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Retrospective analysis of pembrolizumab-related adverse reactions and death outcomes based on the FAERS database

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Abstract

Objective This study aimed to analyze the characteristics of adverse reactions in cancer patients treated with Pembrolizumab based on the U.S. Food and Drug Administration's Adverse Event Reporting System (FAERS) database, and to assess the characteristics and risk factors of fatality reports.

Methods The study data was sourced from the FAERS database, collecting adverse event reports related to Pembrolizumab from 2013 to June 2024. The main analysis variables included gender, age, cancer type, country, reporter type, and adverse reaction outcomes. Descriptive statistics, univariate analysis, and multivariate Logistic regression models were used to assess the relationship between each variable and fatal outcome.

Results A total of 46,883 adverse reactions were collected, including 5,483 reports with fatal outcomes. The number of events has been increasing since 2013, especially peaking in 2022 and 2023. The United States and Japan had the highest number of adverse reaction reports. The number of serious events reported increased significantly with age, especially in the 51–65 and 66–80 age groups. The age of patients who died was concentrated in the elderly group (≥ 65 years old), and the median treatment duration time of pembrolizumab was 17 days. Analysis showed that gender (OR = 0.75; 95%CI: 0.71–0.80, $p < 0.01$), age (OR = 0.89; 95%CI: 0.84–0.96, $p < 0.01$), and ingredients count (OR = 1.92; 95%CI: 1.84–2.01, $p < 0.01$) were significantly associated with the treatment duration of pembrolizumab.

Conclusion The serious adverse reactions in cancer patients treated with Pembrolizumab are closely related to patient individual characteristics and cancer types. It is necessary to strengthen the monitoring of high-risk groups such as the elderly in clinical treatment to reduce the risk of fatal outcomes.

Keywords Adverse reactions, Immunotherapy, Pembrolizumab, Prognostic factors, FAERS

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Introduction

Pembrolizumab is a monoclonal antibody targeting the immune checkpoint programmed death receptor 1 (PD-1) [1]. In the field of cancer treatment, pembrolizumab has triggered a revolution in immunotherapy, especially in the treatment of a variety of advanced and metastatic tumors [2, 3]. Since it was first approved by the U.S. Food and Drug Administration (FDA) for the treatment of advanced melanoma in 2014 [2, 4], the indications of pembrolizumab have gradually expanded to multiple tumor types, including non-small cell lung cancer [5], head and neck cancer [6], and hepatocellular carcinoma [7]. Its wide application further establishes the advantages of immune checkpoint inhibitors (ICIs) in modern tumor treatment.

Although pembrolizumab has significant anti-tumor activity and improves the overall survival of multiple tumors, its accompanying immune-related adverse events (irAEs) have also received increasing attention [8]. Compared with traditional chemotherapy or targeted therapy, ICIs induce a wide range of irAEs, involving multiple organ systems, including the skin, gastrointestinal tract, liver, endocrine system, lungs, and heart [8]. These irAEs are usually highly heterogeneous, ranging from self-limiting rashes or fatigue to fatal complications such as immune myocarditis, myasthenia gravis, and acute liver failure [9]. Therefore, how to timely identify, intervene, and manage these adverse reactions has become an important direction in clinical tumor treatment.

The U.S. FSA Adverse Event Reporting System (FAERS) is a global voluntary reporting database for adverse drug events [10], providing a valuable real-world data resource that can help us identify and evaluate adverse reactions of drugs in a wide range of populations. Through a large-scale retrospective analysis of the FAERS database, healthcare providers may capture the spectrum of adverse reactions associated with pembrolizumab, especially those rare or serious adverse events that may not be fully reflected in clinical trials.

Existing studies have shown that the incidence of adverse reactions to pembrolizumab varies with individual patient differences and different medication regimens [11, 12]. For example, elderly patients and patients with certain specific cancer types may be more susceptible to severe immune-related adverse reactions [13]. In addition, drug use patterns and adverse drug reaction reporting systems in different countries and regions may also affect the reporting frequency and pattern of adverse events [14]. Therefore, in-depth analysis of adverse reactions in pembrolizumab treatment combined with real-world data from different populations and regions is worthy for optimizing tumor immunotherapy strategies and improving patient safety.

The purpose of this study is to systematically review the adverse reaction reports of pembrolizumab treated cancer patients in the FAERS database, focusing on the characteristics of adverse reactions in patients who died. By evaluating the differences between patients with severe adverse reactions and those with non-serious adverse reactions in terms of baseline characteristics, cancer type, adverse reaction spectrum, and reporter type, we aim to reveal potential factors that may be associated with the severity of adverse reactions and provide real-world evidence for clinical treatment.

Methods

Data source

The data for this study came from the FAERS database. FAERS is a spontaneously reported adverse event database that is regularly updated and open to the public, and contains reports of various adverse reactions that occur after the use of drugs [15]. This study collected all adverse reaction reports related to pembrolizumab from January 2013 to June 2024. Although Pembrolizumab was approved for clinical use in 2014, adverse event reports related to the drug were included in the FAERS database starting from 2013, reflecting reports from clinical trials and investigational use before its official market approval. These reports include patient demographic characteristics, drug information, cancer type, severity of adverse reactions, event outcomes (such as death or non-death), reporter type, and the country where the event occurred.

Data filtering

The steps of data screening are shown in Fig. 1. In order to ensure the accuracy of the data and the relevance of the research, this study screened the data according to the following criteria:

Inclusion criteria: All adverse event reports that identified pembrolizumab as "Primary Suspect Drug" (PSD) were screened, and the outcome of the adverse reaction (death or non-death) must be clearly stated in the report. This study specifically focuses on reports where the patient experienced a fatal outcome, and the death was considered possibly related to pembrolizumab treatment. Not all patients in the study had fatal outcomes.

