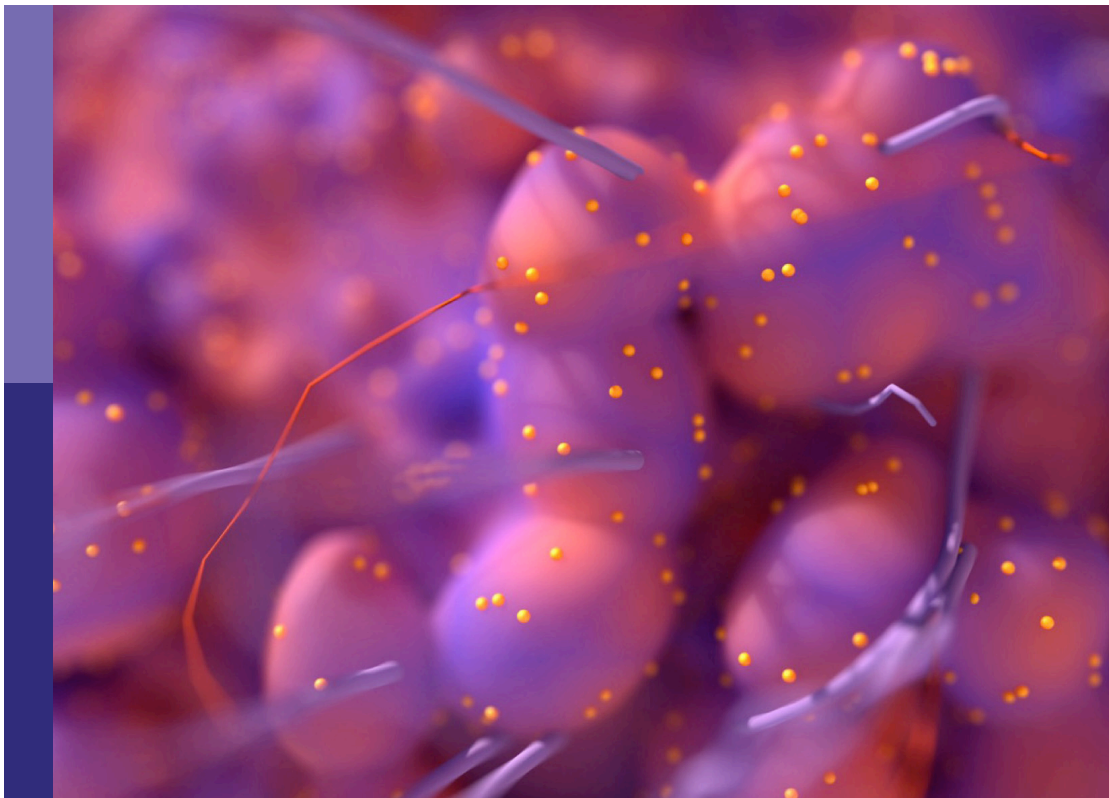
frontiers | Research Topics

Immune-checkpoint inhibitors in anti-cancer armamentarium: a double-edged sword in risk of developing autoimmunity and immune-related adverse effects

Edited by
Maria-Ioanna Christodoulou, Giacomo Cafaro, Yannick Degboé, Flavia Sunzini and Aysin Tulunay Virlan

Published in
Frontiers in Oncology
Frontiers in Pharmacology



ISSN 1664-8714
ISBN 978-2-8325-5877-5
DOI 10.3389/978-2-8325-5877-5

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Immune-checkpoint inhibitors in anti-cancer armamentarium: a double-edged sword in risk of developing autoimmunity and immune-related adverse effects

Topic editors

Maria-Ioanna Christodoulou — European University Cyprus, Cyprus
Giacomo Cafaro — University of Perugia, Italy
Yannick Degboé — Centre Hospitalier Universitaire de Toulouse, France
Flavia Sunzini — University of Glasgow, United Kingdom
Aysin Tulunay Virlan — University of Glasgow, United Kingdom

Citation

Christodoulou, M.-I., Cafaro, G., Degboé, Y., Sunzini, F., Virlan, A. T., eds. (2025). *Immune-checkpoint inhibitors in anti-cancer armamentarium: a double-edged sword in risk of developing autoimmunity and immune-related adverse effects*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-5877-5

Table of contents

frontiers | Frontiers in Oncology

TYPE Editorial
PUBLISHED 26 August 2024
DOI 10.3389/fonc.2024.1476475

OPEN ACCESS

EDITED BY
Olivier Feron,
Université catholique de Louvain,
Belgium

*CORRESPONDENCE
Maria-Ioanna Christodoulou
mar.christodoulou@euc.ac.cy

RECEIVED 05 August 2024
ACCEPTED 12 August 2024
PUBLISHED 26 August 2024

CITATION
Tulunay Virlan A, Cafaro G, Sunzini F, Degboe Y and Christodoulou M-I (2024) Editorial: Immune-checkpoint inhibitors in anti-cancer armamentarium: a double-edged sword in risk of developing autoimmunity and immune-related adverse effects.
Front. Oncol. 14:1476475.
doi: 10.3389/fonc.2024.1476475

Editorial: Immune-checkpoint inhibitors in anti-cancer armamentarium: a double-edged sword in risk of developing autoimmunity and immune-related adverse effects

Aysin Tulunay Virlan[1], Giacomo Cafaro[2], Flavia Sunzini[1], Yannick Degboe[3] and Maria-Ioanna Christodoulou[1,4]*

[1]School of Infection & Immunity, University of Glasgow, Glasgow, United Kingdom, [2]Rheumatology Unit, Department of Medicine and Surgery, University of Perugia, Perugia, Italy, [3]Rheumatology Centre, Toulouse University Hospital and University Toulouse III, Toulouse, France, [4]Tumor Immunology and Biomarkers Laboratory, Basic and Translational Cancer Research Center, Department of Life Sciences, School of Sciences, European University Cyprus, Nicosia, Cyprus

