Immune Checkpoint Inhibitors-related Myocarditis in Patients With Cancer: an Analysis of International Spontaneous Reporting Systems

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Abstract

Background: Immune checkpoint inhibitors induced myocarditis presents unique clinical challenges. Here, we assessed post-marketing safety of PD-1, PD-L1 and CTLA-4 inhibitors by mining the real-world data reported in two international pharmacovigilance databases.

Methods: We analyzed immune checkpoint inhibitors (ICIs)-associated fatal adverse drug events (ADRs) reports from the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) collected from July 1, 2014, to December 31, 2019, and data from EudraVigilance (EV) database accessed on February 29, 2020. Three different data mining methods were used to detect the signal of five fatal toxic effects caused by ICIs.

Results: Based on 7613 ICIs-related ADEs reported to the EV database and 5786 ICIs-associated ADEs submitted to the FAERS database, the most frequently reported ADEwasipilimumab-related colitis. For myocarditis, nivolumab-associated myocarditis was the most common. Among the five fatal toxic effects associated with ICIs, the lethality rate of myocarditis was the highest. Elderly patients and male patients were more likely to develop ICIs-related myocarditis.The results of signal detection showed that the risk of avelumab-related myocarditis detected by reporting odds ratio (ROR) method and proportional reporting ratios (PRR) method was the highest, whereas the signal strength of ipilimumab-related myocarditis detected by Bayesian confidence propagation neural networks (BCNPP)method was the strongest.

Conclusion: The findings of this study showed the risk of developing myocarditis and other fatal ADRs when using ICIs, which are consistent with the results of previous clinical trials and can provide a reference for clinical workers when using ICIs.

Introduction

Immune checkpoint inhibitors (ICIs), such as cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), programmed cell death-1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors that can inhibit the co-inhibitory immune checkpoint pathways have completely changed the treatment landscape of many different malignant tumors[1]. However, with the applications of ICIs increasing, immune-related adverse events (irAEs) associated with ICIs can be induced [2, 3]. These irAEs may affect any body system and organ, such as skin, lung, liver, gastrointestinal tract and so on[4–6]. Though the severe adverse events (AEs) related to ICIs remaining rare, they can be fatal if these side effects cannot be aware by clinicians when using these agents. A systematic review and meta-analysis demonstrated that the fatal ICIs-associated AEs were mainly colitis, hepatitis, pneumonitis, myocarditis, and neurologic effects[4]. Among these fatal toxic effects, myocarditis had the highest fatality rate because it might cause fatal heart failure, arrhythmias and so on, thus drawing people's attention to this incident. Another research also highlighted the high mortality rate of severe ICIs-associated myocarditis[7]. However, the published articles about ICIs-related myocarditis are mainly from case reports[8, 9] and clinical trials[10], which usually cannot detect the rare adverse drug reactions (ADRs) and reflect the real risk of ICIs-associated AEs when patients receiving ICIs treatment. Therefore, the risks of fatal ICIs-related myocarditis are necessary to be further investigated based on the data from the real-world.

The US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) is one of the international spontaneous reporting systems, that is designed to support the FDA's post-marketing safety surveillance program for drugs approved by the FDA. This database includes all information on adverse drug events (ADEs) and medication errors collected by the FDA. EudraVigilance (EV) is another international spontaneous reporting pharmacovigilance database for ADEs maintained by the European Medicines Agency. Data from these databases can be acquired by the public and utilized to provide evidence for the safe use of the drugs, especially for newly marketed drugs and uncommon ADRs. The objective of this study is to analyze the several ICIs-associated fatal ADRs, especially myocarditis, and to determine the signals of ICIs-associated myocarditis by mining the data reported in the FAERS database.

Methods

Data sources

In this study, seven ICIs namely pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab, cemiplimab and ipilimumab were chosen as the study drugs. Given that the drug names in the EV and FAERS databases are not standardized, all drug names of ICIs were unified into generic names through DrugBank before data analysis. Spontaneous ADE reports related to ICIs were retrieved from July 1, 2014 to December 31, 2019 in the FAERS database (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html), and EV (http://www.adrreports.eu/en/search.html) was accessed and queried on February 29, 2020. All ADEs reported in these databases are coded by preferred terms (PTs) from the Medical Dictionary for Drug Regulatory Activities (MedDRA). Fatal ICIs-associated ADRs including myocarditis, colitis, hepatitis, pneumonitis, and nephritis were analyzed in this study by signal-detection algorithms.

