,147 adverse event reports analyzed, 315 myocarditis cases were identified as being related to ICIs. Males were more likely to experience myocarditis compared with females (58.41% vs. 31.11%). Ma and colleagues (2021) retrieved 1,235 fatal IRIrM cases from the FDA FAERS and EV databases and identified male participants ($n = 745$) were more likely to develop ICIrM (60% male vs. 33% female vs. 7% unknown). Mahmood and colleagues (2018) created a multicenter registry of eight sites, reporting 35 participants diagnosed with ICIrM, of which 71% were male ($n = 25$).

Five studies reported a higher incidence of ICIrM in men compared with women; however, statistical testing between sexes was not performed (Oren et al., 2020; Palaskas et al., 2020; Puzanov et al., 2021; Salem et al., 2018; Zlotoff et al., 2021). While Zlotoff and colleagues (2021) did not directly compare male ($n = 99$) vs. female ($n = 41$) ICIrM cases, 70.7% of males were diagnosed with ICIrM compared with 29.3% of females in the ICIrM study group. In a smaller study of 12 participants diagnosed with ICIrM, Oren and colleagues (2020) reported 66% were men. Palaskas and colleagues (2020) retrospectively reviewed 28 patients suspected to have ICIrM and who underwent a diagnostic EMB. Palaskas and colleagues reported 78% of men were EMB positive ($n = 14$) compared with 22% of women who were EMB positive ($n = 4$). Similarly, from a retrospective single-center study conducted from January 2016 to January 2020, Puzanov and colleagues (2021) identified 15 participants with probable ICIrM of which 11 participants were male (73%). Using data from VigiBase, Salem and colleagues (2018) conducted a retrospective, pharmacovigilance study and reported 67% of ICIrM occurred in men ($n = 78$) as compared with 33% of women ($n = 39$).

Finally, Noseda and colleagues (2020) conducted a study with 62% of male participants in both the matched case and control study groups. No statistical tests were completed evaluating differences between patient sex.

Body Mass Index

According to the Centers for Disease Control and Prevention (CDC, 2022), a body mass index (BMI) between 25 kilograms per meters squared (kg/m^2) to less than 30 kg/m^2 is considered overweight, while a BMI greater than or equal to 30 kg/m^2 falls within the range of obesity. Three of the studies investigating the impact of a participant's BMI and ICI treatment-related irAEs reported a significant association between a BMI greater than 27.8 kg/m^2 and incidence of ICIrM (Awadalla et al., 2019; Mahmood et al., 2018; Zlotoff et al., 2021). Awadalla and colleagues (2019) derived 101 cases of myocarditis from a 16-center institutional registry with a control study group of 201 participants gathered from a single-center registry. Awadalla and colleagues concluded that participants with a BMI of 28 $kg/m^2 \pm 7$ were at a significant increased risk of myocarditis ($p = .01$). Mahmood and colleagues (2018) reported the ICIrM participant group with a BMI of 29 $kg/m^2 \pm 8.4$ ($n = 35$) was at a significantly higher risk than the control group with a BMI of 26 $kg/m^2 \pm 6$ ($n = 105$, $p = .02$). Zlotoff and colleagues (2021) echoed these findings, reporting that study participants with myocarditis ($n = 140$) were found to have a higher BMI of 28 $kg/m^2 \pm 6.1$ than controls ($n = 170$) with a BMI of 26 $kg/m^2 \pm 5.8$ ($p = .002$).

While no statistical analysis was completed in the following two studies, Oren and colleagues (2020) reported 25% of the 12 participants diagnosed with ICIrM met the criteria for obesity with a BMI greater than or equal to 30 kg/m^2. Palaskas and colleagues (2020) evaluated 28 participants who were all suspected to have ICIrM, and 64% of participants were found to be overweight or with obesity, with a BMI greater than 25 kg/m^2.

