Observational Study

Medicine

OPEN

Adverse events associated with the use of nivolumab in the middle-aged and older population (>45 years)

A pharmacovigilance analysis based on the FAERS database

Lei Xu, MS[a], Ren-xian Xie, MS[b], Shan-shan Cai, PhD[c], Dai-feng Yang, PhD[d], Can-gui Wu, MD[e], Chun-hua Wang, MS[f,*]

Abstract

The clinical use of nivolumab has significantly improved the prognosis for survival in patients with a wide range of advanced malignancies. Given the increased incidence of tumors, there is a need to gain insight into the true extent of adverse events (AEs) associated with the nivolumab drug in the middle-aged and elderly population. This pharmacovigilance study was based on an analysis of reports from the US Food and Drug Administration's adverse event reporting system for the period January 1, 2014 to December 31, 2024, and compared AEs of the drug nivolumab in the middle-aged and elderly populations using proportional reporting ratio, reporting odds ratio, BCPN, and multi-item gamma Poisson shrinker methods. The analyses showed the presence of AEs in a variety of systems, mainly involving several systems such as endocrine disorders, nervous system disorders, skin and subcutaneous tissue disorders. The immune-related AEs listed in the package insert were validated by us and their clinical significance warrants careful consideration to further guide clinical dosing, adjust therapeutic decision-making, and develop age-adapted dosing algorithms for population pharmacokinetic development in order to minimize potential risks to patients. With the exception of reports of an unspecified nature, a greater proportion of the sample was male (65.7%) than female (32.5%), indicating significant variations. The highest percentage of reports was observed in patients aged between 65 and 85 years and in patients with a body mass index ranging from 50 to 100 kg/m^2. The primary indication was non-small cell lung cancer. The top 3 AE signals reported with nivolumab were malignant neoplasm progression, death, and pyrexia, with the majority of AE cases occurring within the first month following nivolumab initiation.

Abbreviations: AE = adverse event, BCPNN = Bayesian confidence propagation neural network, FAERS = US Food and Drug Administration adverse event reporting system, ICI = immune checkpoint inhibitor, irAE = immune-related adverse event, MGPS = multi-item gamma Poisson shrinker, PD-1 = programmed death receptor-1, PRR = proportional reporting ratio, PT = preferred terminology, ROR = reporting odds ratio, SOC = system organ classification.

Keywords: adverse events, Food and Drug Administration adverse event reporting system, immune checkpoint inhibitors, pharmacovigilance, real world

1. Introduction

The clinical use of immune checkpoint inhibitors (ICIs) has resulted in a substantial improvement in the survival prognosis of patients diagnosed with a wide range of advanced malignancies. The programmed death receptor-1 (PD-1) inhibitor, Nivolumab, has been the most widely utilized.[1,2] However, the unique mechanism of action of ICIs may trigger immune-related adverse events (irAEs), the incidence and severity of which may vary significantly between age groups.[3-5] Patients of middle and advanced age (>45 years) may be more susceptible to irAEs due to a combination of factors, including,

LX and R-xX contributed to this article equally.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available.

Supplemental Digital Content is available for this article.

[a] Department of Clinical Laboratory, Tenth People's Hospital of Tongji University, Shanghai, China, [b] Department of Radiation Oncology, Cancer Hospital of Shantou University Medical College, Shantou, Guangdong, China, [c] Division of Biomedical and Life Sciences, Faculty of Health and Medicine, Lancaster University, Lancaster, United Kingdom, [d] School of Computing, Engineering and Digital Technologies, Teesside University, Middlesbrough, United Kingdom, [e] Department of Breast Oncology, Jieyang People's Hospital, Jieyang, Guangdong, China, [f] Department of Oral Bioscience, Tokushima University Graduate School of Biomedical Sciences, Tokushima, Japan.

** Correspondence: Chun-hua Wang, Department of Oral Bioscience, Tokushima University Graduate School of Biomedical Sciences, 3-18-15 Kuramoto, Tokushima 770-8504, Japan. (e-mail: c302451008@tokushima-u.ac.jp).*

How to cite this article: Xu L, Xie R-x, Cai S-s, Yang D-f, Wu C-g, Wang C-h. Adverse events associated with the use of nivolumab in the middle-aged and older population (>45 years): A pharmacovigilance analysis based on the FAERS database. Medicine 2026;105:14(e48180).

Received: 3 November 2025 / Received in final form: 6 March 2026 / Accepted: 11 March 2026

http://dx.doi.org/10.1097/MD.0000000000048180

Table 1

Formulas and signal detection criterias for reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPNN) and multi-item gamma Poisson shrinker (MGPS).

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

BCPNN = Bayesian confidence propagation neural network, MGPS = multi-item gamma Poisson shrinker, PRR = proportional reporting ratio, ROR = reporting odds ratio.

but not limited to, age-related immunosenescence, increased comorbidity burden and multi-drug combination therapies.[6] A decline in the functionality of T-cells, alongside heightened baseline levels of inflammation (termed "inflammatory senescence") in middle-aged and older adults, has the potential to curtail the occurrence of irAEs. However, this phenomenon can concomitantly compound the challenge of tissue restoration following injury.[7,8] Therefore, in the event of irAEs (e.g., pneumonia, colitis) occurring, the severity may be increased and the recovery time prolonged, especially in patients with combined cardiopulmonary disease or renal insufficiency. Furthermore, pharmacokinetic studies have demonstrated that, as a monoclonal antibody, nivolumab is predominantly metabolized by lysosomal protein hydrolysis, and its clearance does not exhibit a significant correlation with hepatic and renal function.[9,10] This property suggests that dose adjustment may not be necessary in patients with hepatic or renal impairment. However, in the middle-aged and elderly population, age-related changes in tissue protease activity may affect drug exposure and thus potentially alter the risk profile of irAEs. However, the paucity of systematic safety studies in this population is a matter of concern.[11]

The US Food and Drug Administration adverse event reporting system (FAERS) is a significant resource for the identification of drug safety signals following marketing, as it is the world's largest pharmacovigilance database.[12] A substantial proportion of preceding studies have concentrated on the safety profile of ICIs in the general population. However, there has been a paucity of analyses of risk differences in age stratification, particularly in the middle-aged and elderly subgroups.[13] Notably, the middle-aged and elderly population over 45 years of age dominates the incidence of malignant tumors and the volume of ICI prescriptions, and their altered immune microenvironment and pharmacokinetics may affect the clinical presentation and prognosis of irAEs.[14,15] Moreover, the existing guidelines are deficient in their provision of targeted recommendations for the management of irAEs in middle-aged and elderly patients.[16]

The present study is the first to systematically assess the AE profile of nivolumab in the middle-aged and elderly population >45 years old, and to identify high-risk signals through data mining algorithms. The results of the study are expected to provide an evidence-based basis for optimizing risk stratification, monitoring strategies and individualized treatment in middle-aged and elderly patients.