Only FAERS, can realize signal detection by using open database, but if you pay for it, other databases can also do it. Therefore, this study used the open database to obtain the total number of fatal ICIs-associated ADRs in two major databases, the fatality rate caused by ICIs-associated ADRs in EV database, the age and gender distribution of ICIs-associated myocarditis in EV and FAERS databases, and the signal detection of five fatal ICIs-associated ADRs in FAERS database.

Data mining algorithm

The data mining methods used to detect the ADR signals in spontaneous reporting systems are mainly the disproportionality methods[11, 12], which are based on spontaneous reports submitted for a lot of drugs and ADRs[13].

To detect the ADRs signals, both Frequentist (non-Bayesian) methods and Bayesian methods were used to calculate disproportionality by using reporting odds ratio (ROR)[14], proportional reporting ratios (PRR)[15] and information component (IC) of Bayesian confidence propagation neural networks (BCNPP)

[16], which are mainly based on a two by two contingency table (Table 1).

Table 1
A 2 × 2 Contingency Table for Disproportionality Analysis

Database	Target AEs	All other AEs	Total
Target drug	a	b	a + b
All other drugs	c	d	c + d
Total	a + c	b + d	a + b + c + d
Abbreviations: AEs, adverse events.			

The calculation formulas of ROR and PRR are ROR=(a/c)/(b/d), PRR = a(c + d)/c(a + b), respectively. BCNPP method uses the Bayesian discrimination principle based on the fourfold table. The core of the BCNPP method is to calculate IC. The calculation formula of the IC is IC = $\log_2\left(\frac{P_{x,y}}{P_x P_y}\right)$ .For ROR and PRR, the signal judgment criteria are a ≥ 3 and the lower bound of the 95% two-sided CI > 1. For the IC, the conditions for signal generation are IC > 0 and the lower bound of the 95% two-sided CI > 0.

Results

Descriptive analysis

During the study period, a total of 7613 fatal ICIs-associated ADRs were reported to the EV system: 2849 (37.42%) for colitis, 2806(36.85%) for pneumonitis, 1022(13.42%) for hepatitis, 625(8.21%) for myocarditis, and 311(4.09%) for nephritis. The 7613 reports consisted of 2962(38.91%) for nivolumab, 1664(21.86%) for pembrolizumab, 1935(25.24%) for ipilimumab, 725(9.52%) for durvalumab, 272(3.57%) for atezolizumab, 40(0.53%) for avelumab, and 15(0.20%) for cemoplimab (Fig. 1A,1B,1C). Besides, the FAERS database received a total of 5786 fatal ICIs-associated toxic effects. The total numbers of ADR cases for colitis, pneumonitis, hepatitis, myocarditis, and nephritis were 2378(41.10%), 1939(33.51%), 666(11.51%), 610(10.54%), and 193(3.34%), respectively. The most frequently reported drug was nivolumab (2599,44.92%), followed by ipilimumab (1946,33.63%), pembrolizumab (558,9.64%), atezolizumab (527,9.11%), durvalumab (83,1.43%), avelumab (55,0.95%), and cemoplimab (18,0.31%) (Fig. 1D,1E,1F). We noted that the most frequently reported fatal ICIs-associated ADR was ipilimumab-related colitis, which was 1257 cases of EV database and 1091 cases of the FAERS system. Taken together, among the five fatal ICIs-associated ADRs, colitis caused by ipilimumab was the most common.

Lethality rates of five fatal ICIs-related ADRs

To determine the fatal risk, we measured the lethality rates of five fatal ICIs-related ADRs reported in the EV database. We found that although the incidence rate of myocarditis was relatively low, the fatality rate of myocarditis was the highest. The average fatality rate of myocarditis caused by the target drugs was 21,76%. Besides, we noted that the lethality rate of myocarditis caused by avelumab was the highest (50%), followed by pembrolizumab (26.55%). Moreover, although the incidence rate of ICIs-related colitis was high, its fatality rate was low. The fatality cases of cemiplimab were 0, which might be due to its short time on the market. To sum up, the fatality rate of myocarditis was the highest, which is consistent with the results of the previous study[4] (Fig. 2).

