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Myocarditis following the use of different immune checkpoint inhibitor regimens: A real-world analysis of post-marketing surveillance data

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ABSTRACT

Backgrounds: Although myocarditis has been reported in patients treated with immune checkpoint inhibitors (ICIs), there are few real-world studies to compare the occurrences and characteristics of myocarditis after different ICI regimens.

Methods: Disproportionality analysis and Bayesian analysis were utilized for data mining of the suspected adverse events of myocarditis after ICIs use based on the Food and Drug Administration's Adverse Event Reporting System (FAERS) from January 2004 to June 2018. The times to onset and fatality rates of myocarditis following different ICI regimens were also compared.

Results: A total of 315 reports of myocarditis adverse events were identified with ICIs. Among 6 ICI monotherapies, avelumab had the highest association with myocarditis based on the highest reporting odds ratio (ROR = 42.65, 95% two-sided CI = 15.86–114.72), proportional reporting ratio (PRR = 42.61, $\chi 2 = 159.63$) and empirical Bayes geometric mean (EBGM = 41.87, 95% one-sided CI = 15.57). The combination therapies of ipilimumab plus pembrolizumab or nivolumab had higher RORs, PRRs and EBGMs than did pembrolizumab or nivolumab monotherapy. Myocarditis associated with the ipilimumab plus nivolumab treatment appeared to have earlier onset (16.5 [IQR 14–29.75] days vs 32 [IQR 16–77] days, $p < 0.01$) and higher fatality rate (65.75% vs 50.40%, $p < 0.05$) than that associated with nivolumab monotherapy.

Conclusions: Analysis of FAERS data provides more precise profile on the occurrences and characteristics of myocarditis after different ICI regimens. The findings support continued surveillance, risk factor identification, and comparative studies.

1. Introduction

Immune checkpoint inhibitors (ICIs) have transformed the landscape of cancer management [1]. To date, the US Food and Drug Administration (FDA) has approved 6 ICIs for cancer therapy, including 1 cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor, ipilimumab; 2 programmed cell death protein 1 (PD-1) inhibitors, pembrolizumab and nivolumab; and 3 programmed cell death 1 ligand 1 (PD-L1) inhibitors, atezolizumab, avelumab and durvalumab (Table 1). By releasing the restrained antitumour immune responses, ICIs have demonstrated significant efficacy against a wide spectrum of cancers [2–5]. Moreover, combination therapy of ipilimumab plus nivolumab has also been approved for several cancers with further reduction in mortality [6–8]. Clinical trials on novel ICIs and ICI combinations are still under way [9,10].

Despite favourable benefits, the use of ICIs is also accompanied by a unique spectrum of side effects, referred to as immune-related adverse events (irAEs), which occur due to inflammatory reactions against normal tissues. Common irAEs include dermatitis, endocrinopathies, colitis, hepatitis, and pneumonitis [11]. Recently, cases of myocarditis have been reported in cancer patients treated with ICIs [12–14]. Although recognized as an uncommon adverse reaction, ICI-related myocarditis may result in poor outcomes, especially when these agents are used in combination [15,16].

Although there is increasing evidence indicating that ICIs carry a potential risk of myocarditis, most evidence comes from case reports [12–16] or clinical trials [17,18], which is insufficient to provide an overview of the risk of rare adverse events such as myocarditis. Pharmacovigilance studies about this issue are still scarce and mainly focus on toxicities between generations of ICIs or their combination [19,20].

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Table 1
Summary of FDA-approved ICIs.

Generic name	Brand name	Target	Approval year
Ipilimumab	Yervoy	CTLA-4	2011
Pembrolizumab	Keytruda	PD-1	2014
Nivolumab	Opdivo	PD-1	2014
Atezolizumab	Tecentriq	PD-L1	2016
Avelumab	Bavencio	PD-L1	2017
Durvalumab	Imfinzi	PD-L1	2017

Abbreviations: FDA: Food and Drug Administration; ICIs: immune checkpoint inhibitors; CTLA-4: cytotoxic T lymphocyte-associated antigen 4; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1.