2. Materials and methods

2.1. Data sources

This study utilized data from the FAERS, a comprehensive and publicly accessible post-marketing pharmacovigilance database containing spontaneous reports of AEs submitted by healthcare professionals, patients and manufacturers. The data set was extracted from Q1 2014 to Q4 2024, focusing on middle-aged and older adults aged 45 years or older who had received the drug "Nivolumab" (both generic and brand names). Duplicate reports were eliminated through the utilization of the primaryid and caseid fields, in accordance with Food and Drug Administration guidelines. In the present study, cases defined as AE reports in which the reporter referred to the target drug as the "prime suspect" were selected, and all AEs were reported using the Medical Dictionary for Regulatory Activities, MedDRA version 27.0. The coding of all AEs was conducted utilizing the preferred terminology (PT) and system organ classification (SOC) in the Medical Dictionary for Regulatory Activities, MedDRA version 27.0, a widely adopted medical terminology employed in pharmacovigilance and regulatory activities.

2.2. Statistical analysis

In this study, both descriptive and analytical statistical methods were employed. Descriptive statistics were first used to summarize the demographic and clinical characteristics of nivolumab-related adverse event (AE) reports, including gender, age, body weight, time to onset, and distribution across SOCs. These data are presented as frequencies and percentages. Analytical statistics focused on signal detection using disproportionality analysis and Bayesian algorithms. Four complementary methods were applied to identify potential AE signals associated with nivolumab: reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPNN), and multi-item gamma Poisson shrinker (MGPS). The formulas and signal detection criteria for each method are detailed in Table 1. Briefly, ROR and PRR are frequentist approaches that compare the proportion of a specific AE for the drug of interest versus all other drugs; a signal is considered positive when the lower limit of the 95% confidence interval for ROR > 1 and PRR ≥ 2 with $x^2 > 4$ and case count ≥ 3.[17] BCPNN and MGPS are Bayesian methods that reduce false positives in sparse data; a signal is deemed positive when the lower bound of the information component (IC025) > 0 for BCPNN and the lower bound of the empirical Bayesian geometric mean (EBGM05) > 2 for MGPS.[18] To ensure robustness, a positive AE signal was defined only when all 4 methods simultaneously met their respective criteria. All statistical analyses were performed using Microsoft Excel 2020 and R software (version 4.3.1). Graphical visualizations were generated using the online platform ChiPlot (https://www.chiplot.online/).

2.3. Ethical approval

This study used publicly available data from the FAERS. The FAERS database is de-identified and compliant with patient confidentiality regulations. As this study did not involve human subjects research and utilized only anonymized, publicly accessible data, institutional review board approval and informed consent were not required.

Table 2

Demographic information reported by AE in FAERS.

Nivolumab (n = 41014)	n (%)
Sex	
Female	13,335 (32.5%)
Male	26,952 (65.7%)
Unknow	727 (1.8%)
Age	
>85	750 (1.8%)
45–65	17,083 (41.7%)
65–85	23,181 (56.5%)
WT	
<50 kg	1579 (3.9%)
>100 kg	1349 (3.3%)
50–100 kg	12,632 (30.8%)
Unknow	25,454 (62.1%)
Years	
2014	56
2015	973
2016	2638
2017	3592
2018	4908
2019	5927
2020	5141
2021	5880
2022	5584
2023	3191
2024	3124
Geographical distribution	
Australia	969 (2.4%)
Austria	207 (0.5%)
Belgium	449 (1.1%)
Brazil	265 (0.6%)
Canada	1127 (2.7%)
China	1563 (3.8%)
France	4572 (11.1%)
Germany	2518 (6.1%)
India	713 (1.7%)
Italy	1241 (3.0%)
Japan	8120 (19.8%)
Netherlands	381 (0.9%)
Spain	693 (1.7%)
Switzerland	325 (0.8%)
Taiwan	323 (0.8%)
United Kingdom	684 (1.7%)
United States	13,303 (32.4%)
Others	
Indication	
Non-small cell lung cancer	5459 (13.3%)
Malignant melanoma	5297 (12.9%)
Renal cell carcinoma	2793 (6.8%)
Gastric cancer	2336 (5.7%)
Product used for unknown indication	2335 (5.7%)
Metastatic malignant melanoma	2245 (5.5%)
Metastatic renal cell carcinoma	1946 (4.7%)
Lung neoplasm malignant	1939 (4.7%)
Non-small cell lung cancer recurrent	1463 (3.6%)
Renal cancer	851 (2.1%)
Squamous cell carcinoma of head and neck	767 (1.9%)
Oesophageal carcinoma	703 (1.7%)
Lung adenocarcinoma	671 (1.6%)
Head and neck cancer	666 (1.6%)
Others	
Occupation code	
CN	8398 (20.5%)
HP	9069 (22.1%)
LW	14 (0.0%)
MD	12,847 (31.3%)
OT	8138 (19.8%)
PH	2448 (6.0%)
Missing	100 (0.2%)
Outcome code	
CA	5 (0.0%)
DE	11,439 (27.9%)
DS	263 (0.6%)
HO	14,402 (35.1%)
LT	2265 (5.5%)
Missing	3022 (7.4%)
OT	9604 (23.4%)
RI	14 (0.0%)

AE = adverse event, FAERS = US Food and Drug Administration adverse event reporting system.