Characteristics of the patients with ICIs-related myocarditis

Given that the fatality rate of myocarditis was the highest, we analyzed the characteristics of the patients with ICIs-related myocarditis reported in two spontaneous reporting pharmacovigilance systems. We found that patients over 64 years old are more likely to suffer ICIs-associated myocarditis, especially aged between 65 and 85 years old. Besides, in terms of gender distribution, male patients were more likely to develop myocarditis than female patients (Table 2).

Table 2
Gender and Age Distribution of ICIs-Related Myocarditis

	Pembrolizumab		Nivolumab		Atezolizumab		Avelumab		Durvalumab		Cemiplimab		Ipilimumab	
	EV	FAERS	EV	FAERS	EV	FAERS	EV	FAERS	EV	FAERS	EV	FAERS	EV	FAERS
Total	177	46	296	309	26	70	2	16	18	11	2	13	104	155
Age distribution														
< 18Y	0	6	0	43	0	5	0	1	0	1	0	3	0	20
18-64Y	37	14	55	93	11	33	0	7	3	0	0	0	19	41
65-85Y	96	26	82	176	2	31	2	9	8	5	0	0	28	96
> 85Y	6	6	3	3	0	0	0	0	1	1	0	0	0	0
Unknown	38	0	156	0	3	0	0	0	6	0	2	0	57	0
Gender distribution														
Female	50	15	94	113	12	27	0	5	5	0	0	0	34	53
Male	117	25	188	172	14	40	2	10	11	10	0	10	65	89
Unknown	10	6	14	24	0	3	0	1	2	1	2	1	5	13

Abbreviations: EV, EudraVigilance; FAERS, Food and Drug Administration (FDA) Adverse Event Reporting System.

Signal mining of ICIs-associated myocarditis

ROR, PRR, and BCNPP methods were used to detect the signal values of myocarditis associated with ICIs in the FAERS database. Similar results emerged by using ROR and PRR methods: the ROR value of myocarditis was 28.07 (95%CI 17.13,46.02) for avelumab, and the PRR for myocarditis was 27.74 (17.02,45.19) avelumab. The signal value of avelumab-related myocarditis was the highest, whereas the signal value of pembrolizumab-related myocarditis was the weakest [11.44(8.57,15.31) for ROR and 11.39(8.52,15.22) for PRR] (Fig. 3A,3B). The highest signal value measured by the IC method was ipilimumab-related myocarditis [4.33(4.09,4.57)] (Fig. 3C). It was worth noting that the IC025 of cemiplimab-related myocarditis was less than 0, so there was no signal generated.

Also, we use the signal mining methods to detect the signal values of the other four fatal ADRs and found that the signal value of ipilimumab-related colitis was the highest, followed by atezolimumab-related nephritis (Supplementary material, Table S1).

Discussion

There is no doubt that immunotherapy based on ICIs are the biggest breakthrough in the field of tumor treatment in recent years, which has brought a satisfactory efficacy for the patients with advanced or refractory tumors and greatly improved the prognosis of the tumor patients. However, the global increase in ICIs use not only brings a satisfactory curative effect for tumor patients but also brings a unique spectrum of fatal toxic side-effects, such as myocarditis, colitis, pneumonitis, hepatitis, and nephritis[5]. Although the risk for mortality of ICIs-related fatal ADRs is lower than common oncologic interventions, clinicians need to raise the awareness of the severity of these toxic effects.