Little is known about the accurate safety profile of myocarditis after each ICI regimen in clinical practice. Herein, we aimed to evaluate and compare links between various ICI regimens and myocarditis in a large real-world patient population by analysing adverse events in the FDA's Adverse Event Reporting System (FAERS) until recently. In addition, we further investigated the times to onset and fatality rates for myocarditis after the administration of different ICI regimens.

2. Material and methods

2.1. Data source

We performed a retrospective pharmacovigilance study using data from the FAERS database covering the period from January 2004 to June 2018. The FAERS is a public voluntary spontaneous reporting database that provides information on adverse event and medication error reports submitted by health professionals, consumers, and manufacturers not only domestically but also from other countries. FAERS data files contain demographic and administrative information (DEMO), drug information (DRUG), the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) coded for the adverse event (REAC), patient outcomes (OUTC), report sources (RPSR), therapy start dates and end dates for reported drugs (THER), and indications for use (INDI).

In total, 9,354,226 reports were retrieved from the FAERS database. A deduplication procedure was performed according to the FDA's recommendations, selecting the latest FDA_DT when the CASEIDs were the same and selecting the higher PRIMARYID when the CASEID and FDA_DT were the same, resulting in a reduction in the number of reports to 9,352,387.

2.2. Adverse event and drug identification

Adverse events were investigated using the MedDRA term "myocarditis" in the REAC files. The drugs in the FAERS database can be input arbitrarily; therefore, the MICROMEDEX® (Index Nominum) was utilized as a dictionary for the ICIs (Table 1).

2.3. Data mining

Based on the disproportionality analysis and Bayesian analysis, we used the reporting odds ratio (ROR), the proportional reporting ratio (PRR), the Bayesian confidence propagation neural network (BCPNN) and the multi-item gamma Poisson shrinker (MGPS) algorithms to identify an association between a drug and an adverse event.

The equations and criteria for the four algorithms [21–26] are shown in Table 2. In this study, adverse events were extracted when at least 1 of 4 indices met the criteria.

The associations between myocarditis and different ICI regimens (monotherapies and combination therapies) were compared. Monotherapy here was defined as a specific ICI used alone which meant this specific ICI was "primary suspect" in ROLE_COD field of DRUG files and with no other ICI in the same report as "second suspect", "concomitant" or "interacting". Combination therapy here was defined as concurrent administration of CTLA-4 inhibitor and PD-1 or PD-L1 inhibitors which meant a specific ICI was "primary suspect", and another ICI was "second suspect", "concomitant" or "interacting". The time to onset of myocarditis was evaluated for each ICI regimen. It was defined as the interval between the EVENT_DT (adverse event onset date) and the START_DT (start date of ICIs use). However, reports with input error (EVENT_DT earlier than START_DT) or inaccurate date entry were excluded. In addition, reports with fatal events attributed to drug toxicity were counted, and the fatality rate was calculated as the number of fatal events divided by the total number of events of myocarditis associated with each ICI regimen.

Table 2
Summary of major algorithms used for signal detection.

Algorithms	Equation	Criteria
ROR	$ROR = ad/c/b$ $95\%\ CI = e^{\ln(ROR) \pm 1.96(1/a+1/b+1/c+1/d)^{\wedge}0.5}$	95% CI > 1, N ≥ 2
PRR	$PRR = a(c+d)/c/(a+b)$ $\chi^2 = [(ad-bc)^{\wedge}2](a+b+c+d)/[(a+b)(c+d)(a+c)(b+d)]$	PRR ≥ 2, $\chi^2 \geq 4$, N ≥ 3
BCPNN	$IC = \log_2 a(a+b+c+d)(a+c)(a+b)$ $95\%\ CI = e^{\ln(IC) \pm 1.96(1/a+1/b+1/c+1/d)^{\wedge}0.5}$	IC025 > 0
MGPS	$EBGM = a(a+b+c+d)/(a+c)/(a+b)$ $95\%\ CI = e^{\ln(EBGM) \pm 1.96(1/a+1/b+1/c+1/d)^{\wedge}0.5}$	EBGM05 > 2, N > 0