KEYWORDS

cancer immunotherapy, immune-checkpoint inhibitors (ICIs), immune-related adverse events (irAEs), autoimmunity, anti-CTLA-4, anti-PD-1/PD-L1

Editorial on the Research Topic

Immune-checkpoint inhibitors in anti-cancer armamentarium: a double-edged sword in risk of developing autoimmunity and immune-related adverse effects

Immunotherapy represents a hopeful approach to managing cancer patients, mostly due to its relatively high safety and durable effects (1). Despite its benefits, emerged autoimmunity and immune-related adverse events (irAEs) are considered the vulnerable points of treatment with anti-CTLA-4 and/or anti-PD-1/PD-L1 antibodies (2). Additionally, individuals with pre-existing autoimmunity comprise a specific group of cancer patients who exhibit a high risk of autoimmune flare-up or irAEs upon IC inhibition (ICI) treatment (2). The incidence of autoimmune and/or immune-related complications is probably undervalued due to relatively short follow-ups, delayed onset, unclear etiology of symptoms, and cancer-associated death prior to their development (3). Furthermore, the landscape of cellular and molecular pathogenetic networks on the ground of immunotherapy is not fully understood. It is probably associated with series of events including expansion of low-avidity T cells and depletion of regulatory T cells, cross-presentation of neoantigens, and epitope spreading (2).

This Research Topic gathered up-to-date original articles, systematic reviews, reviews and case-reports on (auto)immune-mediated AEs in cancer patients upon mono- or combinatorial therapy with antibodies against ICs. Issues addressed regard their incidence, patient follow-up and monitoring, state-of-the art technologies for the elucidation of underlying pathogenetic mechanisms and detection of predictive biomarkers, as well as certain concerns about patients with pre-existing autoimmunity and misdiagnosis of irAEs.

The study by Li et al. provided for the first time data on ICI-associated toxicities in the hematologic and lymphatic systems. The authors worked on about 11.000 cases from more than 35 million reports deposited in the U.S. Food and Drug Administration Adverse Event Reporting System database and suggested that the incidence of hematologic and lymphatic AEs depends on the specific ICI drug, with anti-PD-1/anti-PD-L1 monotherapy linked with greater incidence compared to anti-CTLA-4 treatment, and atezolizumab (PD-L1 inhibitor) adding the highest risk. They also highlighted the involvement of sex dimension, reporting that these AEs appeared more often in female than male in ICI-treated patients. Anti-PD-1/PD-L1 therapy increases significantly the risk also for cardiovascular (CVD) AEs when administered with chemotherapy compared to chemotherapy alone, or as a monotherapy when compared to placebo, according to the systematic review by Zhang et al. Nevertheless, in this case dual therapy with anti-PD-1/PD-L1 plus anti-CTLA-4 antibodies correlates with a higher risk for CVD AEs than anti-PD-1/PD-L1 treatment alone.

The article by Lin et al. offered a comprehensive review of the current state of clinical research on immune checkpoint inhibition-related pneumonitis (CIP); a condition with ever growing incidence, not easily diagnosed due to individual-specific pathogenetic characteristics, and often related to poor prognosis. The authors summarized the risk factors associated with CIP, which include underlying lung disease and smoking that associate with a pro-inflammatory status in the lung, the use of anti-PD-1 rather than anti-PD-L1 regimens, prior radiotherapy associated with DNA damage and secretion of pro-inflammatory cytokines and chemokines, pre-existing autoimmunity or infection, and the type of cancer e.g. squamous cell carcinoma. Immunophenotyping of the inflamed lung tissue, peripheral blood and the bronchoalveolar lavage fluid provide useful predictive and diagnostic indicators of CIP in patients with solid tumors treated with ICI. The authors also reported current advances in the CIP management including pulsed corticosteroid therapy, or, in the cases of steroid-refractory CIP, tocilizumab (anti-human IL-6 receptor antibody) or nintedanib (anti-VEGF/anti-FGFR/anti-PDGFR small molecule tyrosine-kinase inhibitor). However, all the above strategies are in need of further exploration.

In the context of predictive biomarkers, Cao et al., listed a nice summary of cutaneous irAEs-specific indicators per tumor type, that can be assessed in the serum, peripheral blood, or the tumor site of patients. Captivatingly, the authors highlighted the role of multi-omics approaches in the elucidation of pathogenetic mechanisms and pinpointing key deregulated molecular networks in cutaneous irAEs, and further promoting the discovery of potential predictive biomarkers towards precise and personalized clinical approaches. Indicatively, they reviewed proposed single- or multi-gene and protein models, immunophenotyping panels, HLA haplotypes, miRNA/SNPs and tumor microenvironment (TME) parameters for the prediction of ICI-induced AEs or resistance to ICIs, all unraveled upon genomics, transcriptomics, proteomics, and radiomics research. Importantly though, the authors mentioned the need for future confirmation of the predictive ability of the above in larger clinical cohorts and the development of laboratory assays that can be used in clinical routine practice.

Another aspect of the ICI-induced irAEs was the focus of the systematic review article by Liang et al., who explored their effect on survival rates of patients with non-small cell lung cancer. Remarkably, the study revealed that mild and early irAEs (but not severe ones) associate with better overall (OS) and progression-free survival (PFS) compared to the absence of them. Also, irAEs affecting the skin and the endocrine system tend to associate with more favorable survival prognosis than hepatitis or those affecting the gastrointestinal tract or the lung.