Exclusion criteria: Reports lacking key information (such as age, gender, event outcomes, etc.) and reports with duplicate records were excluded. All included reports were strictly deduplicated to ensure that each patient's report was unique.

Adverse reaction classification

Adverse events were coded and classified according to the Preferred Terms (PT) of the International Medical Dictionary for Respiratory Diseases (MedDRA), and further classified into the corresponding System Organ

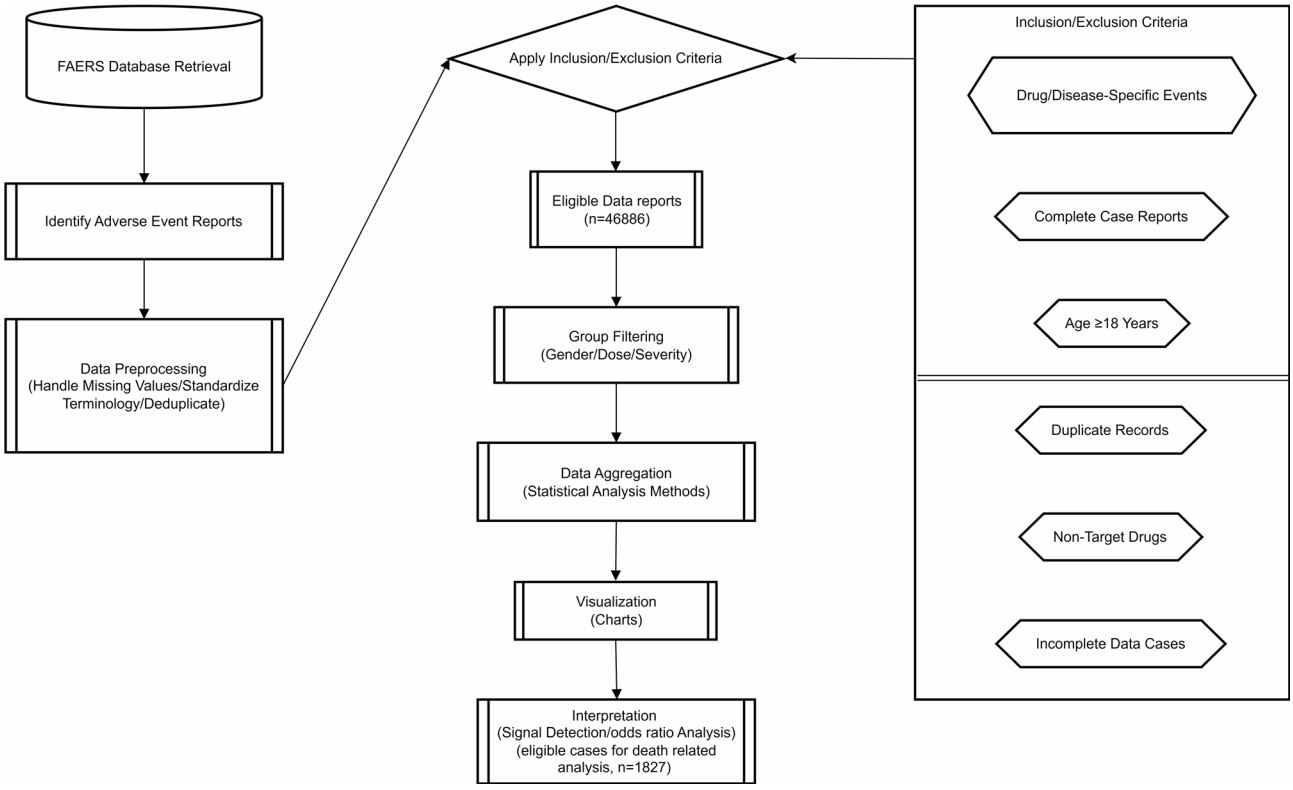

Fig. 1 Flow chart of identifying eligible reports

Class (SOC) [15]. Serious adverse events (SAEs) and non-serious adverse events (NSAEs) were focused on, and death reports were analyzed according to event outcomes. Case priority events refer to adverse reactions that are classified as requiring expedited reporting due to their severity and potential impact on patient safety, as defined by the FAERS database [15].

Statistical analysis

Data processing and statistical analysis were performed using R 4.4.1 and python 3.12 software. The classification of adverse reaction types used the MedDRA terminology set, and data were extracted using the FAERS dashboard [16]. Baseline characteristics of all patients and adverse events included in the study were analyzed. Continuous variables were described using mean ± SD or median (interquartile range, IQR), and categorical variables were expressed as frequency. The differences between groups in categorical variables were analyzed using the Chi-square test or Fisher's exact test, and independent sample t-test or Mann-Whitney U test were used for continuous variables. Logistic regression models were used to evaluate the associations between gender, age, cancer type, and reporting country with adverse reaction outcomes (SAEs or NSAEs). The results were expressed as odds ratios (OR) and their 95% confidence intervals (CI). The Proportional Reporting Ratio (PRR), Reporting Odds Ratio (ROR), and Relative Reporting Ratio (RRR) are key statistical measures used in pharmacovigilance to detect signals of adverse drug reactions (ADRs) [17]. PRR compares the frequency of an adverse event for a specific drug to other drugs, highlighting potential safety concerns when the ratio is greater than 1. ROR assesses the odds of an adverse event being reported for a drug compared to all other drugs, suggesting a possible association if the value is significantly greater than 1. RRR quantifies the relative incidence of adverse events for a specific drug, providing insights into its relative safety profile. To analyze the risk factors of death, subgroups were set according to treatment duration time for analysis to further explore the risk factors that may affect the duration time of pembrolizumab. All analyses were considered statistically significant at $p \leq 0.05$.