Abbreviations: a: the number of reports with suspect adverse drug event (ADE) of the suspect drug; b: the number of reports with the suspect ADE of all other drugs; c: the number of reports with all other ADEs of the suspect drug; d: the number of reports with all other ADEs of all other drugs; ROR: reporting odds ratio; CI: confidence interval; N: the number of co-occurrences; PRR: proportional reporting ratio; χ^2: chi-squared; BCPNN: Bayesian confidence propagation neural network; IC: information component; IC025: the lower limit of the 95% two-sided CI of the IC; MGPS: multi-item gamma Poisson shrinker; EBGM: empirical Bayesian geometric mean; EBGM05: the lower 95% one-sided CI of EBGM.

2.4. Statistical analysis

Descriptive analysis was used to summarize the clinical characteristics of the patients with ICI-associated myocarditis collected from the FAERS database. The times to onset of ICI-associated myocarditis between different ICI regimens were compared using non-parametric tests (the Mann-Whitney test for dichotomous variables and the Kruskal-Wallis test when there were more than two subgroups of respondents) because the data were not normally distributed. Fatality rates were compared between different ICI regimens using Pearson's chi-square test or Fisher exact test. The statistical significance was determined at $p < 0.05$ with 95% confidence intervals. Data mining and all statistical analyses were performed with SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Descriptive analysis

Overall, 43,147 adverse events related to ICIs and 4007 reports related to myocarditis were documented in the FAERS database between January 2004 and June 2018. Among them, ICI therapy was identified as the suspected drug causing myocarditis in 315 reports, and the clinical characteristics of these patients are presented in Table 3. The highest number of myocarditis reports was for nivolumab monotherapy (n = 125), followed by ipilimumab plus nivolumab combination therapy (n = 73). Myocarditis adverse events were most commonly reported in patients with lung cancer (33.33%). The patients affected were more often males than females (58.41% vs 31.11%). The majority

Table 3
Clinical characteristics of patients with ICI-associated myocarditis collected from the FAERS database (January 2004 to June 2018).

Characteristics	Reports, no. (%)
Reporting region	
Europe	128 (40.63)
Americas	127 (40.32)
Asia	45 (14.29)
Australia	14 (4.44)
Africa	1 (0.32)
Reporters	
Health-care professional	250 (79.37)
Non-health-care professional	65 (20.63)
Reporting year	
2018	132 (41.90)
2017	109 (34.60)
2016	60 (19.05)
2015	11 (3.49)
2013	2 (0.63)
2012	1 (0.32)
Patient sex	
Male	184 (58.41)
Female	98 (31.11)
Unknown or missing	33 (10.48)
Patient age group (years)	
< 18	0 (0.00)
18–44	18 (5.71)
45–64	70 (22.22)
65–74	101 (32.06)
> 75	60 (19.05)
Unknown or missing	66 (20.95)
ICI drug as suspected drug	
Monotherapy	
Ipilimumab	19 (6.03)
Pembrolizumab	69 (21.90)
Nivolumab	125 (39.68)
Atezolizumab	18 (5.71)
Avelumab	4 (1.27)
Durvalumab	3 (0.95)
Combination therapy	
Ipilimumab plus nivolumab	73 (23.17)
Ipilimumab plus pembrolizumab	4 (1.27)
Indications	
Tumours of the lung, pleura, thymus and heart	115 (36.51)
Skin tumours	94 (29.84)
Unspecified malignant neoplasm	40 (12.70)
Tumours of the urinary system and male genital organs	38 (12.06)
Tumours of the digestive system	17 (5.40)
Tumours of haematopoietic and lymphoid tissues	5 (1.59)
Tumours of the central nervous system	3 (0.95)
Head and neck tumours	1 (0.32)
Tumours of endocrine organs	1 (0.32)
Tumours of female reproductive organs	1 (0.32)