Since human cardiomyocytes express immune checkpoint receptors, ICIs may cause fatal myocarditis while eliminating cancer cells[17]. Several studies reported that the myocarditis associated with PD-1/PD-L1 inhibitors occurred to melanoma patients, which has aroused people's attention[18–20]. A preclinical research revealed that the left ventricle ejection fraction and global radial strain in transplantable melanoma mice treated with anti-PD-1 antibodies were reduced, compared to the control group, and the analysis of metabolites and lipids indicated dysfunctional energy metabolism, suggesting that immunotherapy based on PD-1 can disturb cardiac function and disrupt cardiomyocyte functional integrity[21]. Javid JJ et al.[7] identified 101 cases of reports submitted to WHO-Vigibase. In these 101 reports of patients with severe myocarditis after treatment with ICIs, most patients (57%) received anti-PD-1 monotherapy, while 27% of patients received anti-PD-1/PD-L1 plus anti-CTLA-4 combination therapy. The results of this study showed that 46 patients died, and the mortality rate of patients with combination therapy was higher than that of patients with monotherapy[7]. It was worth noting that there were 3 deaths in 5 patients because of ipilimumab-related myocarditis and the reporting of AEs has increased dramatically over time. Besides, Wang DY et al.[4] retrieved 3545 ADRs reports related to immunosuppressive therapy from 7 academic centers in the WHO-Vigbase database, and systematically reviewed the published researches involved in ICIs. They found that the death of patients treated with anti-PD-1 and anti-CTLA-4 antibodies was usually caused by colitis [32 (37.0%)] and myocarditis [22 (25.0%)], and the fatal toxic effects usually occurred early after therapy initiation for combination therapy. Among these fatal ADRs, the lethality rate of myocarditis was the highest [39.7% (52 of 131 reported cases)]. Furthermore, Mahmood SS et al.[10] created a multicenter registry with 8 sites after observing sporadic cases of ICIs-related myocarditis. 35 patients with ICIs-associated myocarditis were compared with a random sample of 105 patients without myocarditis treated by ICIs. All patients (29% for female patients) were 65 ± 13 years old, and 54% of patients had no other irAEs. The results showed that the prevalence of myocarditis was 1.14% and the median time of onset was 34 days (interquartile range: 21 to 75 days). Taken together, assessing the marketing safety of target drugs by mining the real-world data reported in pharmacovigilance databases is of great significance, and we can fully understand the safety profiles of target drugs by signal detection.

In this study, we analyzed spontaneous reports of five fatal ADRs related to seven ICIs submitted to EV and FAERS databases, and detect signals of ICIs-associated ADRs by data mining methods. The findings showed that a total of 7613 fatal ICIs-associated ADEs were reported to the EV database, whereas a total of 5786 fatal toxic effects related to ICIs were submitted to the FAERS database. Among these ADRs, the numbers of ICIs-associated myocarditis were 625 for the EV system, and 507 for the FAERS system, respectively. Although the prevalence rate of myocarditis was not the highest, its risk for lethality was the highest, especially the mortality rate of avelumab-related myocarditis was as high as 50%, suggesting that clinicians should take notice of these toxic effects when using immune strategies based on ICIs for tumor patients. We also noted that the most frequently reported ADR was colitis, which was consistent with the results of several systematic reviews[4, 22, 23]. Besides, we found that elderly patients (older than 65-year-old), especially those aged between 65 and 85 years old, were more likely to suffer from myocarditis compare to young patients by analyzing the characteristics of the patients developed myocarditis associated with ICIs, which can be partially explained by the fact that the immune function of elderly is low and the tumor incidence rate of elderly is higher than young people. Gender distribution of patients with ICIs-related myocarditis showed that male patients are more likely to develop myocarditis compared to female patients, suggesting that male patients have a higher risk of myocarditis caused by ICIs, which may be associated with that men play a dominant role in the development of acute myocarditis(sex ratio = 6.75)[7]. And this finding may also be related to the fact that the incidence rate and mortality rate of malignant tumors in males were higher than those in females[24]. Furthermore, the results of signal mining showed that the signal value of avelumab-related myocarditis detected by ROR and PRR methods was the highest, and the highest signal value measured by the IC method was ipilimumab-related myocarditis, suggesting that there is a high risk of myocarditis caused by avelumab or ipilimumab. The fatality cases of cemiplimab-related myocarditis were 0 and there was no signal generated, which may be related to its short time on the market, and further study needs to be explored the risk of cemiplimab-related ADRs. Among these ADEs, the signal value of ipilimumab-related colitis was the highest by using both three data mining methods, which is consistent with the conclusion that colitis is the most common ADE of treatment with CTLA-4 inhibitors (ipilimumab)[5].

This study is mainly to analyze the post-marketing safety of ICIs and detect signals of ICIs-associated myocarditis reported in EV and FAERS databases via ROR, PRR, and BCNPP methods. The data of this study were obtained from two international pharmacovigilance databases in the real world, which could provide evidence for the safe use of ICIs to some extent. However, this study has several limitations. First of all, the ADR reports submitted to the EV database and FAERS database usually conclude missing data, duplicate data, the irregular spelling of drug and ADR names, and so on. And most ADRs reports come from America and Europe, while there are few data from Asia or Africa. Secondly, although the pharmacovigilance databases are recognized as an important tool to assess the post-marketing safety of drugs by data mining algorithm and the signal detected by data mining methods indicated that the target drug and the target ADR are statistically correlated, that does not mean the target drug and the target ADR have a biological causal relationship, which needs to be further observation and verified through several large-scale clinical trials.