3. Results

3.1. General characteristics

From January 1, 2014 to December 31,2024, a total of 1,88,72,987 reports of AE in people aged 45 years and older were identified from the FAERS database. Of these, 41,014 AEs were reported for nivolumab. The clinical characteristics of the reported cases and details of the reports are shown in Table 2. From 2014 to 2024, the number of AEs reported for nivolumab exhibited a linear increase with an overall "M" shaped magnitude, peaking at 5927 cases in 2019 (Fig. 1A). The United States was the most frequently reported country (32.4%), followed by Japan (19.8%; Fig. 1B). With the exception of cases for which the specific reason was not documented, a greater proportion of the reported cases involved males (65.7%) compared to females (32.5%), indicating significant variation (Fig. 1C). The greatest percentage of reports occurred in patients aged 65 to 85 years and in patients weighing 50 to 100 kg (Fig. 1D, E). The predominant indications were Non-small cell lung cancer (13.3%) and malignant melanoma (12.9%; Fig. 1F). It is noteworthy that almost half of the reports were submitted by health professionals. From January 1, 2014 to December 31, 2024 (an 11-year period), a total of 1,88,72,987 reports of AE in people aged 45 years and older were identified from the FAERS database. Of these, 41,014 AEs were reported for Nivolumab. From 2014 to 2024, the number of AEs reported for Nivolumab exhibited a linear increase with an overall "M" shaped magnitude, peaking at 5927 cases in 2019.

3.2. Signal AE mining and analysis of AE signals at the PT level

In this study, AE signals were analyzed using ROR, PRR, BCPNN and MGPS, a total of 601 signals were obtained for nivolumab, next we analyzed all signals at the PT level, all AE signals are shown in Table S1, Supplemental Digital Content, https://links.lww.com/MD/R590.

The 3 most frequently reported AE signals for nivolumab were malignant neoplasm progression (n = 5299), death (n = 4903), and pyrexia (n = 1637). These were attributed to neoplasms benign, malignant, and unspecified (including cysts and polyps) and general disorders and administration site conditions, respectively. The top 3 AE signals in terms of PRR and ROR were acquired generalised lipodystrophy (ROR = 301.78, 95% CI = 55.27–1647.66, PRR = 301.77), Stauffer's syndrome (ROR = 226.33, 95% CI = 37.82–1354.57, PRR = 226.33) and leukaemia (ROR = 191.84, 95% CI = 131.43–280.03, PRR = 191.75) for skin and subcutaneous tissue disorders and hepatobiliary disorders, respectively.

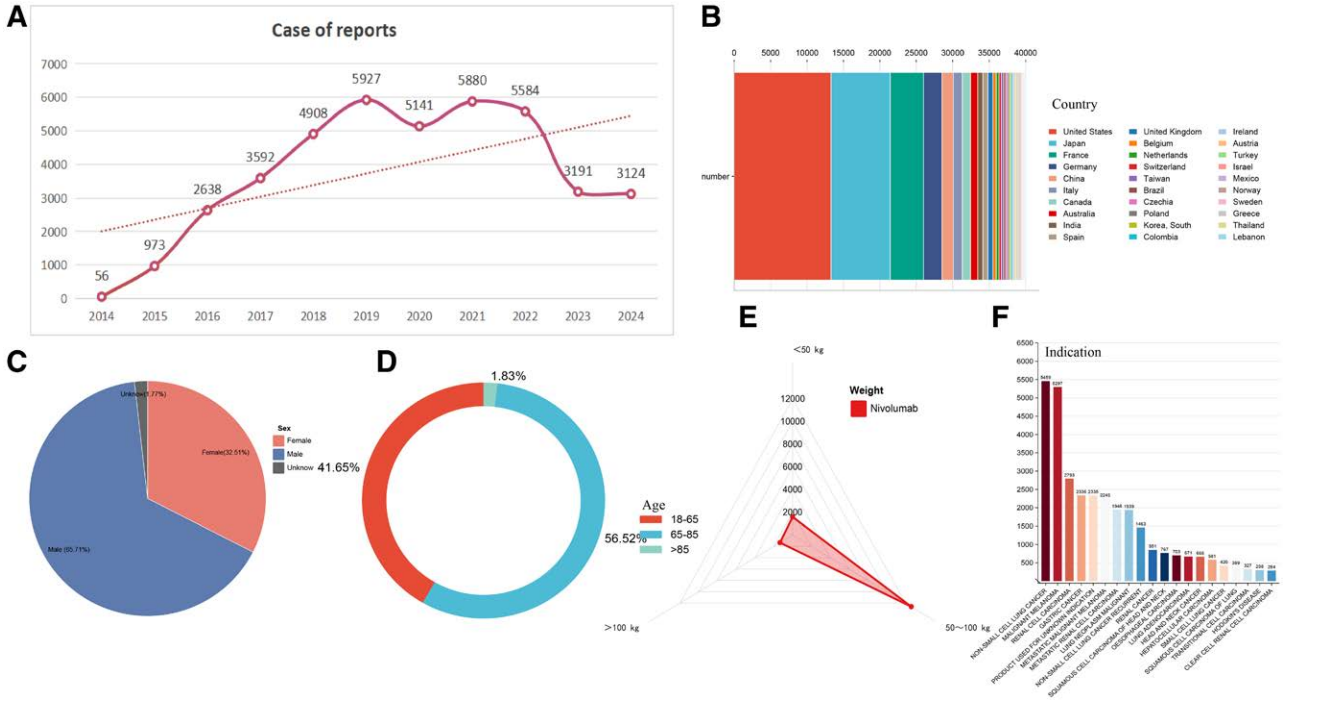

Figure 1. Demographic information on AE reporting in FAERS. (A) Number of drug AEs reported per year; (B) histogram of country distribution of reported drugs; (C) percentage of drug AEs reported by gender subgroups; (D) percentage of drug AEs reported by age group; (E) number of drug AEs reported by body weight; and (F) histogram of drug indications. AE = adverse event, FAERS = US Food and Drug Administration adverse event reporting system.