Abbreviations: ICI: immune checkpoint inhibitor; FAERS: Food and Drug Administration's Adverse Event Reporting System.

of patients were ≥65 years (51.11%), with an average age of 66.26 ± 12.86 years for males and 64.69 ± 12.79 years for females. Most of the cases were from Europe (40.63%) and the Americas (40.32%) and were mainly submitted by health-care professionals (79.37%). The number of ICI-related myocarditis reports increased from 2012 to 2018.

3.2. Disproportionality analysis and Bayesian analysis

Overall, based on the criteria for the 4 algorithms, myocarditis signals were detected for all 6 ICI monotherapies and 2 ICI combination therapies. The results are listed in Table 4. Among all ICI monotherapies, the association with myocarditis was noteworthy for avelumab because it had the highest ROR, PRR and EBGM, while ipilimumab appeared to have the relatively weaker associations with myocarditis than others. Among the combinations of dual ICIs, the regimens of ipilimumab plus pembrolizumab or nivolumab were found to have stronger associations with myocarditis than did pembrolizumab or nivolumab alone based on higher RORs, PRRs and EBGMs. No cases were reported for other combination therapies of anti-CTLA-4 plus anti–PD-1/PD-L1.

3.3. Time to onset of ICI-associated myocarditis

Generally, the median time to event onset of ICI-related myocarditis was 23 (inter-quartile range [IQR] 14–55) days. The times to onset following each ICI regimen are shown in Fig. 1. Interestingly, it can be seen from the data that the adverse event of myocarditis occurred as soon as after the first dose of several ICI monotherapies, including pembrolizumab, nivolumab and atezolizumab, with median times to onset of 22 (IQR 10.25–64) days, 32 (IQR 16–77) days, and 28 (IQR 8–89) days, respectively. There were no significant differences in the times to onset among these monotherapies ($p = 0.215$). However, patients treated with a combination of ipilimumab and nivolumab appeared to have earlier onset of myocarditis compared with that in those receiving nivolumab alone (16.5 [IQR 14–29.75] vs 32 [IQR 16–77], $p = 0.005$). Because there was only one report of myocarditis following the ipilimumab plus pembrolizumab treatment available for the calculation of the time to onset, a comparison with pembrolizumab monotherapy could not be made.

3.4. Fatality due to ICI-associated myocarditis

To determine the prognosis of myocarditis after ICIs use, we assessed the rates of fatality due to myocarditis adverse events following various ICI regimens, and the results are shown in Fig. 2. It was observed that myocarditis generally portended poor outcomes with approximately half of cases (51.11%) resulting in death. Among the monotherapies, nivolumab appeared to present the relatively high risk of death, with 63 (50.40%) deaths among 125 cases, while atezolizumab appeared to have the relatively low risk of death, with 4 (22.22%) deaths among 18 cases. Fatal events also occurred in 3 (75.00%) of 4 patients with avelumab and 2 (66.67%) of 3 patients with durvalumab, although the number of reports were not enough to draw a conclusion. Based on the collected data, there was no significant difference in fatality rates across different ICI monotherapies (Fisher exact test for overall comparison between ipilimumab, pembrolizumab, nivolumab, atezolizumab, avelumab and durvalumab, $p = 0.184$). Among the combination therapies, more deaths occurred in myocarditis cases with ipilimumab plus nivolumab combination than with nivolumab monotherapy (65.75% vs 50.40%, $p = 0.036$). As for the combination of ipilimumab plus pembrolizumab, there were only 4 myocarditis cases and no fatal event, while death occurred in 30 (43.48%) of 69 patients with pembrolizumab used alone.