Three case reports were also included in this Research Topic. In the first, Daetwyler et al. described the case of a male patient with Hodgkin's lymphoma who after the 6th cycle of treatment with pembrolizumab (anti-PD-1 antibody), developed monocular optic neuropathy, treated successfully with high-dose steroid therapy. Yet, when the second eye was affected, amelioration of symptoms was managed after extended combinatory immunosuppressive therapy. Xiong et al. described the cases of two cancer patients with pre-existing paraneoplastic dermatomyositis and "seronegative" paraneoplastic demyelinating neuropathy, respectively, treated with ICIs, the effectiveness of which were not compromised by intravenous immunoglobulin used for the neuromuscular events. On the occasion of these cases, the authors conducted also a review of the related literature. Lastly, Torres-Zurita et al. reported the case of a patient with advanced, metastatic hepatocellular carcinoma, undergoing second-line treatment with nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4 antibody), who developed sarcoidosis-like reaction (SLR). The authors emphasized the fact that the SLR mimics disease progression, and raised awareness about possible misdiagnosis.

In summary, this Research Topic gathered articles on the current biomedical and clinical research on irAEs being developed in ICIs-treated cancer patients, and adds significant value to the existing knowledge about the utmost importance for their optimal prediction, diagnosis and management, given that these therapeutic approaches become ever more widely used.

Author contributions

ATV: Writing – review & editing. GC: Writing – review & editing. FS: Writing – review & editing. YD: Writing – review & editing. M-IC: Writing – original draft, Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Hoos A. Development of immuno-oncology drugs - from CTLA4 to PD1 to the next generations. *Nat Rev Drug Discovery*. (2016) 15:235–47. doi: 10.1038/nrd.2015.35

2. June CH, Warshauer JT, Bluestone JA. Is autoimmunity the Achilles' heel of cancer immunotherapy? *Nat Med*. (2017) 23:540–7. doi: 10.1038/nm.4321

3. Freeman-Keller M, Kim Y, Cronin H, Richards A, Gibney G, Weber JS. Nivolumab in resected and unresectable metastatic melanoma: characteristics of immune-related adverse events and association with outcomes. *Clin Cancer Res*. (2016) 22:886–94. doi: 10.1158/1078-0432.CCR-15-1136

frontiers | Frontiers in Immunology

TYPE Case Report
PUBLISHED 09 May 2023
DOI 10.3389/fimmu.2023.1171981

OPEN ACCESS

EDITED BY
Giacomo Cafaro,
University of Perugia, Italy

REVIEWED BY
Dimitra Grapsa,
National and Kapodistrian University of Athens, Greece
Sudhakar Tummala,
University of Texas MD Anderson Cancer Center, United States

*CORRESPONDENCE
Heinz Läubli
heinz.laeubli@usb.ch

RECEIVED 22 February 2023
ACCEPTED 27 April 2023
PUBLISHED 09 May 2023

CITATION
Daetwyler E, Zippelius A, Meyer P and Läubli H (2023) Pembrolizumab-induced optic neuropathy – a case report. *Front. Immunol.* 14:1171981. doi: 10.3389/fimmu.2023.1171981

Pembrolizumab-induced optic neuropathy – a case report

Eveline Daetwyler[1], Alfred Zippelius[1,2], Peter Meyer[3] and Heinz Läubli[1,2]*

[1]Division of Medical Oncology, University Hospital Basel, Basel, Switzerland, [2]Department of Biomedicine, University of Basel, Basel, Switzerland, [3]Eye Clinic, University Hospital Basel, Basel, Switzerland

Background: Immune checkpoint inhibitor (ICI) treatment has become important for treating various cancer types, including Hodgkin's lymphoma. However, ICI can overstimulate the immune system, leading to a broad range of immunological side effects, known as immune-related adverse events (irAEs). Here, we report a case of optic neuropathy caused by pembrolizumab.

Case presentation: A patient with Hodgkin's lymphoma received pembrolizumab every three weeks. Twelve days after the sixth cycle of pembrolizumab, the patient was admitted to the emergency department with blurred vision, visual field impairment and altered color perception affecting the right eye. The diagnosis of immune-related optic neuropathy was established. Pembrolizumab was stopped permanently and high-dose steroid treatment was immediately started. This emergency treatment led to a satisfactory binocular vision and an improvement of visual acuity testing results. After another 7 months, the left eye was affected with the same symptoms. At this time, only an extended immunosuppressive therapy consisting of high-dose steroid treatment, plasmapheresis, immunoglobulin treatment, retrobulbar injection of steroids and mycophenolate mofetil, successfully reduced the symptoms.

Conclusions: This case highlights the need for prompt recognition and treatment of rare irAEs, such as optic neuropathy. Urgent treatment with initial high-dose steroid treatment is required to avoid persistent loss of visual acuity. Options for further treatment are mainly based on small case series and case reports. In our case, a retrobulbar injection of steroids in combination with mycophenolate mofetil showed significant success in treating steroid-refractory optic neuropathy.

KEYWORDS

immune-related adverse event(s), optic neuropathy, immune checkpoint inhibitor (ICI), neuropathic, PD-1/L1, case report

Introduction

Immune checkpoint inhibitor (ICI) treatment has established its relevance in refractory and relapsed Hodgkin's lymphoma (1, 2). While being effective, ICI treatment is associated with a broad spectrum of immune-related adverse events (irAEs) (3–5). Thereby, ocular irAEs are rare side effects, but can have a major impact on the quality of life in the case of impaired vision or complete loss of vision, respectively (3–7). In this report, we present a challenging case of pembrolizumab-induced bilateral optic neuropathy. It first occurred in the right eye, which was successfully treated with high-dose steroids. Seven months later, the left eye was affected too and despite high-dose steroids, plasmapheresis and immunoglobuline treatment, no persistent clinical benefit was achieved. Only the administration of a retrobulbar injection of steroids in combination with mycophenolate mofetil led to a sustained success.

Case presentation

A 67-year-old woman was diagnosed with Hodgkin's lymphoma (initial disease stage according to Ann Arbor classification: IIA, without risk factors) which continued to progress after initial standard treatment with ABVD (liposomal doxorubicin, bleomycin, vinblastine, dacarbazine). Due to disease progression, two cycles of ICE (ifosfamide, carboplatin, etoposide) were applied, followed by brentuximab vedotin which had to be stopped after four months due to polyneuropathy. Stem cell transplantation was not possible due to a relevant pre-existing medical condition (congestive heart failure). Pembrolizumab was then started in this refractory situation. It was administered every three weeks with a dosage of 200mg intravenously. Two months after starting pembrolizumab a complete remission was achieved.