Results

Overall trends of pembrolizumab related adverse events

This study collected a total of 46,883 adverse event reports related to pembrolizumab, including 43,131 serious adverse events (SAEs), accounting for approximately 91.98%, and 3,752 non-serious adverse events (NSAEs), accounting for approximately 8.02%. From 2013 to 2023, the number of adverse event reports (Fig. 2A) and the number of deaths (Fig. 2B) of pembrolizumab showed

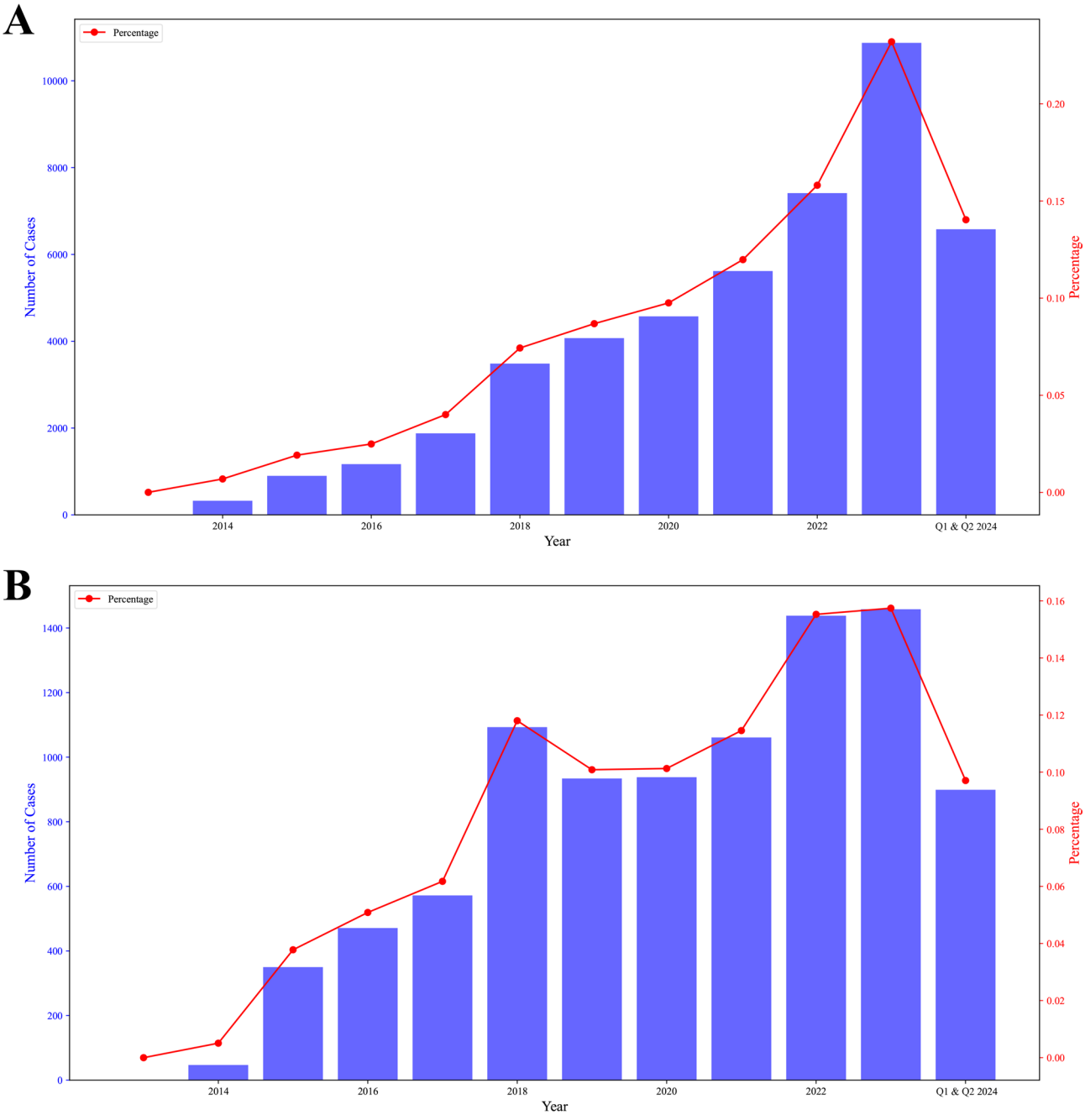

Fig. 2 Overall trends of pembrolizumab related adverse events in recent years. **A** number of adverse events by years (2013–2023 and 2024 Q1-Q2); **B** number of died cases by years (2013–2023 and 2024 Q1-Q2)

an upward trend, especially in 2022 and 2023, when the reports reached a peak.

Patient characteristics

In terms of gender (Fig. 3A), the cumulative number of adverse event reports in male patients was higher than that in female patients (57452 for male vs. 51422 for female). Although the overall number of adverse event reports in male patients was higher, certain adverse reactions, such as Social Circumstances, Endocrine Disorders, and Reproductive System and Breast Disorders, were more commonly reported in females. For outcomes, high-risk outcomes (hospitalizations, life-threatening events) demonstrated exponential growth (43% annual increase) from 2013 to 2023, peaking at 5,535 and 700 cases respectively (Fig. 3B). Anomalous 2023 surges (e.g., 6,754 "Other Outcomes") suggests systemic reporting inconsistencies or external interventions requiring