4. Discussion

To the best of our knowledge, this is the first study to describe differences in the associations, timing and prognosis of myocarditis following the use of various ICI regimens in the real-world practice based on the FAERS pharmacovigilance database, and it is the largest collection of such cases to date. The study showed that all of the 6 studied ICIs were associated with adverse event of myocarditis, however, there were distinctions across regimens.

Ipilimumab, as the first FDA approved ICI in 2011, demonstrate a survival benefit in patients with metastatic melanoma. It presented uncommon cardiac adverse events in the early clinical trials, but notable cardiovascular toxicities, including fatal myocarditis, were reported post-marketing [12,19]. Then, pembrolizumab and nivolumab were approved for the treatment of metastatic melanoma in 2014. In both clinical trials and post-marketing surveillance, myocarditis associated with these two PD-1 inhibitors was noted as an adverse drug reaction [18,27,28]. Cases of myocarditis were also found in patients

Table 4
Associations of different ICI regimens with myocarditis.

ICI regimens	N	ROR	PRR	IC	EBGM
		(95% two-sided CI)	(χ^2)	(95% two-sided CI)	(95% one-sided CI)
Monotherapy					
Ipilimumab	19	5.35 (3.41, 8.4)	5.33 (66.7)	52.4 (33.37, 82.28)	5.32 (3.39)
Pembrolizumab	69	17.39 (13.69, 22.08)	17.11 (1039.74)	54.44 (42.88, 69.13)	16.99 (13.38)
Nivolumab	125	16.04 (13.42, 19.18)	15.57 (1696.81)	56.29 (47.08, 67.31)	15.48 (12.94)
Atezolizumab	18	15.19 (9.54, 24.16)	15.12 (235.93)	50.74 (31.89, 80.75)	15.03 (9.45)
Avelumab	4	42.65 (15.86, 114.72)	42.61 (159.63)	44.93 (16.7, 120.83)	41.87 (15.57)
Durvalumab	3	20.72 (6.65, 64.6)	20.71 (55.77)	45.12 (14.47, 140.67)	20.53 (6.59)
Combination therapy					
Ipilimumab plus pembrolizumab	4	47.9 (17.79, 128.98)	47.86 (179.83)	44.76 (16.62, 120.52)	46.91 (17.42)
Ipilimumab plus nivolumab	73	36.85 (29.18, 46.53)	36.2 (2461.53)	53.54 (42.4, 67.6)	35.66 (28.24)

Abbreviations: ICI: immune checkpoint inhibitor; N: the number of reports of ICI-associated myocarditis; ROR: reporting odds ratio; CI: confidence interval; PRR: proportional reporting ratio; χ^2: chi-squared; IC: information component; EBGM: empirical Bayes geometric mean.