Despite the limitations, the results of this study showed that the application of ICIs is associated with an increase in fatal toxic effects, especially myocarditis, which is consistent with previous studies. It is suggested that clinicians should pay attention to these fatal ICIs-associated ADRs and take preventive measures when treating tumor patients with immunotherapy based on ICIs. The findings of this study also provided objective evidence for post-marketing safety of ICIs, so as to ensure the safe use of these drugs and improve the prognosis of patients with cancer.

Abbreviations

ICIs, immune checkpoint inhibitors; ADRs,adverse drug events;FDA, Food and Drug Administration; FAERS,FDAAdverse Event Reporting System;EV, EudraVigilance;ROR,reporting odds ratio; PRR,proportional reporting ratios;BCNPP,Bayesian confidence propagation neural networks;ICIs, immune checkpoint inhibitors; CTLA-4, cytotoxic T-lymphocyte-associated protein-4; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1;irAEs,immune-related adverse events;AEs,adverse events;ADEs,adverse drug events;PTs,preferred terms;MedDRA,the Medical Dictionary for Drug Regulatory Activities;IC,information component.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published articleand its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

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None.

Authors' contributions

RulanMa collectedthe data,wrote the manuscript. Quanziang Wang and Deyu Meng analyzed the data. Kang Li and Yong Zhang designed this study and reviewed the manuscript.