Twelve days after the sixth cycle of pembrolizumab, the patient presented herself to the emergency department with blurred vision, visual field impairment and altered color perception affecting the right eye. Fundus examination showed papilledema in the right temporal optic disc (Figure 1A). Further testing revealed a visual acuity of 0.05 on the right side and a horizontal visual field loss (Figure 1B). The brain magnetic resonance imaging (MRI) showed no abnormality. The cerebrospinal fluid (CSF) analysis including extensive infectious parameters (including Borrelia species, Flavirus, Treponema pallidum, different herpes virus, measles and mumps virus), neuronal and paraneoplastic antibodies (including anti-amphiphysin antibodies, anti-Hu/anti-Yo/anti-Ri/anti-Ma/anti-Tr antibodies, anti-SOX1 antibodies, anti-ZiC4 antibodies, anti-collapsin-responsive mediator protein 5 antibodies [CRMP 5], anti-glutamic acid decarboxylase antibodies [anti-GAD], anti-angiotensin converting enzyme [ACE] antibodies), oligoclonal bands, malignant cells, flow cytometry remained without any relevant findings, despite a slightly elevated total protein level. Moreover, aquaporin-4 immunoglobulin G antibodies (ACQ4) as well as myelin oligodendrocyte glycoprotein antibodies (MOG) were not pathologically elevated. Considering these diagnostic results, the patient was diagnosed with an immune-related optic neuropathy due to PD-1 blockade with pembrolizumab. High-dose

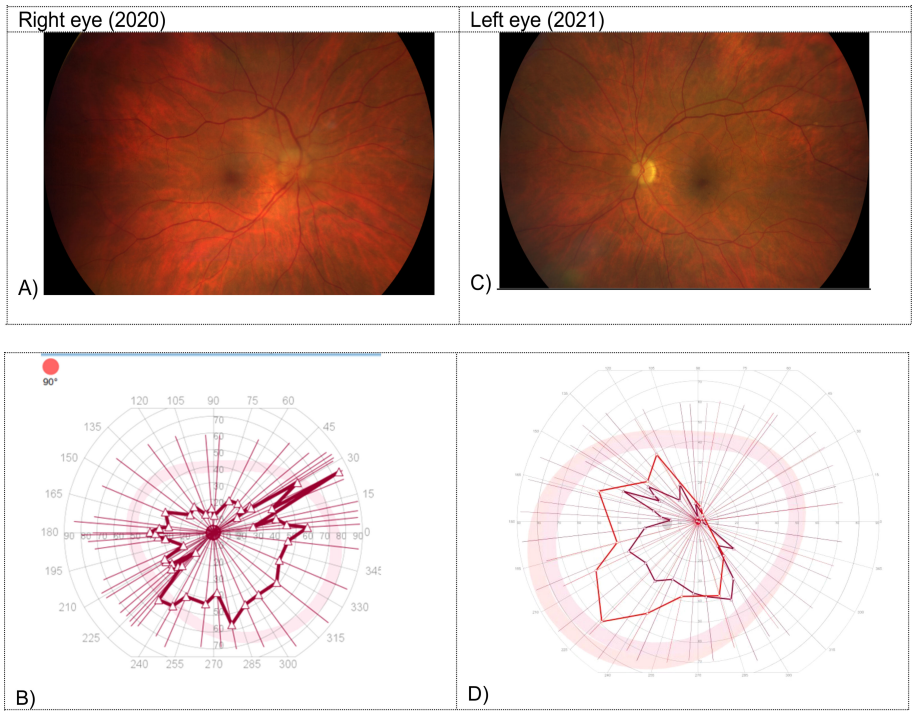


FIGURE 1
Fundus examination and visual field testing on the right in 2020 **(A, B)** and on the left side in 2021 **(C, D)**. **(A)** Papilledema in the right temporal optic disc. **(B)** Horizontal visual field loss in the visual field testing on the right side. **(C)** Sectorial papilledema in the left optic disc. **(D)** Horizontal visual field loss in the visual field testing on the left side.

10.3389/fimmu.2023.1171981

steroid treatment was immediately initiated (125mg intravenous methylprednisolone for five days), followed by tapering of prednisone over a period of four months. The symptoms showed partial regression (visual acuity of 0.3). Additional treatment was not necessarily due to a satisfactory clinical outcome regarding binocular vision. The treatment with pembrolizumab was stopped permanently. There was no sign of tumor activity.

Seven months after the initial presentation with optic neuropathy on the right side, the patient was admitted to the hospital again with complaints of blurred vision, visual field impairment and altered color perception, affecting now the left eye. Fundus examination revealed sectorial papilledema in the left optic disc (Figure 1C). A visual acuity of 0.4 in the left side (preliminary recording: 0.8) with horizontal visual field loss was documented (Figure 1D). The brain MRI revealed an increasing cerebrospinal fluid (CSF) signal along the left optic nerve with continued minimal contrast uptake (Figure 2). Again, an extensive examination of the CSF (same parameters as in the initial examination) showed no abnormal finding, despite a slightly elevated total protein level. In the imaging of the whole body, there was no signs of lymphoma activity. The patient was diagnosed with immune-related optic neuropathy on the left side. Treatment with high-dose steroids was immediately started (500mg intravenous methylprednisolone). In addition, plasmapheresis was performed five times after a deterioration in the symptoms as a result of a reduced high-dose steroid treatment (250mg intravenous methylprednisolone). The symptoms improved and the steroid dosage was gradually reduced. At a dosage of 80mg prednisone (1mg per kg bodyweight) the symptoms worsened again (visual acuity 0.2) and the irAE was interpreted as steroid-refractory. Immunoglobulins were intravenously administered for five days. Due to the absence of relevant clinical improvement, a retrobulbar injection of steroids was administered and treatment with mycophenolate mofetil (1000mg peroral twice daily) was started. This treatment improved the symptoms so that the steroid treatment could finally be stopped after six months of tapering. The dosage of mycophenolate mofetil could gradually be reduced (after 12 months: current dosage of 250mg peroral twice daily) without recurrence of symptoms. A visual acuity of 0.8 could be measured on the left side, corresponding to the baseline assessment. Six months after affecting the left eye the patient is independent again in everyday life. So far, there is no sign of tumor activity.