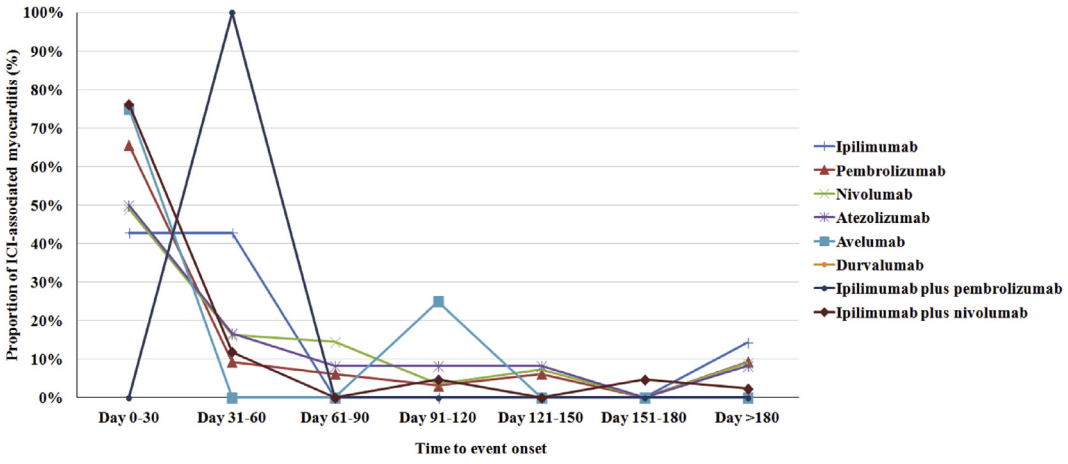
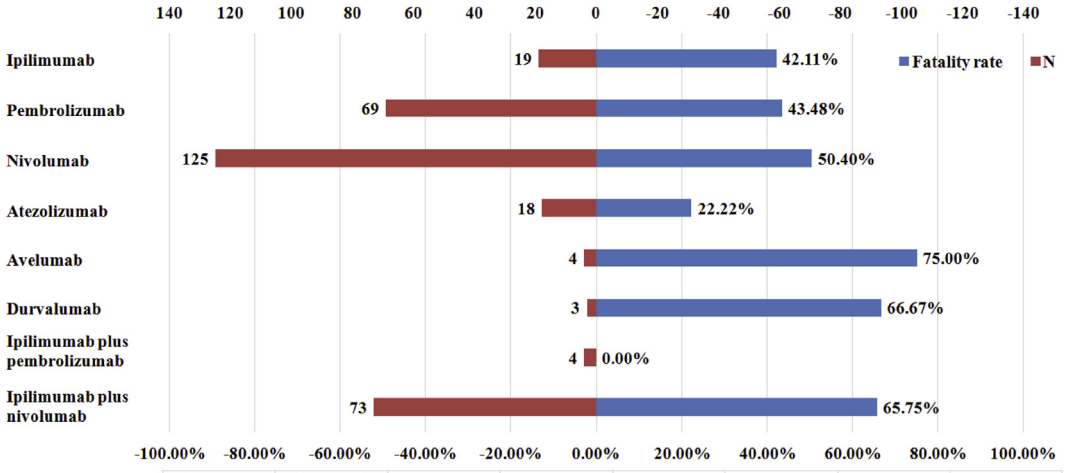


Fig. 1. Time to event onset of myocarditis following different ICI regimens. ICI indicates immune checkpoint inhibitor.



	Ipilimumab plus nivolumab	Ipilimumab plus pembrolizumab	Durvalumab	Avelumab	Atezolizumab	Nivolumab	Pembrolizumab	Ipilimumab
Fatality rate	65.75%	0.00%	66.67%	75.00%	22.22%	50.40%	43.48%	42.11%
N	73	4	3	4	18	125	69	19

Fig. 2. Number of reports and fatality rates for ICI-associated myocarditis. N indicates the number of reports of ICI-associated myocarditis; ICI indicates immune checkpoint inhibitor.

treated with other ICIs, such as avelumab [29], atezolizumab [30] and durvalumab [31]. As the combination of CTLA-4 and PD-1/PD-L1 inhibitors manifested further clinical benefits, dual ICIs given in a concurrent regimen were applied for the treatment of many cancers. After Johnson et al.'s report about fulminant myocarditis associated with this 2-drug regimen [15], the risk of severe myocarditis induced by ICI combination therapy has attracted a great deal of attention. However, the assessment and characterization of ICI-associated myocarditis is quite challenging because of its low incidence and various manifestations. Hence, it is important to recognize the associations of particular ICI regimens with myocarditis as well as the clinical features, and to develop awareness of the possibility of this adverse event among oncologists, cardiologists, emergency department physicians, pharmacists and other specialists.