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Figures

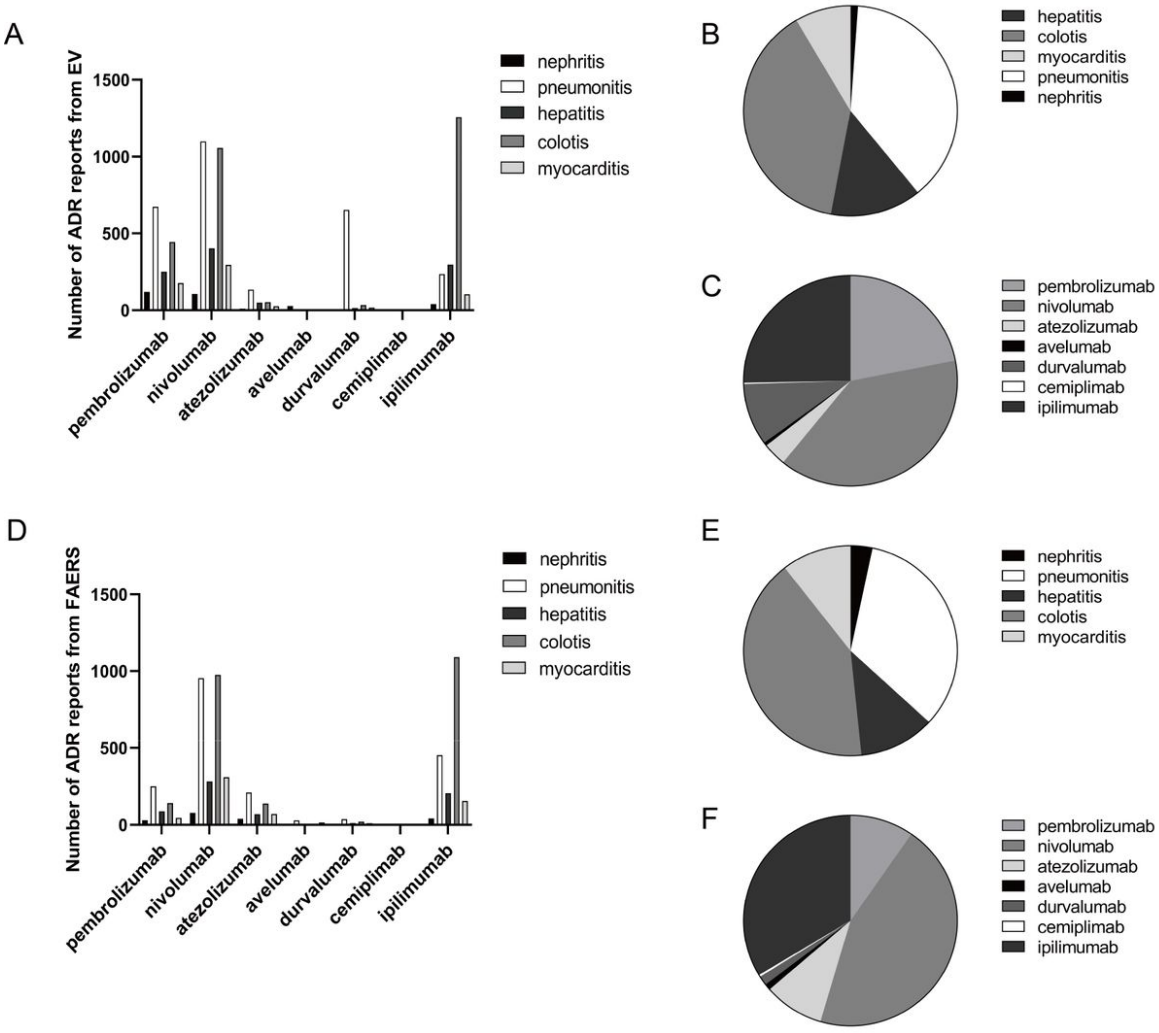

Figure 1

The number of ICIs-associated ADR reports submitted to FAERS and EV databases. (A) The number of ICIs-related ADR reports submitted to EV database. (B,C) The proportion of different ICIs-related ADR reports from EV database. (D) The number of ICIs-related ADR reports submitted to FAERS database. (E, F) The proportion of different ICIs-related ADR reports from FAERS database. ADR, adverse drug reaction; EV, EudraVigilance; FAERS, Food and Drug Administration (FDA) Adverse Event Reporting System.