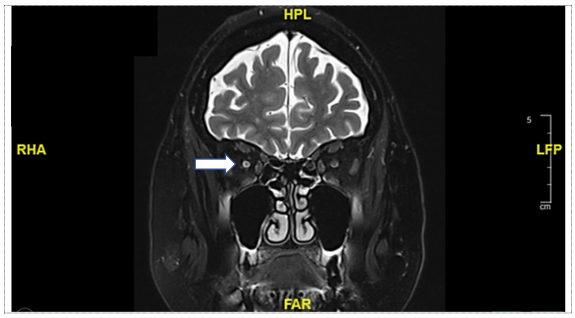


FIGURE 2
Coronal T2-weighted magnetic resonance imaging (MRI): Increasing cerebrospinal fluid (CSF) signal along the left optic nerve with continued minimal contrast uptake (white arrow).

Discussion

Ocular side effects are rare after ICI treatment (3–7). They occur in approximately 3% of patients treated with ICI, according to the FDA Adverse Event Reporting System (FAERS) pharmacovigilance database (7). It is believed that this rare occurrence is primarily due to the immune-privileged location (8). However, this can be nullified under certain conditions leading to ocular irAEs (4). Hereby, the combination of anti-CTLA-4 and PD-(L)1 is associated with a higher risk of the occurrence of these side effects compared to a monotherapy of ICI (7). The spectrum of ocular irAEs ranges from the most common ocular side effects, including ophthalmoplegia, uveitis and keratoconjunctivitis sicca (dry eye syndrome), to optic neuropathy which is much rarer (3–7, 9). In our case report, we highlight the rare complication of ICI-treatment leading to an optic neuropathy.

The clinical presentation of ICI-induced optic neuropathy is not entirely consistent with the classic triad (unilateral decreased vision, dyschromatopsia, pain), known in optic neuropathy associated with multiple sclerosis. The leading symptoms of our patient were complaints of blurred vision, visual field impairment and altered color perception which occurred with a time delay on the right, then seven months later on the left side. Pain was not reported. This is also supported by a study with 11 patients, whereas the vast majority showed painless decreased vision, floaters or both (10). Sixty-four percent of these patients showed bilateral optic neuropathy (10). Optic neuropathy occurs on average 10-20 weeks after the initiation of ICI treatment, but can also have the potential of later occurrence (6, 9, 10). The diagnosis requires observed abnormalities in optic nerve enhancement on the MRI and the clinical presentation which is consistent with the diagnosis of an optic neuropathy (3–5, 11). Therefore, prompt involvement of an ophthalmologist is mandatory (3–5). To exclude other aetiologies of optic neuropathy, such as neuromyelitis optica, autoimmune diseases, infectious or parainfectious causes, an extensive diagnostic pathway is necessary, including laboratory examinations of the blood as well as cerebral fluid analysis (3–5, 12).

After the diagnostics, the initial treatment has to be started immediately. Steroid treatment remains the backbone of this treatment, mentioned in the publications and guidelines cited below (3–6, 9, 10, 13–20) (Table 1). Options for further treatment are mainly based on case series and case reports. In the literature, the following additional interventions are described: plasmapheresis (n=4), intravenous immunoglobulin (n=2), infliximab (n=1), rituximab (n=1), mycophenolate mofetil (MPA) (n=1) (10, 13, 16, 20) (Table 1).

MPA was used in our patient due to its convincing drug characteristics, including the good tolerability and safety profile as well as its simple oral intake (23, 24). MPA reversibly inhibits the

10.3389/fimmu.2023.1171981

TABLE 1 Systemic therapeutic recommendations for ICI-induced optic neuropathy in the literature, according to the guidelines and publications (N/A = not applicable).

Systemic therapeutic recommendations for ICI-induced optic neuropathy						
guidelines, publication date author, publication date, study design with number of patients (n)	**Treatment options**					**Ocular outcome**
	steroid treatment	topical treatment	plasma-pheresis	Intra-venous immune-globulin	other immune-suppressive treatment	
ESMO guidelines, 2022 (3)	✓ systemic corticosteroids depending on severity					
SITC guidelines, 2020 (4, 21)	✓ systemic corticosteroids depending on severity					
ASCO guidelines 2021 (5)	✓ systemic corticosteroids depending on severity					
Boisseau et al., 2017, case report (n=1) (13)	✓ intravenous methyl-prednisolone 1g for 3 days, then oral steroid taper		✓ 10 sessions			n=1 with complete regression (visual acuity, MRI, optical coherence tomography)
Francis et al., 2020, case series (n=11) (13) (n=10 with treatment)	✓ oral prednisone (60mg, 80mg daily), then oral steroid taper (n=4)	✓ topical prednisolone, timolol/ dorzolamide (n=1)				n=2 with complete regression (optic nerve examination, visual field pattern)
	✓ intravenous dexamethasone 3g, then oral steroid taper (n=1)		✓ 5 sessions	✓ 1 application	✓ rituximab 3 applications	n=1 with residual defect (optic nerve examination, visual field pattern)
	✓ intravenous methyl-prednisolone 1g for 2-5 days, then oral steroid taper (n=4)	✓ topical timolol/ dorzolamide, difluprednate, brimonidine (n=1)				n=3 with residual defect (optic nerve examination, visual field pattern), n=1 with abnormal optic nerve examination (visual field pattern NA)
	✓ intravenous methyl-prednisolone 1g for 5 days, then oral steroid taper (n=1)		✓ 5 sessions			n=1 with abnormal optic nerve examination (visual field pattern NA)
Kartal et al., 2018, case report (n=1) (14)	✓ intravenous corticosteroids 1g for 5 days, no taper					n=1 with improvement (visual acuity)
Kaur et al., 2019, case description (n=1) (15)	✓ high-dose corticosteroids					n=1 with improvement (symptoms)
Kim et al., 2019, case description (n=1) (16)	✓ intravenous corticosteroids			✓ (N/A)	✓ infliximab	n=1 with residual defect (optic nerve examination, visual field pattern)
Mori et al., 2018, case report (n=1) (17)	✓ intravenous methyl-prednisolone 1g for 3 days, then oral steroid taper					n=1 with residual defect (visual field pattern), but normalization of the optic nerve examination and visual acuity
Noble et al., 2019, case description (n=1) (6)	✓ intravenous high-dose corticosteroids					n=1 with improvement (visual acuity, visual field pattern)