Although clinical trials are mandatory to establish efficacy for novel drugs, there are limitations on the ability to draw definitive conclusions about drug safety due to the strict study entry criteria, relatively small sample sizes, finite scope and time frame. Nevertheless, spontaneous reporting systems (SRSs) can serve as a primary source of post-marketing data and play an important role in the detection of safety issues, including ICI-related irAEs [32,33]. According to our study based on the FAERS, a substantial increase in reporting incidence over time, especially in the first half of 2018. It is speculated that this may due to rapid expanding of varieties and indications of ICIs as well as heightened recognition of this new clinical entity [20]. ICI-associated myocarditis seemed to predominately affect men (58.41%), which confirmed the findings of Salem et al. who also found such adverse events occurred mainly in men (67%) based on the data from VigiBase [34]. However, it should be noted that there were inadequate inclusion of women in both clinical trials and clinical practice for ICI treatment because of higher risk of autoimmune diseases that women carry [35,36]. Therefore, further research is required to provide evidence of the true incidence of ICI-associated myocarditis among men and women. The current study also indicated that ICI-related myocarditis was mainly detected in elderly patients (51.11% $\geq$65 years vs 27.94% < 65 years), which has similarity with conclusions of the multicentre observational study by Mahmood et al. [37]. As is known, advancing age is an important risk factor for cancer [38]. Data from the Surveillance, Epidemiology, and End Results Program 2012–2016 reveals that the median age at diagnosis across all cancer types is 66 years, with > 50% of new cancer cases being diagnosed in patients 65 years or older [39]. However, evidence of the safety of ICI treatment in elderly adults is still limited because of inadequate enrolment in clinical trials. Most immunotherapy clinical trials included approximately 20%–40% patients above the age of 65 years [40]. While, the wide use of ICIs in cancer patients over 65 years in the real-world setting has been observed in several recent retrospective studies [41,42]. Unfortunately, it is difficult to control such confounding factor as age in this study because of the limitation of FAERS database. Further research is needed to explore the link between advanced age and incidence of ICI-related myocarditis. Even so, our results suggested that more attention should be paid to elderly patients, which is also emphasized in the 2017 Chinese Lung Cancer Summit expert panel [43].

Using pharmacovigilance analysis, all ICIs were found to be associated with myocarditis, and therefore this appears to be a class effect. Surprisingly, avelumab seems to have the strongest association with myocarditis among all ICI monotherapies, which has not been reported previously. Regarding the increased risk of myocarditis caused by ICI combinations, there are contrasting reports on the incidence rates. According to the study by Sznol et al., no occurrence of myocarditis was identified after a pooled analysis of 448 patients administered the combination therapy of ipilimumab plus nivolumab [44]. Conversely, Johnson et al. proposed that patients who received combined ipilimumab and nivolumab therapy developed myocarditis more frequently than those who received nivolumab alone (0.27% vs. 0.06%; $p < 0.001$) [15]. Another cohort study of 964 patients from a multicentre registry showed that the prevalence of myocarditis was 1.3% in patients receiving pembrolizumab alone and 0.6% in patients receiving nivolumab alone and that the prevalence increased to 2.4% in patients receiving anti-CTLA4/anti-PD1combined therapy [37]. In the current study, when nivolumab or pembrolizumab was administered concurrently with ipilimumab, stronger associations with myocarditis were found than those with nivolumab or pembrolizumab treatment. Although the true incidence rates need to be further investigated by a well-designed clinical trial of different ICI regimens, current results indicated a higher risk of myocarditis reporting with the use of combined regimens.

Another important finding was that the median time to the onset of myocarditis was 23 (IQR 14–55) days after the initiation of ICI treatment, which was earlier than the time to onset of 34 (IQR 21–75) days reported in a cohort study by Mahmood et al. [37]. According to the reports collected in this study, myocarditis could occur as soon as after the first dose for pembrolizumab, nivolumab and atezolizumab monotherapy. Besides, the nivolumab plus ipilimumab regimen was found to result in an earlier occurrence of myocarditis than did nivolumab alone. This finding is consistent with those of Johnson et al., who found the median onset time of the nivolumab plus ipilimumab regimen was 17 (range 13–67) days. However, it is difficult to determine the median time to onset of myocarditis after the initiation of ipilimumab plus pembrolizumab combination therapy due to quite limited report available for time calculation in the FAERS database, and that may be partly because this combined therapy has not been approved by the FDA for wide application and is still in the clinical trial stage [9,10]. Further surveillance about new ICI regimens is needed.