Cardiovascular Medications

Three of the reviewed studies reported a significantly higher number of myocarditis cases in participants who were prescribed CV medications prior to starting ICI therapy. Awadalla and colleagues (2019) completed a case-control study with 101 participants who developed ICIrM compared with 201 controls who also received ICI therapy and did not develop myocarditis. One hundred thirteen recorded incidences of CV medications in the myocarditis cases were reported compared with 213 recorded incidences of CV medications in the control group. Baseline data demonstrated a significant number of ICIrM cases for those reported to receive statins (n = 32) as a pre-ICI home CV medication (p = .02). Using a registry of retrospective and prospective myocarditis cases and controls on ICI therapy, Mahmood and colleagues (2018) noted a significantly higher prevalence of ICIrM in those receiving an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB; n = 15) compared with controls (n = 26; p = .007). The Noseda and colleagues (2020) retrospective matched case-control study used CV drugs as a proxy for preexisting CV diseases and/or CV risk factors. The data demonstrated a moderate association between the use of pre-ICI home drugs for underlying CV diseases and ICIrM (p = .026).

While statistical significance was not reached, it is worth noting Awadalla and colleagues (2019 reported an increased incidence of ICIrM in participants prescribed an ACE-I, ARB, or a calcium channel blocker.

DISCUSSION

Collectively, the findings of this review support an association of ICIrM with age, obesity, and CV medications pre-ICI treatment. Study participants' sex was not a determinate factor.

Age

Of the seven studies reviewed that applied statistical analysis to the age factor, four of the studies reported advanced age as significantly associated with ICIrM (Oren et al., 2020; Shah et al., 2020; Zamami et al., 2019; Zlotoff et al., 2021). This finding may be associated with the increased diagnosis of cancer in the older patient (National Cancer Institute, 2021), opportunity to receive ICI as cancer treatment, and resulting higher incidence of ICIrM. Immunosenescence may play a role in this elevated risk for malignancies, as increasing age tends toward decreased innate and adaptive immunity and the ability to effectively respond to cancer cells (Fulop et al., 2013; Ma et al., 2021). A greater incidence of ICIrM in older patient populations may, therefore, be related to a lower functioning immune system with increased autoimmune reactions in a chronic proinflammatory state (Aiello et al., 2019; Ma et al., 2021).

Shah and colleagues (2020) proposed that accumulated heart damage in older patients caused by atherosclerosis may increase the risk of myocarditis in older patients. For persons aged 60 to 79 years old, 22% of males and 13.4% of females had coronary heart disease, and in those aged 80 years or older, 33.9% of males and 21.6% of females had CV disease with hypertension (Virani et al., 2021). This correlates with the Oren and colleagues (2020) study that reported three predicative factors for ICIrM that included age 80 years or older, history of acute coronary artery syndrome, and history of heart failure.

The Zamami and colleagues (2019) study reported patients 75 years or older receiving ICI therapy were 7.61 times more likely to be diagnosed with ICIrM. The authors note that comorbidities, cancer types, and specific drug regimens were not evaluated in comparison with participants younger than 75 years old, and any imbalance in these factors may impact the reported findings.

While three studies reported age as not significantly associated with an increased risk of ICIrM, this may be due to the underrepresentation of older patient populations in ICI randomized clinical trials. Ninomiya and colleagues (2020) reported 43% of patients 65 years or older with cancer and receiving ICI treatment were represented in randomized clinical trials despite

the cancer incidence at its highest for this age group. This underrepresentation may contribute to the nonsignificance of results.

Sex

This review did not find convincing evidence to support or rule out a patient's sex as a risk factor for ICIrM. Of the articles reviewed, a single statistically significant study by Zamami and colleagues (2019) reported females were 1.92 times more likely to experience ICIrM compared with male participants. The remaining studies reported that male cancer participants had a higher percentage of ICIrM cases. These findings may reflect the overall higher incidence rate of cancer in males and the disproportionate inclusion of male participants in both studies in the ICI clinical trial setting (Islami et al., 2021; Salem et al., 2018; Wilcox et al., 2022).

Body Mass Index

The studies reviewed support an association between ICIrM and overweight and obese participants with a reported body mass index average greater than 27.8 kg/m^2 (Awadalla et al., 2019; Mahmood et al., 2018; Oren et al., 2020; Palaskas et al., 2020). The link between obesity and the development of CV diseases is supported in literature and may be a contributing factor to the increased incidence of ICIrM (Dwivedi et al., 2020; Neeland et al., 2019; Powell-Wiley et al., 2021). Visceral adiposity is fundamental to the development of atherosclerosis; this proinflammatory cytokine state may induce autoimmune cardiac dysfunction (Powell-Wiley et al., 2021; Shah et al., 2020). Further research evaluating obesity as a contributing risk factor to ICIrM is needed.