(Continued)

10.3389/fimmu.2023.1171981

TABLE 1 Continued

Systemic therapeutic recommendations for ICI-induced optic neuropathy						
Sengul Samanci et al., 2019, case report (n=1) (18)	✓ intravenous methyl-prednisolone 2mg/kg body weight, then oral steroid taper					n=1 with residual defect (visual field pattern, visual field acuity), but normalization of the optic nerve examination
Sun et al., 2008, case report (n=1) (19)	✓ intravenous dexamethasone, then intravenous methyl-prednisolone 250mg, then oral steroid taper					n=1 with residual defect (optic nerve examination, visual field pattern, visual acuity)
Wilson et al., 2016, case report (n=1) (20)	✓ intravenous methyl-prednisolone, then oral steroid taper		✓ 5 sessions in steroid-refractory situation		✓ myco-phenolate mofetil in steroid-refractory situation	n=1 with regression (visual field pattern, optic nerve examination) in one eye; atrophic optic nerve in the other eye
Yeh et al., 2015, case report (n=1) (22)		✓ topical prednisolone, atropine				n=1 with residual defect (optic nerve examination, visual field pattern, visual acuity)
Zhou et al., 2021, case series (n=3) (8)	✓ intravenous methyl-prednisolone					n=3 with complete regression

inosine monophosphate dehydrogenase which is involved in guanosine nucleotide synthesis, on which the T and B lymphocytes are exclusively dependent for proliferation (25). In addition, MPA also affects intracellular signalling pathways for lymphocyte metabolic programming (25). The efficacy of MPA is also described in optic neuropathy associated with autoimmune inflammatory disorder (23, 24). Moreover, MPA is the only drug described in steroid-refractory optic neuropathy (20). However, further investigations into the agents themselves and into the optimal sequence of these immunosuppressive interventions are required.

Conclusion

In conclusion, we report a case with severe optic neuropathy due to PD-1 blockade showing a bilateral involvement, first of the right and then some months later of the left eye. On the right side, prompt high-dose steroid treatment showed partial success. On the left side, despite the initiation of high-dose steroid treatment at the beginning, followed by plasmapheresis and immunoglobulin treatment, the situation could only be stabilized with a retrobulbar injection of steroids and the start of treatment with mycophenolate mofetil (MPA). We emphasize the need of prompt recognition, involvement of ophthalmologists and necessity of urgent treatment to avoid substantial morbidity.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Author contributions

ED, AZ, PM, HL participated in the care of the patient. ED drafted the manuscript. AZ, PM and HL have revised the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

AZ: received consulting/advisor fees from Bristol-Myers Squibb, Merck Sharp & Dohme, Hoffmann–La Roche, NBE Therapeutics, Secarna, ACM Pharma, and Hookipa, and maintains further non-commercial research agreements with Secarna, Roche, Vectorbiopharma, T3 Pharma and Bright Peak Therapeutics. HL: received travel grants and consultant fees from Bristol-Myers Squibb, Alector, and MSD. HL received research support from Bristol-Myers Squibb, Novartis, GlycoEra and Palleon Pharmaceuticals.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Chen R, Zinzani PL, Lee HJ, Armand P, Johnson NA, Brice P, et al. Pembrolizumab in relapsed or refractory Hodgkin lymphoma: 2-year follow-up of KEYNOTE-087. *Blood.* (2019) 134(14):1144–53. doi: 10.1182/blood.2019000324

2. Kuruvilla J, Ramchandren R, Santoro A, Paszkiewicz-Kozik E, Gasiorowski R, Johnson NA, et al. Pembrolizumab versus brentuximab vedotin in relapsed or refractory classical Hodgkin lymphoma (KEYNOTE-204): an interim analysis of a multicentre, randomised, open-label, phase 3 study. *Lancet Oncol* (2021) 22(4):512–24. doi: 10.1016/S1470-2045(21)00005-X

3. Haanen J, Obeid M, Spain L, Carbonnel F, Wang Y, Robert C, et al. Management of toxicities from immunotherapy: ESMO clinical practice guideline for diagnosis, treatment and follow-up☆. *Ann Oncol* (2022) 33(12):1217–38. doi: 10.1016/j.annonc.2022.10.001

4. *SITC immunotherapy.pdf* . Available at: http://dx.doi.org/jitc-2021-002435.