To further investigate differences in the severity of myocarditis associated with ICIs, the rates of fatality due to myocarditis following various ICI regimens were assessed and compared. It was observed that myocarditis generally portended poor outcomes with approximately half of cases (51.11%) resulting in death. With respect to monotherapy, nivolumab appeared to present the relatively high fatality rate (50.40%), while atezolizumab appeared to have the relatively low fatality rate (22.22%). The risk of fatality was higher in patients who developed myocarditis after receiving ipilimumab plus nivolumab combination therapy than in those who received nivolumab monotherapy (65.75% vs 50.40%, $p = 0.036$), which is in line with the results of previously published case series that also reported more frequent death due to myocarditis associated with 2-ICI regimen [15,37,45]. Based on the study by Salem et al., ICI combination therapy was the only fatality-related risk factor for ICI-associated myocarditis [34]. However, it is difficult to accurately determine the risk of death due to the use of avelumab or durvalumab monotherapy as well as the ipilimumab plus pembrolizumab combination therapy, because only 3 or 4 available reports were collected for each regimen, and the continued surveillance is needed.

As the application of immune therapies continues to rise in oncology, it is necessary for practising clinicians to be vigilant for ICI-associated myocarditis and the different characteristics of that myocarditis across ICI regimens. Early screening is encouraged to be applied to patients with risk factors, at least when the use of combination therapy is intended [19]. The present findings need to be considered in clinical decisions on ICI treatment and in further clinical trials regarding various ICI regimens.

Although the data mining techniques used in this study have many advantages, it should be noted that this method cannot solve all the problems with the detection and analysis of adverse drug reaction signals based on spontaneous reporting systems. Therefore, unavoidably, this study has certain limitations. First, data mining technology cannot remedy the inherent limitations of SRSs, such as underreporting, false reporting, incomplete reporting, inaccuracy and arbitrariness, all of which might result in reporting bias. Second, SRSs are only used in qualitative research and cannot quantify the adverse reaction signals of myocarditis based on the total number of adverse

reactions and cannot calculate the incidence of ICI-associated myocarditis. Due to a lack of information in the FAERS database, it is difficult to control for confounding factors such as age, indication for drug use, pre-existing cardiovascular diseases, comorbidities or other factors that might have an impact on the myocarditis risk. Third, although data mining techniques can provide a profile of ICI-associated myocarditis through signal detection, it in itself is generally insufficient to prove a causal relationship. While pharmacovigilance studies using the FAERS database have limitations, as mentioned above, they are able to identify signals between ICI regimens and myocarditis, which provides clues for further well-organized clinical studies with respect to ICI-associated myocarditis.

5. Conclusions

Our analysis of the FAERS database identified signals for myocarditis associated with various ICI regimens in real-world practice. The clearest finding to emerge from this study is that avelumab was noteworthy for its relatively stronger association with myocarditis than other ICI monotherapies, while combined ICI regimens presented stronger associations with myocarditis than did monotherapies. Moreover, myocarditis associated with the ipilimumab plus nivolumab treatment appeared to have earlier onset and higher fatality rate than those associated with nivolumab monotherapy. Further pharmacoepidemiological studies are required to test the hypotheses generated by this study. Our findings provide a foundation for continued surveillance and investigation into this matter.

Authors' contributions

QF designed the research, analyzed and interpreted data, plotted figures, and wrote the manuscript draft. YH participated in the interpretation of data and writing of the manuscript draft. CY participated in the study design and collected data. BZ designed and directed the research, and corrected the manuscript.

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Data accessibility statement

All data have been presented in the tables and figures. Other related information is available under request to the corresponding author.

Declaration of competing interest

The authors declare that they have no competing interests.

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