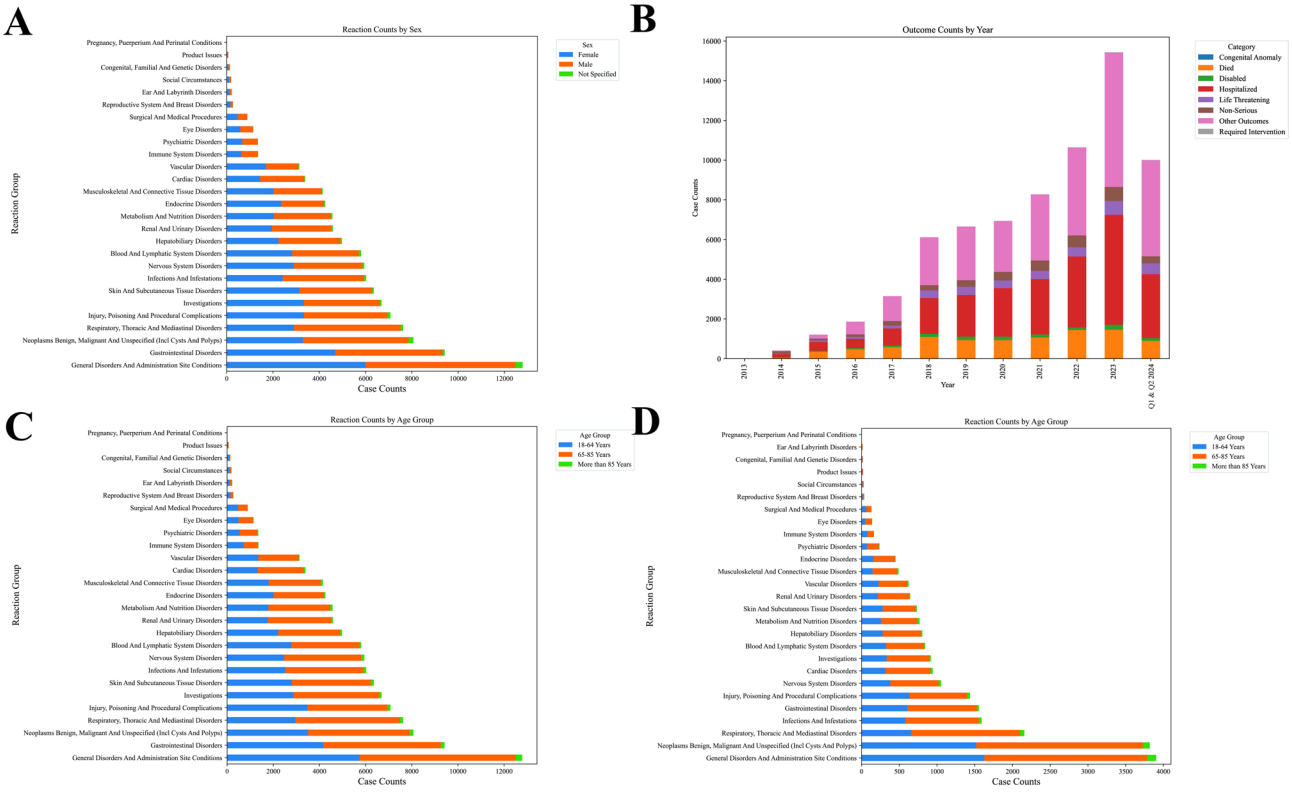

Fig. 3 General features of adverse events in patients treated with pembrolizumab. **A** number of cases in different reaction groups by sex; **B** number of various outcomes in different years (2013–2023 and 2024 Q1-Q2); **C** number of cases in different reaction groups by age; **D** number of died cases in different reaction groups by age

validation of data integrity and classification criteria (Fig. 3B). In terms of age, the incidence of serious adverse events in elderly patients (≥ 65 years old) was significantly higher than that in young patients, and the mortality rate in elderly patients was higher (Fig. 3C and D). In terms of adverse reaction types, the most common adverse reactions related to pembrolizumab included: progression of malignant tumors (6052, 12.91%), diarrhea (2412, 5.14%), death (2241, 4.78%), fatigue (2113, 4.51%), in addition to other adverse reactions such as loss of appetite, fever and rash (Fig. 3). In terms of geographical distribution, adverse event reports from Japan and the United States accounted for the largest proportion, with 12,616 cases reported in Japan and 11,045 cases reported in the United States, accounting for a total of 50.50% of global reports.

Analysis of risk factors related to serious adverse reactions

Logistic regression analysis showed that gender, age, and reporter type were significantly associated with the severity of adverse events. Specifically, the odds ratio of serious adverse events in female patients was 0.76 (95% CI: 0.73–0.79; $P < 0.01$), indicating that the risk of serious adverse events in female patients was significantly lower than that in male patients. The risk of elderly patients increased with age, with the odds ratio of serious adverse events increasing by 1.01 (95% CI: 1.007–1.011; $P < 0.01$) for every 1-year increase in patient age, indicating that age increase was statistically significantly associated with increased severity of adverse events. In addition, the severity of case priority events was significantly higher than that of other types, with an odds ratio as high as 2.47 (95% CI: 2.32–2.64; $P < 0.01$). At the same time, we also found that the odds ratios of regimen ingredient count of less than 2 (OR = 0.92; 95%CI:0.901–0.934; $P < 0.001$), and reporter type of medical staff (OR = 1.17; 95%CI:1.083–1.271; $P < 0.001$) showed statistical significance, suggesting that these factors may also be a risk factor for serious adverse events.

Baseline characteristics of deceased patients

After screening, 1827 death reports were finally included in the analysis (Table 1). Among the 1827 patients who died, 39.1% (715 cases) were female, 58.0% (1060 cases) were male, and 2.8% (52 cases) were of unknown gender. The most commonly used treatment regimen was single-agent pembrolizumab treatment, accounting for about 35.3% (645 cases). Among other treatment regimens, pembrolizumab combined with lenvatinib accounted for 20.9% (381 cases), and pembrolizumab combined with carboplatin and pemetrexed accounted for 7.5% (137

Table 1 Baseline characteristics of died patients related to adverse events of pembrolizumab by sex