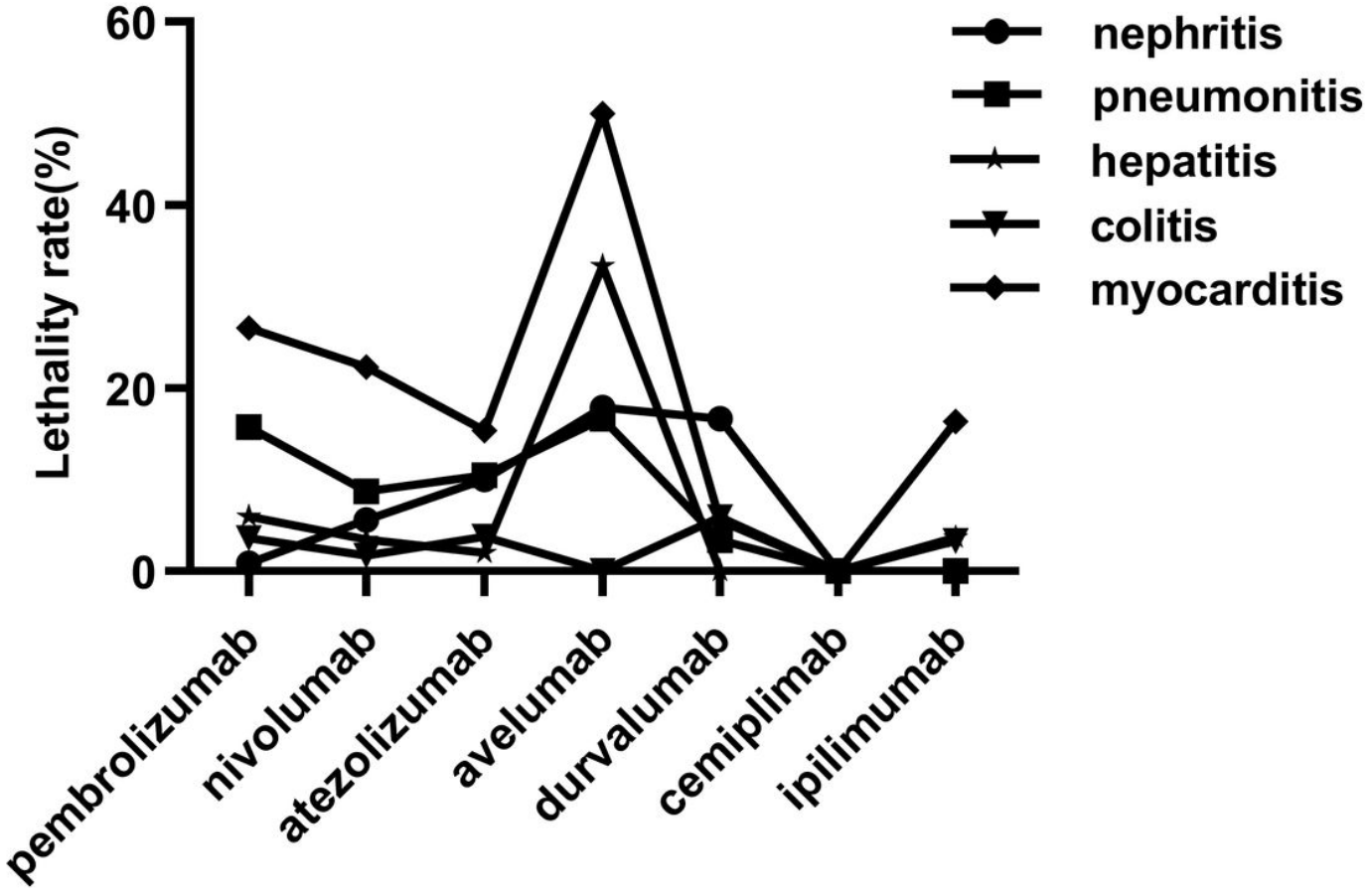

Figure 2

Lethality rates of five fatal ICIs-associated ADRs.

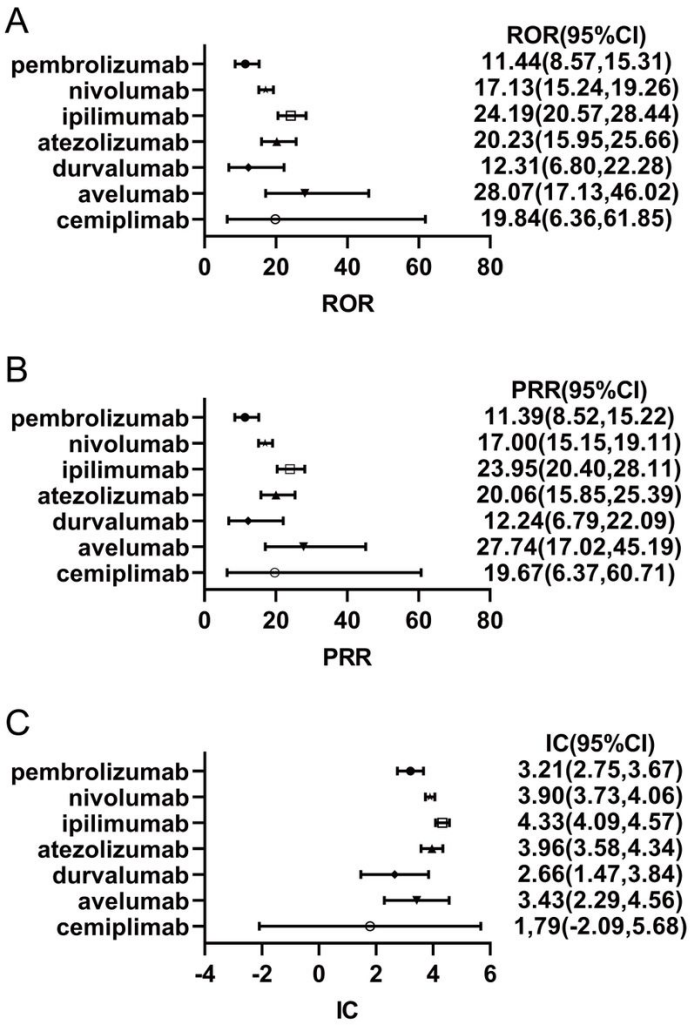

Figure 3

Signal values of ICIs-associated myocarditis. (A) Singal values of ICIs-related myocarditis was detected by using ROR method. (B) Singal values of ICIs-related myocarditis was detected by using PRR method. (C) Singal values of ICIs-related myocarditis was detected by using IC method. ROR, reporting odds ratio; PRR, proportional reporting ratios; IC,information component.

Supplementary Files

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