Table 3

The top 30 positive signals at the PT level and the positive signals at the SOC level in FAERS database.

		Nivolumab				
No	**PT**	**Case reports**	**PRR (χ2)**	**ROR (95% CI)**	**EBGM (EBGM05)**	**IC (IC025)**
1	Malignant neoplasm progression	5299	22.49 (94,906.75)	23.45 (22.77–24.15)	19.7 (19.22)	4.3 (4.26)
2	Death	4903	2.55 (4609.97)	2.61 (2.54–2.69)	2.52 (2.46)	1.34 (1.29)
3	Pyrexia	1637	2.24 (1114.23)	2.26 (2.15–2.37)	2.22 (2.13)	1.15 (1.08)
4	Decreased appetite	1366	2.33 (1028.91)	2.35 (2.22–2.48)	2.31 (2.21)	1.21 (1.13)
5	Colitis	945	11.33 (8288.07)	11.41 (10.68–12.2)	10.61 (10.04)	3.41 (3.31)
6	Hypothyroidism	930	13.83 (10,146.99)	13.93 (13.02–14.9)	12.75 (12.05)	3.67 (3.57)
7	General physical health deterioration	903	3.5 (1578.85)	3.52 (3.29–3.76)	3.44 (3.26)	1.78 (1.69)
8	Pneumonitis	895	13.14 (9239.81)	13.23 (12.35–14.17)	12.17 (11.49)	3.6 (3.5)
9	Interstitial lung disease	798	5.83 (3076.23)	5.86 (5.46–6.29)	5.65 (5.32)	2.5 (2.39)
10	Sepsis	647	2.41 (527.21)	2.42 (2.24–2.61)	2.39 (2.24)	1.26 (1.14)
11	Adrenal insufficiency	588	22.63 (10,572.06)	22.73 (20.84–24.79)	19.81 (18.42)	4.31 (4.18)
12	Pleural effusion	569	3.7 (1096.4)	3.71 (3.42–4.04)	3.64 (3.39)	1.86 (1.74)
13	Immune-mediated enterocolitis	521	64.43 (22,802.07)	64.7 (58.39–71.7)	45.45 (41.71)	5.51 (5.36)
14	Myocarditis	505	25.36 (10,116.98)	25.46 (23.16–27.98)	21.85 (20.19)	4.45 (4.31)
15	Hepatic function abnormal	486	5.89 (1898.73)	5.91 (5.39–6.47)	5.7 (5.29)	2.51 (2.38)
16	Respiratory failure	475	2.73 (511.66)	2.74 (2.5–3)	2.7 (2.5)	1.43 (1.3)
17	Pemphigoid	428	18.2 (6208.27)	18.26 (16.51–20.18)	16.35 (15.03)	4.03 (3.88)
18	Hyperthyroidism	410	13.06 (4203.2)	13.1 (11.84–14.49)	12.1 (11.12)	3.6 (3.45)
19	Hyponatraemia	395	2.36 (304.09)	2.36 (2.14–2.61)	2.34 (2.15)	1.22 (1.08)
20	Aspartate aminotransferase increased	364	3.98 (792.32)	3.99 (3.6–4.43)	3.9 (3.58)	1.97 (1.81)
21	Diabetic ketoacidosis	357	6.46 (1581.16)	6.48 (5.83–7.2)	6.24 (5.71)	2.64 (2.49)
22	Lung disorder	350	3.11 (490.84)	3.11 (2.8–3.46)	3.07 (2.81)	1.62 (1.46)
23	Alanine aminotransferase increased	346	3.26 (530.48)	3.26 (2.93–3.63)	3.21 (2.94)	1.68 (1.53)
24	Hepatitis	344	6.93 (1668.09)	6.94 (6.23–7.73)	6.67 (6.09)	2.74 (2.58)
25	Febrile neutropenia	343	2.23 (229.08)	2.23 (2.01–2.48)	2.21 (2.02)	1.14 (0.99)
26	Myositis	342	19.24 (5245.94)	19.29 (17.23–21.59)	17.18 (15.63)	4.1 (3.94)
27	Liver disorder	336	3.83 (685.08)	3.84 (3.44–4.27)	3.76 (3.43)	1.91 (1.75)
28	Stomatitis	327	2.27 (228.82)	2.27 (2.04–2.53)	2.25 (2.05)	1.17 (1.01)
29	Hypophysitis	319	62.75 (13,692.01)	62.91 (55.2–71.7)	44.61 (39.99)	5.48 (5.3)
30	Fulminant type 1 diabetes mellitus	305	138.61 (21,718.47)	138.95 (118.93–162.34)	72.72 (63.85)	6.18 (5.98)
NO	SOC					
1	Endocrine disorders	4228	13.22 (44,022.76)	13.65 (13.22–14.09)	12.23 (11.91)	3.61 (3.57)
2	Hepatobiliary disorders	4007	3.38 (6614.58)	3.45 (3.35–3.57)	3.32 (3.24)	1.73 (1.69)

PT = preferred terminology, ROR = reporting odds ratio, SOC = system organ classification.