5. Schneider BJ, Naidoo J, Santomasso BD, Lacchetti C, Adkins S, Anadkat M, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. *J Clin Orthod* (2021) 39 (36):4073–126. doi: 10.1200/JCO.21.01440

6. Noble CW, Gangaputra SS, Thompson IA, Yuan A, Apolo AB, Lee J-M, et al. Ocular adverse events following use of immune checkpoint inhibitors for metastatic malignancies. *Ocul Immunol Inflamm* (2020) 28(6):854–9. doi: 10.1080/09273948.2019.1583347

7. Bomze D, Meirson T, Hasan Ali O, Goldman A, Flatz L, Habot-Wilner Z. Ocular adverse events induced by immune checkpoint inhibitors: a comprehensive pharmacovigilance analysis. *Ocul Immunol Inflamm* (2022) 30(1):191–7. doi: 10.1080/09273948.2020.1773867

8. Zhou R, Caspi RR. Ocular immune privilege. *F1000 Biol Rep* (2010) 2. http://dx.doi.org/10.3410/B2-3. doi: 10.3410/B2-3

9. Zhou L, Wei X. Ocular immune-related adverse events associated with immune checkpoint inhibitors in lung cancer. *Front Immunol* (2021) 12:701951. doi: 10.3389/fimmu.2021.701951

10. Francis JH, Jaben K, Santomasso BD, Canestraro J, Abramson DH, Chapman PB, et al. Immune checkpoint inhibitor-associated optic neuritis. *Ophthalmology.* (2020) 127(11):1585–9. doi: 10.1016/j.ophtha.2020.05.003

11. Yu CW, Yau M, Mezey N, Joarder I, Micieli JA. Neuro-ophthalmic complications of immune checkpoint inhibitors: a systematic review. *Eye Brain.* (2020) 12:139–67. doi: 10.2147/EB.S277760

12. Hoorbakht H, Bagherkashi F. Optic neuritis, its differential diagnosis and management. *Open Ophthalmol J* (2012) 6:65–72. doi: 10.2174/1874364101206010065

13. Boisseau W, Touat M, Berzero G, Savatovsky J, Marabelle A, Touitou V, et al. Safety of treatment with nivolumab after ipilimumab-related meningoradiculitis and bilateral optic neuropathy. *Eur J Cancer.* (2017) 83:28–31. doi: 10.1016/j.ejca.2017.05.036

14. Kartal Ö, Ataş E. Bilateral optic neuritis secondary to nivolumab therapy: a case report. *Medicina* (2018) 54(5). doi: 10.3390/medicina54050082

15. Kaur A, Doberstein T, Amberker RR, Garje R, Field EH, Singh N. Immune-related adverse events in cancer patients treated with immune checkpoint inhibitors: a single-center experience. *Med* . (2019) 98(41):e17348. doi: 10.1097/MD.0000000000017348

16. Kim JM, Materin MA, Sznol M, Kluger HM, Weiss S, Chow J, et al. Ophthalmic immune-related adverse events of immunotherapy: a single-site case series. *Ophthalmology.* (2019) 126(7):1058–62. doi: 10.1016/j.ophtha.2019.01.031

17. Mori S, Kurimoto T, Ueda K, Enomoto H, Sakamoto M, Keshi Y, et al. Optic neuritis possibly induced by anti-PD-L1 antibody treatment in a patient with non-small cell lung carcinoma. *Case Rep Ophthalmol* (2018) 9(2):348–56. doi: 10.1159/000491075

18. Sengul Samanci N, Ozan T, Çelik E, Demirelli FH. Optic neuritis related to atezolizumab treatment in a patient with metastatic non-Small-Cell lung cancer. *JCO Oncol Pract* (2020) 16(2):96–8. doi: 10.1200/JOP.19.00438

19. Sun J, Schiffman J, Raghunath A, Ng Tang D, Chen H, Sharma P. Concurrent decrease in IL-10 with development of immune-related adverse events in a patient treated with anti-CTLA-4 therapy. *Cancer Immun* (2008) 8:9.

20. Wilson MA, Guld K, Galetta S, Walsh RD, Kharlip J, Tamhankar M, et al. Acute visual loss after ipilimumab treatment for metastatic melanoma. *J Immunother Cancer.* (2016) 4:66. doi: 10.1186/s40425-016-0170-9

21. Maus MV, Alexander S, Bishop MR, Brudno JN, Callahan C, Davila ML, et al. Society for immunotherapy of cancer (SITC) clinical practice guideline on immune effector cell-related adverse events. *J Immunother Cancer* (2020) 8(2). doi: 10.1136/jitc-2020-001511

22. Yeh OL, Francis CE. Ipilimumab-associated bilateral optic neuropathy. *J Neuroophthalmol.* (2015) 35(2):144–7. doi: 10.1097/WNO.0000000000000217

23. Huh S-Y, Kim S-H, Hyun J-W, Joung A-R, Park MS, Kim B-J, et al. Mycophenolate mofetil in the treatment of neuromyelitis optica spectrum disorder. *JAMA Neurol* (2014) 71(11):1372–8. doi: 10.1001/jamaneurol.2014.2057

24. Wang Y, Ma J, Chang H, Zhang X, Yin L. Efficacy of mycophenolate mofetil in the treatment of neuromyelitis optica spectrum disorders: an update systematic review and meta -analysis. *Mult Scler Relat Disord* (2021) 55:103181. doi: 10.1016/j.msard.2021.103181

25. Allison AC, Eugui EM. The design and development of an immunosuppressive drug, mycophenolate mofetil. *Springer Semin Immunopathol* (1993) 14(4):353–80. doi: 10.1007/BF00192309

frontiers | Frontiers in Immunology

TYPE Review
PUBLISHED 22 June 2023
DOI 10.3389/fimmu.2023.1207544

OPEN ACCESS

EDITED BY
Maria-Ioanna (Marianna) Christodoulou,
European University Cyprus, Cyprus

REVIEWED BY
Zhen Zong,
Nanchang University, China
Jiatong Ding,
Nanchang University, China
in collaboration with reviewer ZZ
Philippe Lefrançois,
McGill University, Canada

*CORRESPONDENCE
Ying Zou
zouyingsh@163.com

RECEIVED 17 April 2023
ACCEPTED 05 June 2023
PUBLISHED 22 June 2023

CITATION
Cao T, Zhou X, Wu X and Zou Y (2023) Cutaneous immune-related adverse events to immune checkpoint inhibitors: from underlying immunological mechanisms to multi-omics prediction. *Front. Immunol.* 14:1207544. doi: 10.3389/fimmu.2023.1207544