Factors	Groups	Male (*N* = 1060)	Female (*N* = 715)	Unknown (*N* = 52)	Total (*N* = 1827)
Top 9 Regimen	Pembrolizumab	391 (36.9%)	208 (29.1%)	46 (88.5%)	645 (35.3%)
	Other	225 (21.2%)	121 (16.9%)	4 (7.7%)	350 (19.2%)
	Lenvatinib; Pembrolizumab	138 (13%)	243 (34%)	0 (0%)	381 (20.9%)
	Carboplatin; Pembrolizumab; Pemetrexed	107 (10.1%)	30 (4.2%)	0 (0%)	137 (7.5%)
	Carboplatin; Pembrolizumab; Taxane	50 (4.7%)	32 (4.5%)	0 (0%)	82 (4.5%)
	Axitinib; Pembrolizumab	26 (2.5%)	7 (1%)	0 (0%)	33 (1.8%)
	Pembrolizumab; Pemetrexed	16 (1.5%)	11 (1.5%)	1 (1.9%)	28 (1.5%)
	Cisplatin; Pembrolizumab; Pemetrexed	15 (1.4%)	7 (1%)	0 (0%)	22 (1.2%)
	Pembrolizumab; Taxane	92 (8.7%)	56 (7.8%)	1 (1.9%)	149 (8.2%)
Ingredient counts	1	391 (36.9%)	207 (29%)	46 (88.5%)	644 (35.2%)
	2	258 (24.3%)	301 (42.1%)	1 (1.9%)	560 (30.7%)
	3	262 (24.7%)	122 (17.1%)	0 (0%)	384 (21%)
	4	53 (5%)	47 (6.6%)	3 (5.8%)	103 (5.6%)
	5	37 (3.5%)	24 (3.4%)	2 (3.8%)	63 (3.4%)
	6	11 (1%)	5 (0.7%)	0 (0%)	16 (0.9%)
	7	4 (0.4%)	1 (0.1%)	0 (0%)	5 (0.3%)
	8	23 (2.2%)	3 (0.4%)	0 (0%)	26 (1.4%)
	9	21 (2%)	5 (0.7%)	0 (0%)	26 (1.4%)
Cancer related diagnosis	Cervix Cancer	364 (34.3%)	223 (31.2%)	5 (9.6%)	592 (32.4%)
	Cholangiocarcinoma	0 (0%)	1 (0.1%)	0 (0%)	1 (0.1%)
	Colorectal Cancer	22 (2.1%)	10 (1.4%)	1 (1.9%)	33 (1.8%)
	Endometrial Cancer	0 (0%)	145 (20.3%)	0 (0%)	145 (7.9%)
	Head And Neck Cancer	54 (5.1%)	9 (1.3%)	0 (0%)	63 (3.4%)
	Malignancy	52 (4.9%)	24 (3.4%)	44 (84.6%)	120 (6.6%)
	Melanoma	89 (8.4%)	66 (9.2%)	0 (0%)	155 (8.5%)
	Non-Small Cell Lung Cancer	329 (31%)	105 (14.7%)	2 (3.8%)	436 (23.9%)
	Renal Cancer	140 (13.2%)	45 (6.3%)	0 (0%)	185 (10.1%)
	Uterine Cancer	10 (0.9%)	87 (12.2%)	0 (0%)	97 (5.3%)
Case priority	Non-Expedited	120 (11.3%)	114 (15.9%)	0 (0%)	234 (12.8%)
	Expedited	934 (88.1%)	595 (83.2%)	52 (100%)	1581 (86.5%)
	Direct	6 (0.6%)	6 (0.8%)	0 (0%)	12 (0.7%)
Reporter type	Consumer	66 (6.2%)	42 (5.9%)	2 (3.8%)	110 (6%)
	Healthcare Professional	993 (93.7%)	672 (94%)	50 (96.2%)	1715 (93.9%)
	Not Specified	1 (0.1%)	1 (0.1%)	0 (0%)	2 (0.1%)
Age group	< median age	494 (46.6%)	415 (58%)	20 (38.5%)	929 (50.8%)
	≥median age	566 (53.4%)	300 (42%)	32 (61.5%)	898 (49.2%)
Age	Mean ± Standard Deviation	67.7 ± 10.6	64.0 ± 12.1	69.4 ± 9.3	66.3 ± 11.3
Treatment duration (days)	Mean ± Standard Deviation	67.8 ± 134.8	60.8 ± 133.7	163.4 ± 203.2	67.8 ± 137.7

Note: Other in Top 9 Regimen includes a variety of combination therapies that are less commonly used but still reported. Ingredient counts indicate the number of drugs in the treatment regimen (1 = single-drug, up to 9 = nine-drug combinations)

cases). Among the patients who died, non-small cell lung cancer (23.9%) and cervical cancer (32.4%) were the most common types of cancer. Melanoma patients accounted for 8.5%, and renal cancer patients accounted for 10.1%. 88.1% of the patient reports of deaths were classified as "expedited" treatment, and 93.9% of adverse events were reported by medical professionals. The mean age of patients who died was 66.3 years, with a standard deviation of 11.3 years. The mean age of female patients was 64.0 years, and the mean age of male patients was 67.7 years. The mean time to adverse events in patients who died was 67.8 days, with a standard deviation of 137.7 days, indicating that the time to adverse events was highly variable. In the distribution of the number of treatment components, 35.2% of patients received single-drug therapy, while the proportion of multidrug combination therapy was higher (60% of patients received combination therapy with more than two drugs).

Signal mining of adverse events in deceased patients

We analyzed the common pembrolizumab-related adverse events in patients who died and evaluated the signal strength of the top 50 adverse events based on indicators such as the proportional reporting rate (PRR),

relative risk ratio (RRR), and reporting odds ratio (ROR) (Table 2). These adverse events included immune-mediated hyperthyroidism (PRR = 621.98, RRR = 156.24, ROR = 622.32, $n = 3$), immune-mediated hypothyroidism (PRR = 552.87, RRR = 151.51, ROR = 556.10, $n = 32$), tumor pseudoprogression (PRR = 345.54, RRR = 130.20, ROR = 346.49, $n = 15$), and immune-mediated pneumonitis (PRR = 310.99, RRR = 124.99, ROR = 311.84, $n = 15$). Other adverse events with high frequency of reporting include immune-mediated renal disorder (PRR = 233.24, RRR = 110.29, ROR = 233.62, $n = 9$), immune-mediated hepatic disorder (PRR = 225.62, RRR = 108.56, ROR = 227.14, $n = 37$). Some adverse events have high signal strength but low number of reports. For example, immune-mediated pancreatitis and immune-mediated encephalitis have strong signals (ROR 88.90 and 168.85, respectively), but low number of reported events, suggesting that these events are relatively rare adverse reactions.