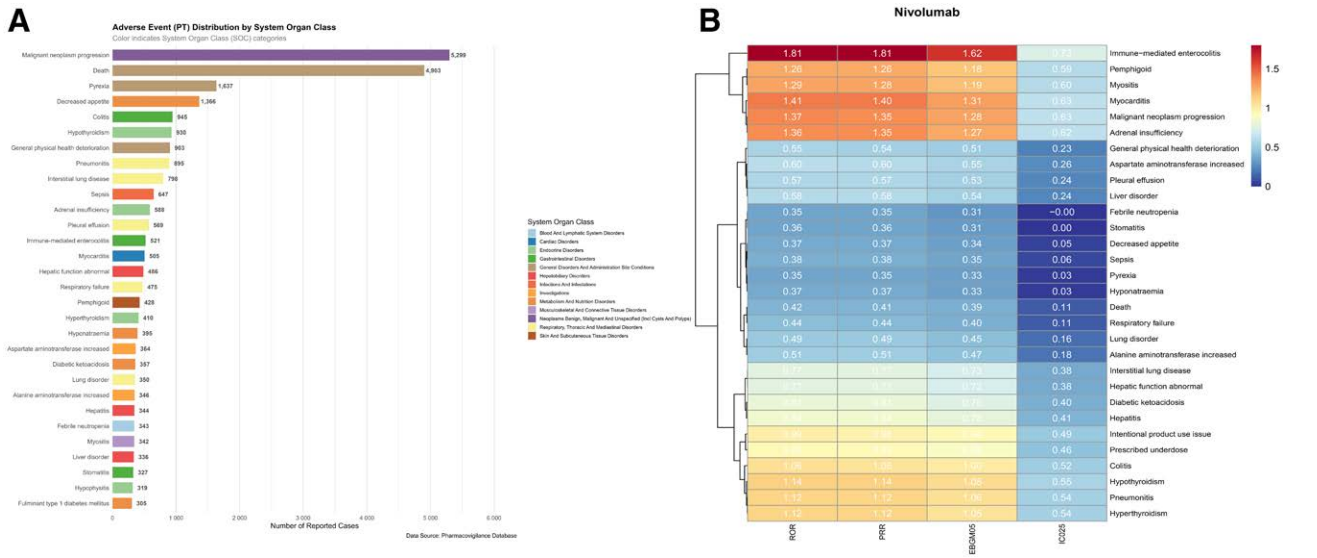

Figure 2. (A) Names and numbers of the top 30 AEs with the highest proportion of drug signals detected in the FAERS database and their corresponding SOCs; (B) Heatmap visualization of signal values for the 4 methods. AE = adverse event, FAERS = US Food and Drug Administration adverse event reporting system, SOC = system organ classification.

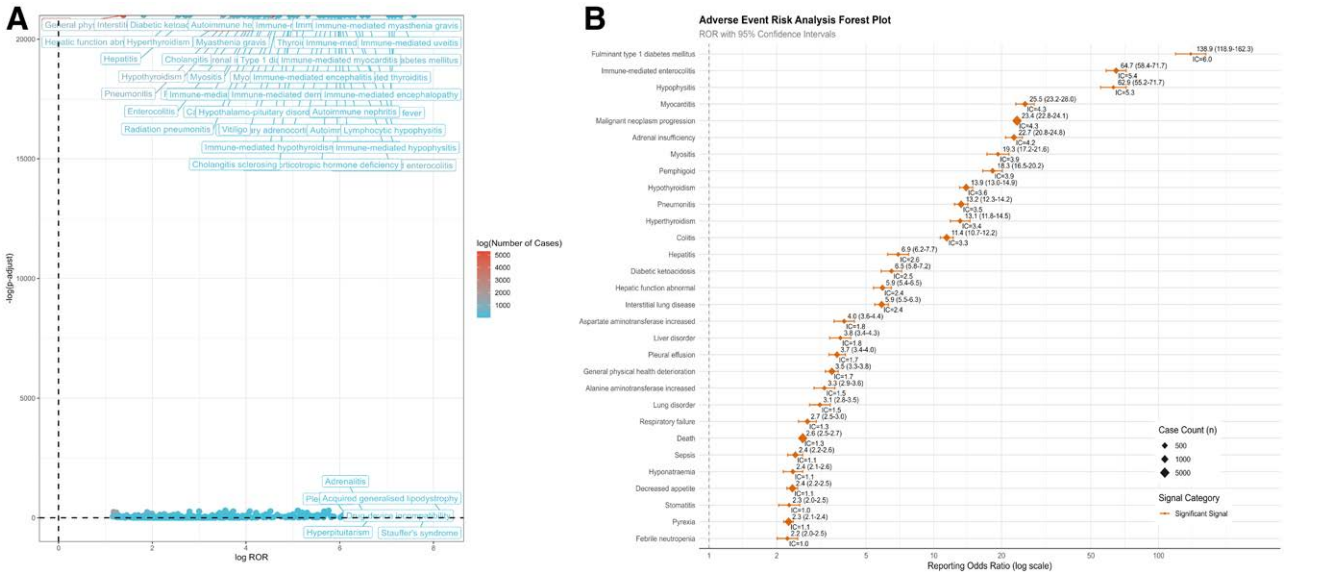

Figure 3. (A) Volcano plot of positive AE signals; (B) ROR forest plot of the first 30 AE signals. AE = adverse event, ROR = reporting odds ratio.

The present study focused on the top 30 most frequent signal strength detections, and employed heatmap visualization of the signal values (Table 3, Fig. 2). The top 30 most frequent signals reported by nivolumb occurred mainly as endocrine disorders and metabolism and nutrition disorders (Fig. 2A). Although some of the PTs were reported in smaller numbers, they should also be of high concern. The application of the logarithm to the signal values for the 4 methods revealed that immune-mediated enterocolitis was of concern (Fig. 2B), and this is attributed to gastrointestinal disorders. The volcano and forest plots of the top 30 signals revealed that the top 3 ROR values were fulminant type 1 diabetes mellitus (ROR = 138.95, 95% CI = (118.93–162.34), immune-mediated enterocolitis (ROR = 64.7, 95% CI = (58.39–71.7) and hypophysitis (ROR = 62.91, 95% CI = (55.2–71.7), attributed to metabolism and nutritional disorders, gastrointestinal disorders, and endocrine disorders, respectively (Fig. 3A, B).

3.3. AE report stratified analysis by SOC and relationship between main AE signals detection and SOCs

To detect SOC signals, we first used MedDRA to classify all positive AE signals for nivolumab according to SOC for the affected organs and systems and found that nervous system disorders (n = 67,11.5%), investigations (n = 54,8.99%), gastrointestinal disorders (n = 53.8, 82%) were the 3 systems with the highest number of SOCs attributed to AE signals reported for nivolumab (Table 4), with the AE with the highest number of occurrences attributed to nervous system disorders being myasthenia gravis.

In addition, on the SOC, we analyzed the signals using ROR, PRR, BCPNN and MGPS and found that the positive signals for nivolumab were endocrine disorders (n = 4228) and hepatobiliary disorders (n = 4007; Table 3), which is consistent with our previous findings.