Cardiovascular Medications

The reviewed literature supports an association between pre-ICI treatment CV medications and the development of ICIrM. The findings of this review did not consistently support a specific class of CV medications, thus limiting the applicability of these results. The Awadalla and colleagues (2019) study reported a significant association with ICIrM incidence and statins. Statins are used to treat atherosclerosis, a chronic inflammatory and immune disease, involving many cell types including T cells. T-cell involvement supports the possible increased risk of myocardial T-cell activation and subsequent myocarditis for patients on a statin. Zlotoff and colleagues (2021) reported opposing findings with no association between statins and myocarditis. Statins have been reported to prevent T-cell activation and proliferation (Spirig et al., 2012). Lack of statin therapy adherence may have contributed to these differences.

Evaluating study participants for pretreatment CV medications serves as a proxy for underlying CV risk factors and diseases. Overall, limited data have been published on patients with ICIrM and a history of atherosclerosis, hyperlipidemia, or acute coronary syndrome to evaluate an association with ICIrM. Prospective studies are needed to flesh out confounding factors and evaluate these findings.

Limitations

Low rates of ICIrM incidence yielded small case numbers, thereby limiting the generalization and power of the studies. Additionally, an underestimation of ICIrM cases may be due to control cohort participants not undergoing testing to exclude myocarditis or participants presenting to a facility outside the study center to receive treatment for ICIrM (Awadalla et al., 2019; Mahmood et al., 2018; Zlotoff et al., 2021). Across all studies, there were variable assessment and diagnostic tests employed or not reported to confirm myocarditis, which may have resulted in underreporting of ICIrM.

The studies varied in their design. Six utilized large adverse drug event self-reporting databases including FAERS, VigiBase, and EV for study participants. These databases may be inherently inaccurate due to health-care professionals, drug manufacturers, and consumers submitting event reports and inherent reporting bias with limited ability to verify the data.

The race or ethnicity of study participants was not reported in the studies reviewed, with the exception of Palaskas and colleagues' (2020), in which 75% of the participants were White, 10% Black, and 15% other. Exclusion of this information not only limits generalizations but may impact overall study findings.

IMPLICATIONS FOR PRACTICE

Maintaining a heightened awareness of ICIrM is imperative for patients and providers, as use of ICIs

for cancer treatment continues to increase. Patients need to be educated on the signs and symptoms of myocarditis and be provided with educational material and tools, such as the Oncology Nursing Society immunotherapy wallet card to show in a medical emergency setting. Advanced practice providers can provide guidance to patients on weight loss and ensure CV health is prioritized in their care plan. Per ASCO practice guidelines for irAE management, prior to initiating ICI therapy, a baseline echocardiogram, electrocardiogram, blood pressure, and troponin are recommended for cardiac assessment (Brahmer et al., 2018; Zhang et al., 2020).

Increased medical provider awareness for ICIrM is equally important. Providers should remain knowledgeable about the signs and symptoms of myocarditis along with appropriate screening, monitoring, and treatment. Patients may present with symptoms of heart failure or acute coronary syndrome reporting dyspnea, chest pain, arrhythmias, elevated troponin, and elevated BNP (Puzanov et al., 2021). Providers should also consider that patients may have a preserved left ventricular ejection fraction in the setting of ICIrM (Mahmood et al., 2018).

CONCLUSIONS

Myocarditis is a rare ICI-related adverse event with a high mortality rate. The findings of this integrative literature review support an association of ICIrM with age, obesity, and pre-ICI treatment CV medications, while study participants' sex was an indeterminate factor. More research is needed on ICIrM. Clinical trials should include equal gender representation with a more racially diverse group of participants.

Advanced practice providers should lead and assist in conducting studies focused on evaluating baseline modifiable and nonmodifiable characteristics of patients treated with ICI and diagnosed with ICIrM in order to further determine who is most at risk and what preventative measures or mitigating actions should be taken.

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