Analysis of treatment duration distributions in died patients

We divided the deceased patients into two groups according to the median duration time. The number of drug components (Fig. 4A), gender (Fig. 4B), age (Fig. 4C), and category of reporting personnel (Fig. 4D) were then analyzed. The results showed that various combination treatment regimens such as "carboplatin + pembrolizumab + pemetrexed" and "carboplatin + pembrolizumab + paclitaxel" showed a significant effect on the treatment duration. Compared with pembrolizumab monotherapy, these combination regimens were significantly associated with a shorter treatment duration (e.g., "carboplatin + pembrolizumab + paclitaxel" OR = 0.26, $p < 0.01$), suggesting that combination therapy may be associated with shorter treatment duration. As the number of drug components increased, the treatment time was also significantly reduced. Compared with a single component, a treatment regimen containing three components was significantly associated with a shorter duration time (OR = 0.40, $p < 0.01$). At the same time, patients who required expedited treatment showed a shorter pembrolizumab treatment time (OR = 0.53, $p < 0.01$), suggesting that expedited cases may be associated with earlier occurrence of adverse events (Table 3).

Discussion

This study, through a retrospective analysis of pembrolizumab-related adverse events in the FAERS database, revealed the diversity and severity of adverse reactions caused by this drug in tumor treatment, especially in elderly patients and male patients, where the incidence of serious adverse reactions (such as death) was significantly higher. Consistent with previous literatures [1, 7, 12], as an immune checkpoint inhibitor, irAEs caused by pembrolizumab involve multiple organ systems, including the gastrointestinal tract, skin, and endocrine system, suggesting that it needs to be closely monitored in clinical applications.

This study found that male patients reported a higher incidence of specific serious adverse events than female patients, especially in the death outcome group. Differences in the reactivity and physiological status of male patients may explain this phenomenon [18]. In addition, elderly patients (≥ 65 years old) are more susceptible to serious adverse reactions, especially in the presence of other chronic diseases or immunosuppression [19]. This result is consistent with the findings of existing studies [18, 19] that elderly patients have a higher incidence of adverse reactions after treatment with ICIs.

The above differences may be linked to immunosenescence and sex-related immune differences [20–22]. Immunosenescence, the gradual deterioration of the immune system with aging, is characterized by reduced T-cell function, chronic low-grade inflammation, and impaired immune homeostasis [23]. These changes could lead to an exaggerated immune response or increased susceptibility to irAEs when exposed to immune checkpoint inhibitors like pembrolizumab [24]. Previous studies have suggested that older patients may have a diminished ability to regulate immune activation, making them more prone to severe toxicities [25]. Sex differences in immune response have also been well-documented. Male patients typically exhibit lower baseline immune activation compared to females, which may partially explain why immune-related toxicities differ between sexes [26]. Additionally, combination therapies involving pembrolizumab and other agents may further modulate immune adverse events. Chemotherapy, for example, has been shown to increase tumor antigen release, thereby enhancing immune activation but also potentially triggering systemic inflammation [27]. Similarly, some tyrosine kinase inhibitors (TKIs) or anti-angiogenic agents used in combination with pembrolizumab could alter the tumor immune microenvironment [28, 29]. These interactions may explain why certain treatment regimens are associated with an increased risk of severe adverse events. Therefore, tailoring immunotherapy based on age, sex, and drug combinations may ultimately help improve outcomes while minimizing toxicities.

In this study, the most common adverse reactions associated with pembrolizumab included diarrhea, and fatigue, which were mainly caused by overactivation of the immune system. These results are highly consistent with irAEs reported in previous literatures [8, 12]. In particular, the death events suggests that pembrolizumab may cause severe immune system reactions in patients with advanced cancer. Based on this, clinicians should