Table 4

Distribution of ae signals in each system organ class.

SOC	Nivolumab	
	n	Percentage
Nervous system disorders	67	11.15%
Investigations	54	8.99%
Gastrointestinal disorders	53	8.82%
Infections and infestations	48	7.99%
Endocrine disorders	45	7.49%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	45	7.49%
Skin and subcutaneous tissue disorders	43	7.15%
Respiratory, thoracic and mediastinal disorders	42	6.99%
Hepatobiliary disorders	29	4.83%
Metabolism and nutrition disorders	22	3.66%
Musculoskeletal and connective tissue disorders	22	3.66%
Blood and lymphatic system disorders	19	3.16%
Eye disorders	18	3.00%
Cardiac disorders	16	2.66%
Renal and urinary disorders	15	2.50%
General disorders and administration site conditions	14	2.33%
Surgical and medical procedures	14	2.33%
Injury, poisoning and procedural complications	12	2.00%
Vascular disorders	9	1.50%
Immune system disorders	8	1.33%
Ear and labyrinth disorders	3	0.50%
Product issues	2	0.33%
Congenital, familial and genetic disorders	1	0.17%

SOC = system organ classification.

Table 5

Subgroups of AE induction times for nabulizumab in middle-aged and older adults aged 45 years or older.

Days	Number	Percentage
0–30	7220	34.56
31–60	3769	18.04
61–90	2260	10.82
91–120	1600	7.66
121–150	1120	5.36
151–180	849	4.06
181–360	2423	11.60
>360	1651	7.90

AE = adverse event.

3.4. Onset events

Exacerbation times for nivolumab-associated AEs were extracted from the database. A total of 20,892 associated AEs reported the time of onset and most AE cases occurred in the first 1 month (n = 7220, 34.56%) and 1 to 2 months (n = 3769, 18.04%) after nivolumab initiation (Table 5, Fig. 4). Analysing the results from the SOC, we found that the time to induction of nivolumab did not differ significantly between systems and that AEs could still occur after 4000 days.

4. Discussion

This study is the first to systematically reveal the characteristics of AEs of nivolumab in a middle-aged and older population >45 years of age based on the FAERS database. By analyzing reports between 2014 and 2024, we identified multiple high-risk AEs, with a high number of AE occurrences attributed to Metabolism and nutrition disorders, gastrointestinal disorders and endocrine disorders. The drug package inserts listed immune-mediated enterocolitis (n = 521), immune-mediated hepatitis (n = 234), immune-mediated myocarditis (n = 213), immune-mediated lung disease (n = 209) and all irAEs were identified through our data mining process.

4.1. Age-specificity of the immunotoxicity profile

As thymic degeneration progresses with age, a decline in initial T-cells is observed. This decline impairs immune tolerance mechanisms and exacerbates autoimmune responses.[19] This explains the high proportion of rare but lethal irAEs (e.g., immune-mediated myocarditis) reported in patients >45 years of age. On the other hand, the mitochondrial dysfunction that accompanies aging may diminish the activation capacity of effector T cells, leading to a lower occurrence of some irAEs (e.g., autoimmune dermatitis; n = 3).[7] This is consistent with the high readmission rate but low reporting rate observed by Wang et al[4] in elderly ICI patients.

4.2. Metabolic and endocrine toxicity dominate the toxicity spectrum

The data demonstrated that nivolumab exhibited a high risk of accumulating metabolic and endocrine toxicity in individuals over 45 years of age, with elevated risk signals including generalised lipodystrophy (ROR = 301.78, 95% CI = 55.27–1647.66, PRR = 301.77) and fulminant type 1 diabetes mellitus (ROR = 138.95, 95% CI = 118.93–162.34) were high risk signals suggestive of age-related susceptibility to metabolic disorders. The potential mechanisms underlying this phenomenon include thymic output reduction in elderly patients, leading to a decrease in CD4+ CD25+ FoxP3+ Treg cells, immune tolerance to autoantigens, and an imbalance between thymic degeneration and Treg cells.[19,20] The occurrence of hypophysitis and thyroid-related diseases in this study and attributed to endocrine disorders corroborates this mechanism. Increased mitochondrial ROS production in senescent cells promotes IL-1β release through activation of NLRP3 inflammatory vesicles, which may be a potential reason for the high signaling values of systemic inflammatory responses, such as Stauffer's syndrome (ROR = 226.33).[21,22]

4.3. Early warning and intervention in lethal toxicity

The present study found that malignant progression (n = 5299) and death (n = 4903) occupied the top 2 reported numbers, and that the inflammatory microenvironment may have driven