Table 2 AEs signal detection in patients who treated with pembrolizumab

Adverse event	PRR	RRR	ROR	Event counts
immune-mediated hyperthyroidism	621.976	156.244	622.315	3
immune-mediated hypothyroidism	552.868	151.509	556.103	32
tumour pseudoprogression	345.542	130.203	346.486	15
immune-mediated adrenal insufficiency	345.542	130.203	346.171	10
immune-mediated pneumonitis	310.988	124.995	311.837	15
immune-mediated thyroiditis	248.79	113.632	249.061	6
immune-mediated renal disorder	233.241	110.29	233.622	9
immune-mediated hepatic disorder	225.619	108.564	227.143	37
immune-mediated dermatitis	190.048	99.634	190.428	11
immune-mediated cholangitis	186.593	98.68	186.898	9
immune-mediated encephalitis	168.452	93.387	168.849	13
krebs lungen-6 increased	165.86	92.589	165.98	4
immune-mediated myocarditis	160.087	90.77	161.874	61
adrenocorticotropic hormone deficiency	142.536	84.873	142.82	11
immune-mediated nephritis	138.217	83.33	138.367	6
tumour hyperprogression	130.942	80.642	131.227	12
immune-mediated adverse reaction	117.671	75.428	118.119	21
hypothalamo-pituitary disorder	103.663	69.442	103.775	6
immune-mediated enterocolitis	99.516	67.565	100.385	48
immune-mediated myasthenia gravis	98.726	67.202	98.905	10
immune-mediated pancreatitis	88.854	62.498	88.902	3
vitiligo	77.747	56.816	77.873	9
limbic encephalitis	77.747	56.816	77.831	6
autoimmune myositis	75.391	55.553	75.445	4
immune-mediated lung disease	74.424	55.029	74.801	28
eastern cooperative oncology group performance status worsened	72.214	53.817	72.619	31
immune-mediated hepatitis	70.735	52.995	71.105	29
blood corticotrophin decreased	69.108	52.081	69.171	5
immune-mediated hypophysitis	69.108	52.081	69.146	3
paraneoplastic neurological syndrome	69.108	52.081	69.146	3
immune-mediated myositis	57.476	45.218	57.766	28
cortisol decreased	56.543	44.641	56.574	3
myasthenia gravis	54.853	43.586	55.438	59
autoimmune colitis	54.559	43.401	54.608	5
autoimmune myocarditis	54.559	43.401	54.608	5
fulminant type 1 diabetes mellitus	54.085	43.102	54.143	6
cholangitis sclerosing	52.487	42.086	52.676	20
pericarditis malignant	48.782	39.681	48.817	4
urogenital fistula	47.844	39.061	47.87	3
encephalitis autoimmune	40.454	34.012	40.511	8
thrombophlebitis migrans	39.491	33.332	39.547	8
malignant neoplasm progression	24.405	21.94	39.038	2112
tumour associated fever	38.873	32.893	38.915	6
iga nephropathy	36.587	31.249	36.606	3
hypopituitarism	33.62	29.069	33.692	12
myasthenia gravis crisis	33.172	28.735	33.196	4
myasthenic syndrome	31.55	27.515	31.589	7
trousseau's syndrome	31.099	27.173	31.132	6
myositis	29.885	26.246	30.14	48
pericardial effusion malignant	29.618	26.041	29.634	3

Abbreviations: PRR: Proportional Reporting Ratio; RRR: Relative Reporting Ratio; ROR: Reporting Odds Ratio

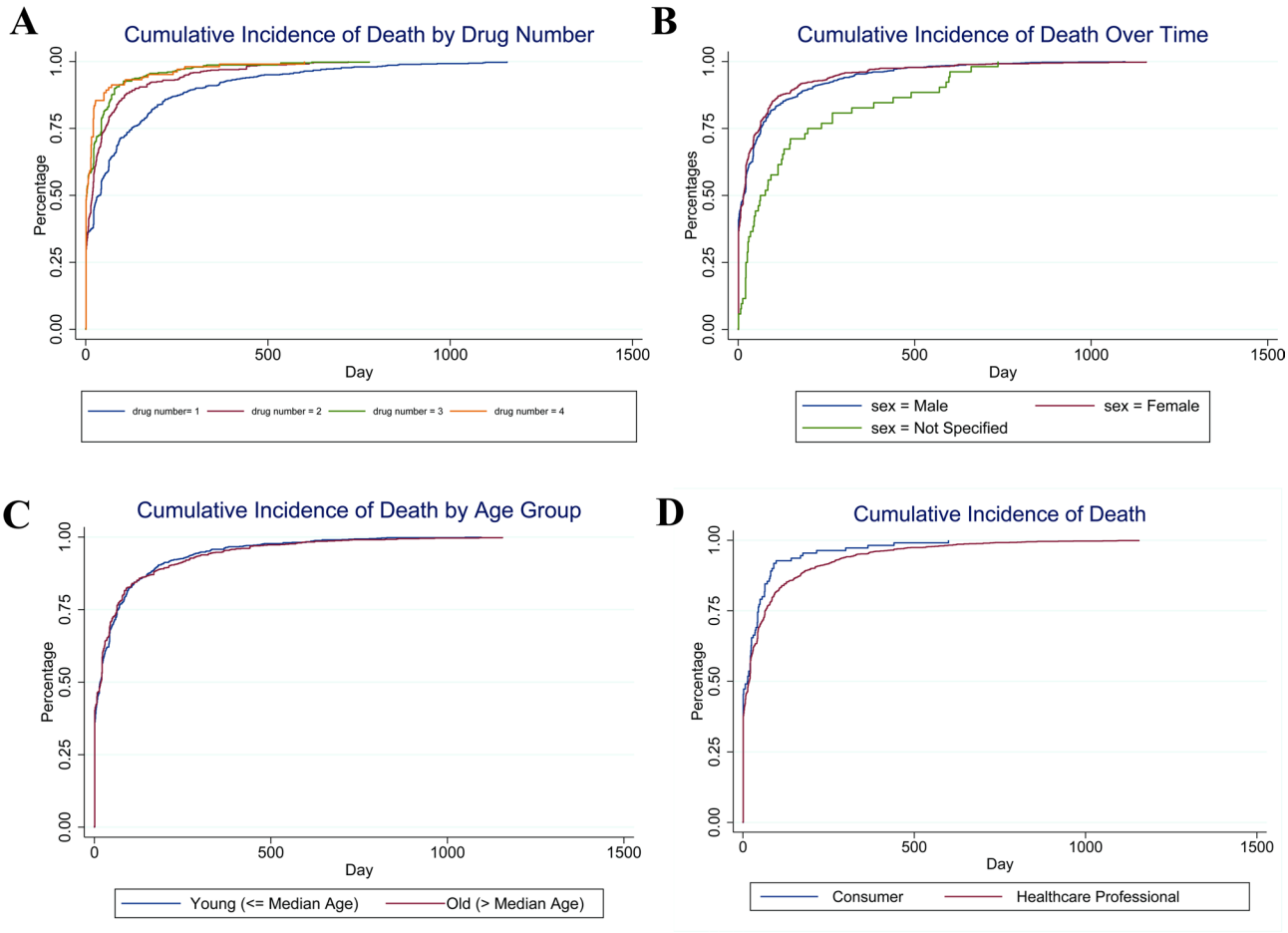

Fig. 4 Treatment time of pembrolizumab in died patients. **A** Treatment time of pembrolizumab by drug number; **B** Treatment time of pembrolizumab by sex; **C** Treatment time of pembrolizumab by median age; **D** Treatment time of pembrolizumab by reporter

be particularly pay attention to the immune response of elderly patients when using this drug, and strengthen monitoring and management. The study found that the United States and Japan are the countries with the most reports of adverse events of pembrolizumab, which may be related to the high frequency of use of pembrolizumab in these two countries and their acceptance of the adverse event reporting system. Most reports were submitted by medical professionals, reflecting those adverse reactions are more adequately monitored in clinical practice. However, the awareness of spontaneous reporting of adverse reactions by patients and the public still needs to be further improved to ensure more comprehensive monitoring.

Although the FAERS database provided a lot of data support for this study, the limitations of its spontaneous reporting system cannot be ignored. The voluntary and incomplete nature of the reports may lead to an underestimation of the incidence of adverse reactions. In addition, the lack of background information of the patients (such as concomitant medication, specific treatment regimen, etc.) limited the in-depth analysis of the effects of certain variables in this study. Therefore, future studies should combine more detailed patient data and further evaluate the safety of pembrolizumab through clinical trials.

This study summarizes a safety reference for the use of pembrolizumab in the treatment of cancer patients. During the diagnosis and treatment process, attention should be paid to the treatment response of elderly patients, and the monitoring of irAEs should be strengthened. At the same time, the geographical distribution differences of adverse reactions and the characteristics of reports mainly submitted by medical professionals suggest that the monitoring of adverse reactions of pembrolizumab in clinical practice is relatively sufficient, but the awareness of spontaneous reporting by patients and the public still needs to be further improved.

Table 3 Analysis of factors related to the treatment time of pembrolizumab in died patients

Factors		< median duration (*N* = 907)	≥median duration (*N* = 920)
Top 9 Regimen	Pembrolizumab	241 (26.6%)	404 (43.9%)
	Other	234 (25.8%)	116 (12.6%)
	Lenvatinib; Pembrolizumab	185 (20.4%)	196 (21.3%)
	Carboplatin; Pembrolizumab; Pemetrexed	66 (7.3%)	71 (7.7%)
	Carboplatin; Pembrolizumab; Taxane	57 (6.3%)	25 (2.7%)
	Axitinib; Pembrolizumab	14 (1.5%)	19 (2.1%)
	Pembrolizumab; Pemetrexed	7 (0.8%)	21 (2.3%)
	Cisplatin; Pembrolizumab; Pemetrexed	17 (1.9%)	5 (0.5%)
	Pembrolizumab; Taxane	86 (9.5%)	63 (6.8%)
Ingredient counts	1	241 (26.6%)	403 (43.8%)
	2	270 (29.8%)	290 (31.5%)
	3	230 (25.4%)	154 (16.7%)
	4	74 (8.2%)	29 (3.2%)
	5	42 (4.6%)	21 (2.3%)
Sex	Male	537 (59.2%)	523 (56.8%)
	Female	364 (40.1%)	351 (38.2%)
Case priority	Non-Expedited	101 (11.1%)	133 (14.5%)
	Expedited	804 (88.6%)	777 (84.5%)
Age group	< median age	466 (51.4%)	463 (50.3%)
	≥median age	441 (48.6%)	457 (49.7%)
Cancer related diagnosis	Cervix Cancer	327 (36.1%)	265 (28.8%)
	Cholangiocarcinoma	15 (1.7%)	18 (2%)
	Colorectal Cancer	70 (7.7%)	75 (8.2%)
	Endometrial Cancer	33 (3.6%)	30 (3.3%)
	Head And Neck Cancer	37 (4.1%)	83 (9%)
	Malignancy	24 (2.6%)	131 (14.2%)
	Melanoma	254 (28%)	182 (19.8%)
	Non-Small Cell Lung Cancer	87 (9.6%)	98 (10.7%)
	Renal Cancer	60 (6.6%)	37 (4%)
Reporter type	Consumer	57 (6.3%)	53 (5.8%)
	Healthcare Professional	848 (93.5%)	867 (94.2%)

Note: Other in Top 9 Regimen includes a variety of combination therapies that are less commonly used but still reported. Ingredient counts represent the number of drugs in the regimen (1 = single-drug, up to 5 = five-drug combinations). The range of Ingredient counts differs from Table 1 as Table 3 focuses on treatment duration subgroups, where regimens with > 5 components were rare

Abbreviations

FAERS	U.S. Food and Drug Administration's Adverse Event Reporting System
FDA	U.S. Food and Drug Administration
ICIs	Immune Checkpoint Inhibitors
irAEs	Immune-Related Adverse Events
PD-1	Programmed Death Receptor 1
KL-6	Krebs Lungen-6
SAEs	Serious Adverse Events
NSAEs	Non-Serious Adverse Events
OR	Odds Ratio
CI	Confidence Interval
PRR	Proportional Reporting Ratio
ROR	Reporting Odds Ratio
RRR	Relative Reporting Ratio
ADR	Adverse Drug Reaction
PSD	Primary Suspect Drug
SD	Standard Deviation
IQR	Interquartile Range
R	Statistical software version 4.4.1
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Terms
SOC	System Organ Class

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Author contributions
HX and DC contributed to the study concept and design, data analysis, and drafting of the manuscript. HX, YH, and HH was involved in data collection and interpretation. NZ and DC performed the statistical analysis. All authors participated in the critical revision of the manuscript for content. All authors read and approved the final manuscript.

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Data availability
The data used in this study were obtained from publicly available database (https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/7a47a261-d58b-4203-a8aa-6d3021737452/state/analysis). The relevant data are available from the corresponding authors upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. As this research was based on publicly available data, no ethical approval was required. Informed consent was not applicable as the study was retrospective design.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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