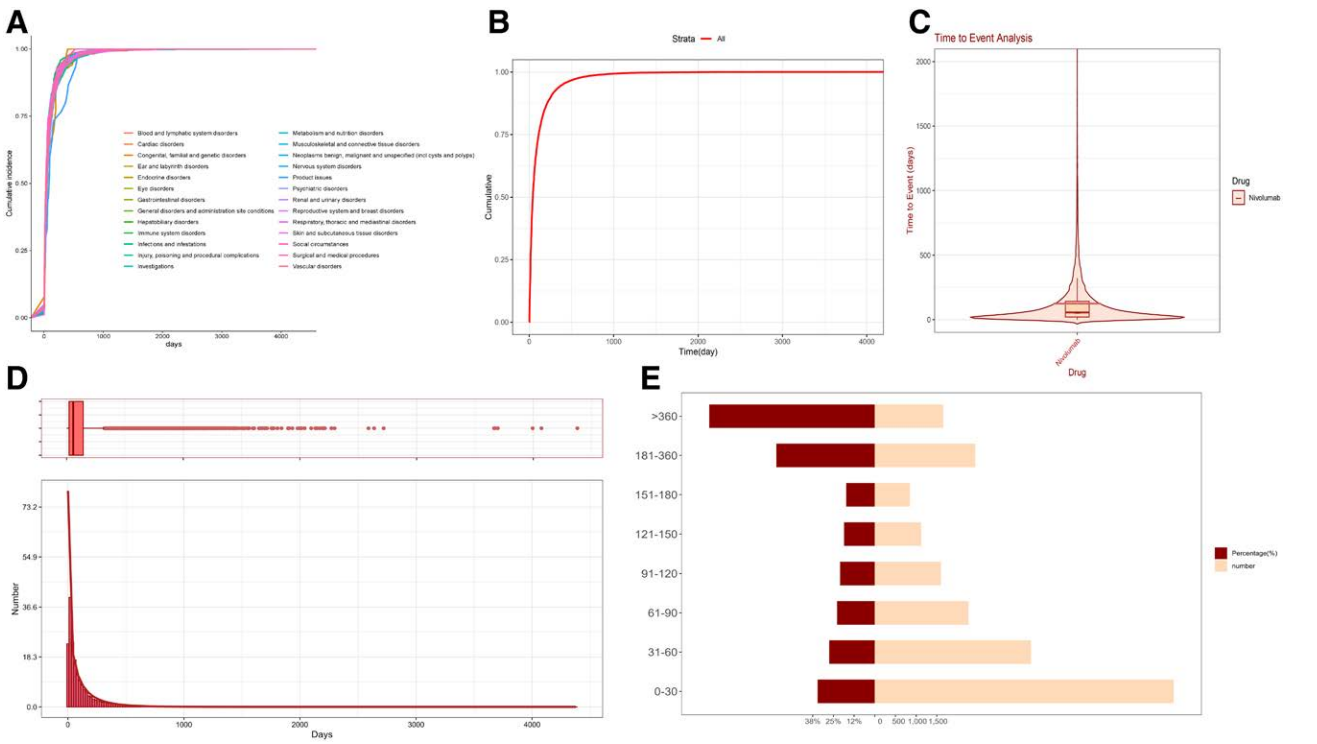

Figure 4. (A) Overall distribution of AE onset time; (B) Violin plot of AE onset time in different age groups; (C) Grouped bar plot of AE onset time by gender; (D) Violin plot of AE onset time in different BMI subgroups; (E) Grouped bar plot of AE onset time by primary indication. AE = adverse event.

hyperprogression and contributed to the patient's death in a synergistic effect of multiorgan toxicity.[23,24] Previous studies have shown that the median time to the onset of irAEs is 15 days after the start of treatment, and nearly one-third of the deaths are due to myocarditis, and/or neurological events. Hepatitis accounted for approximately 20% of each death Cohort.[4,25–27]

4.4. Rare but serious AE warning

Despite the limited number of reported cases of acquired generalized lipodystrophy (4), the ultra-high risk signal (ROR = 301.78) is concerning. Previous studies have also identified severe adipose metabolism disorders following 10 months of treatment of metastatic melanoma with the anti-PD-1 antibody pembrolizumab. These disorders were characterized by loss of subcutaneous adipose tissue, central obesity and insulin resistance with reduced leptin levels. These findings were further validated in our study. This may be associated with impaired M2 macrophage polarization in adipose tissue, induced by PD-1 inhibitor therapy. This, in turn, may result in reduced lipocalin secretion and consequently develop into a state of insulin resistance.[28-30] In future clinical practice for patients with a baseline BMI > 30 kg/m^2 or in the presence of metabolic syndrome, it may be appropriate to recommend pretreatment testing of lipocalin levels and regular post-treatmentscreening for abnormal visceral fat distribution.

4.5. SOC toxicity correlation analysis

The high prevalence of nervous system disorders (11.5%) may be due to blood–brain barrier permeability: the IgG4 nivolumab of nivolumab may cross the blood–brain barrier mediated by FcRn.[10,31] In this study, myasthenia gravis (n = 261) and encephalitis (n = 156) exhibited a high incidence, thus emphasizing the necessity for meticulous monitoring of neurospecific antibodies (e.g., anti-AChR antibodies). Furthermore, the integration of thyroid ultrasound in the preliminary evaluation may facilitate a comprehensive assessment of endocrine dysfunction and metabolic systems. Moreover, the periodic evaluation of thresholds for hepatotoxic interventions is recommended.

4.6. Research limitations and prospects

Limitations of this study include: the US FAERS is a self-reporting database with limitations of imperfect reporting information, uncertainty of the causal relationship between the reported event and the medication, bias in self-reporting, future studies should be based on the AE signals identified in this paper, validation in prospective cohort studies has not been conducted, and development of personalized dosing models: the development of age-adaptive dosing algorithms based on population pharmacokinetics that balancing efficacy and safety.

The present study covers an 11-year period from 2014 to 2024, during which the annual number of reported AEs associated with nivolumab showed a general increasing trend, with peaks observed in 2019 and 2021 (Fig. 1A). Although the primary focus of this analysis was not a formal year-by-year comparison, the consistency of high-signal AEs (e.g., endocrine disorders, gastrointestinal disorders) across the study period suggests that the safety profile of nivolumab in the middle-aged and older population has remained relatively stable over time. However, fluctuations in reporting frequency may reflect changes in drug utilization, increased clinical awareness, or variations in reporting practices. Future studies with access to drug exposure data and longer follow-up periods are warranted to perform formal comparative analyses across different calendar years and to assess temporal trends in the incidence and characteristics of immune-related AEs.

5. Conclusion

In this study, an analysis of the FAERS database was employed to systematically reveal, for the first time, the characteristics of AEs of nivolumab in a middle-aged and elderly population with

a mean age of over 45 years. The analyses demonstrated that AEs were present in a variety of systems, primarily associated with Endocrine disorders, ervous system disorders, Skin and subcutaneous tissue disorders, and so forth. It is noteworthy that the irAEs documented in the package insert were all validated. The clinical significance of these irAEs merits careful consideration to further guide clinical use and adjust therapeutic decisions to minimize potential risks to patients. And future research needs to further develop a new generation of highly selective analogues based on the possible mechanisms of these AEs, with a view to developing targeted therapies and age-adapted dosing algorithms based on population pharmacokinetics to balance efficacy and safety.

Acknowledgments

We sincerely thank the researchers, including clinicians, patients, and regulatory agencies, who contributed to the FAERS data.

Author contributions

Conceptualization: Lei Xu.
Data curation: Lei Xu.
Formal analysis: Ren-xian Xie.
Funding acquisition: Can-gui Wu, Chun-hua Wang.
Investigation: Ren-xian Xie, Shan-shan Cai.
Methodology: Shan-shan Cai.
Resources: Dai-feng Yang, Can-gui Wu, Chun-hua Wang.
Software: Dai-feng Yang.
Validation: Chun-hua Wang.
Visualization: Dai-feng Yang.
Writing – original draft: Lei Xu, Ren-xian Xie.
Writing – review & editing: Shan-shan Cai, Dai-feng Yang.

References

[1] Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med. 2016;375:1856–67.
[2] Kato K, Cho BC, Takahashi M, et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20:1506–17.
[3] Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366:2443–54.
[4] Wang DY, Salem JE, Cohen JV, et al. Fatal toxic effects associated with immune checkpoint inhibitors. JAMA Oncol. 2018;4:1721–8.
[5] Wan G, Chen W, Khattab S, et al. Multi-organ immune-related adverse events from immune checkpoint inhibitors and their downstream implications: a retrospective multicohort study. Lancet Oncol. 2024;25:1053–69.
[6] Fulop T, Larbi A, Dupuis G, et al. Immunosenescence and inflamm-aging as two sides of the same coin: friends or foes? Front Immunol. 2017;8:1960.
[7] Barman PK, Shin JE, Lewis SA, et al. Production of MHCII-expressing classical monocytes increases during aging in mice and humans. Aging Cell. 2022;21:e13701.
[8] van der Geest KSM, Wang Q, Eijsvogels TMH, et al. Changes in peripheral immune cell numbers and functions in octogenarian walkers - an acute exercise study. Immun Ageing. 2017;14:5.
[9] Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012;366:2455–65.
[10] Keizer RJ, Huitema AD, Schellens JH, Beijnen JH. Clinical pharmacokinetics of therapeutic monoclonal antibodies. Clin Pharmacokinet. 2010;49:493–507.
[11] Li H, Ruan Z, Jia Y, et al. Adverse reactions associated with nivolumab and small molecule antiangiogenic drugs: a pharmacovigilance analysis. Br J Clin Pharmacol. 2025;91:166–78.
[12] Sakaeda T, Tamon A, Kadoyama K, Okuno Y. Data mining of the public version of the FDA adverse event reporting system. Int J Med Sci. 2013;10:796–803.
[13] Martins F, Sofiya L, Sykiotis GP, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat Rev Clin Oncol. 2019;16:563–80.
[14] Zhai J, Qin Y, Zhu J, et al. Pharmacokinetics of obinutuzumab in Chinese patients with B-cell lymphomas. Br J Clin Pharmacol. 2017;83:1446–56.
[15] Aymanns C, Keller F, Maus S, Hartmann B, Czock D. Review on pharmacokinetics and pharmacodynamics and the aging kidney. Clin J Am Soc Nephrol. 2010;5:314–27.
[16] Haanen J, Obeid M, Spain L, et al. Management of toxicities from immunotherapy: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022;33:1217–38.
[17] He Q, Li Y, Liu S, et al. Drug-induced liver injury associated with pretomanid, bedaquiline, and linezolid: insights from FAERS database analysis. Br J Clin Pharmacol. 2025;91:799–807.
[18] Zou F, Cui Z, Lou S, et al. Adverse drug events associated with linezolid administration: a real-world pharmacovigilance study from 2004 to 2023 using the FAERS database. Front Pharmacol. 2024;15:1338902.
[19] Carmona-Bayonas A, Jiménez-Fonseca P, Custodio A, et al. Optimizing somatostatin analog use in well or moderately differentiated gastroenteropancreatic neuroendocrine tumors. Curr Oncol Rep. 2017;19:72.
[20] Kishore M, Cheung KCP, Fu H, et al. Regulatory T cell migration is dependent on glucokinase-mediated glycolysis. Immunity. 2017;47:875–89.e10.
[21] Zhou R, Yazdi AS, Menu P, Tschopp J. A role for mitochondria in NLRP3 inflammasome activation. Nature. 2011;469:221–5.
[22] Nakahira K, Haspel JA, Rathinam VA, et al. Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. Nat Immunol. 2011;12:222–30.
[23] Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010;140:883–99.
[24] Ricciardi M, Zanotto M, Malpeli G, et al. Epithelial-to-mesenchymal transition (EMT) induced by inflammatory priming elicits mesenchymal stromal cell-like immune-modulatory properties in cancer cells. Br J Cancer. 2015;112:1067–75.
[25] Hassel JC, Heinzerling L, Aberle J, et al. Combined immune checkpoint blockade (anti-PD-1/anti-CTLA-4): evaluation and management of adverse drug reactions. Cancer Treat Rev. 2017;57:36–49.
[26] Mahmood SS, Fradley MG, Cohen JV, et al. Myocarditis in patients treated with immune checkpoint inhibitors. J Am Coll Cardiol. 2018;71:1755–64.
[27] Johnson DB, Balko JM, Compton ML, et al. Fulminant myocarditis with combination immune checkpoint blockade. N Engl J Med. 2016;375:1749–55.
[28] Haddad N, Vidal-Trecan T, Baroudjian B, et al; PATIO Group. Acquired generalized lipodystrophy under immune checkpoint inhibition. Br J Dermatol. 2020;182:477–80.
[29] Cai J, Song L, Zhang F, et al. Targeting SRSF10 might inhibit M2 macrophage polarization and potentiate anti-PD-1 therapy in hepatocellular carcinoma. Cancer Commun (Lond). 2024;44:1231–60.
[30] Liu N, Zhang J, Yin M, et al. Inhibition of xCT suppresses the efficacy of anti-PD-1/L1 melanoma treatment through exosomal PD-L1-induced macrophage M2 polarization. Mol Ther. 2021;29:2321–34.
[31] Crommentuijn MHW, Schetters STT, Dusoswa SA, Kruijssen LJW, Garcia-Vallejo JJ, van Kooyk Y. Immune involvement of the contralateral hemisphere in a glioblastoma mouse model. J ImmunoTher Cancer. 2020;8:e000323.