Cutaneous immune-related adverse events to immune checkpoint inhibitors: from underlying immunological mechanisms to multi-omics prediction

Ting Cao, Xuyang Zhou, Xingbiao Wu and Ying Zou*

Allergic Dermatoses Clinical Center, Shanghai Skin Disease Hospital, Tongji University School of Medicine, Shanghai, China

The development of immune checkpoint inhibitors (ICIs) has dramatically altered the landscape of therapy for multiple malignancies, including urothelial carcinoma, non-small cell lung cancer, melanoma and gastric cancer. As part of their anti-tumor properties, ICIs can enhance susceptibility to inflammatory side effects known as immune-related adverse events (irAEs), in which the skin is one of the most commonly and rapidly affected organs. Although numerous questions still remain unanswered, multi-omics technologies have shed light into immunological mechanisms, as well as the correlation between ICI-induced activation of immune systems and the incidence of cirAE (cutaneous irAEs). Therefore, we reviewed integrated biological layers of omics studies combined with clinical data for the prediction biomarkers of cirAEs based on skin pathogenesis. Here, we provide an overview of a spectrum of dermatological irAEs, discuss the pathogenesis of this "off-tumor toxicity" during ICI treatment, and summarize recently investigated biomarkers that may have predictive value for cirAEs *via* multi-omics approach. Finally, we demonstrate the prognostic significance of cirAEs for immune checkpoint blockades.

KEYWORDS

immune checkpoint inhibitors, cutaneous immune-related adverse events, multi-omics, biomarkers, cutaneous

1 Introduction

The development of immune checkpoint inhibitors (ICIs), such as monoclonal antibodies targeting programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), has dramatically changed the landscape of therapy for multiple malignancies. ICIs represent one type of immune therapy for cancer, among other options such as, surgery, chemotherapy, radiotherapy, targeted

therapy and immune therapy. In contrast to other therapies that use toxic chemical or physical agents to kill tumors, immunotherapy aims to harness the immune response. Immunotherapy is premised based on the theory that the immune system should be able to eliminate tumors, but the tumors 'escape' by some mechanisms, termed 'immunoediting' (1, 2). Accordingly, immunotherapy kills tumors by enhancing the anti-tumor ability of the immune system or by inhibiting tumor immunoediting. It has been established that checkpoints are some regulators of immune response, and tumors could specifically stimulate some negative checkpoints to suppress the immune response, thus escaping (3). Therefore, the immune system may be used to target tumors by inhibiting negative checkpoints, such as CTLA-4 and PD-1/PD-L1.

The intervention of immune homeostasis by ICIs can enhance the anti-tumor function of the immune system, while also leading to some adverse effects resulting from the systemic immune overactivation (Table 1). These unwanted effects are often termed immune-related adverse events (irAEs). Among all the related organs and systems, the skin is one of the most common targets, of which cutaneous irAEs (cirAEs) are often the first to manifest (5). Since the suppressive effects of checkpoints on the immune response are inhibited by ICIs, lymphocytes become over-activated (22, 23), pro-inflammatory cytokines are abundantly released (24, 25), and immune tolerance is destroyed (26, 27), all of which may contribute to the irAEs. These adverse events present a challenge for cancer patients receiving ICIs and can even force them to withdraw from ICI therapy. However, the precise mechanism of irAE remains unknown, and treatment primarily comprises immunosuppressants, such as glucocorticoids (28). Although there is scant evidence showing that the application of immunosuppressors can offset the anti-tumor effect of ICIs (29), the development of new adverse events (e.g., opportunistic infection, hyperglycemia, fluid retention, anxiety, and osteoporosis) should not be ignored over the long term (30, 31).

Since cirAEs occur often and early, influencing the life quality of patients, which reduces patient compliance to ICIs, the treatment of which also gives rise to a series of new problems, there is an urgent need to identify predictive biomarkers of cirAEs. Several risk factors have been identified by epidemiological investigation, and the serum levels of several molecules in patients suffering from irAEs have been found to exhibit significant differences compared to those without irAEs (Table 2). However, none of these biomarkers have shown satisfying prediction efficacy, which may be due to the heterogeneity and complex mechanisms of irAEs. The recent advent of multi-omics, a combined technology including genomics, transcriptomics, proteomics and metabolomics, has been associated with substantial progress for revealing the mechanism and predicting irAEs. Analyzing the genome helps us to find mutations that are responsible for ICI-resistance and irAEs, thus contributing to uncovering the mechanism of irAEs and predicting the risk. Regarding to the heterogeneity, transcriptomics deals with the distinct expression of genes, providing a context-dependent understanding of what actually occur in the anti-tumor immunity, and proteomics provides functional insight into genomics. Moreover, since the metabolic reprogramming is a hallmark of cancers, which is associated with the tumorigenesis, progression, metastasis and drug-resistance, the screening for metabolomics reveals the current condition or status, helping to determine whether the tumors are responsive to ICIs and whether the immune homeostasis is disturbed to elicit adverse

TABLE 1 Common cirAEs.

cirAEs	Manifestations	Immune checkpoints	Ref.
Pruritus	Inflamed skin and scratch marks	PD-1/PD-L1, CTLA-4	(4–7)
Maculopapular rash	Faint erythematous macules and papules coalescing into plaques	PD-1/PD-L1, CTLA-4	(5, 8, 9)
Bullous pemphigoid (BP)	Large, fluid-filled blisters located in between skin folding or creases of skin	PD-1/PD-L1, CTLA-4	(10–12)
Vitiligo	Patchy loss of skin color, premature whitening or graying of the hair,	PD-1/PD-L1, CTLA-4	(6, 13, 14)
Psoriasiform	Patchy rash varying in color, small scaling spots, dry and cracked skin	PD-1/PD-L1, CTLA-4	(13, 15)
Eczema	Dry and cracked skin, itchiness, rash on swollen skin	PD-1/PD-L1, CTLA-4	(5, 16, 17)
Stevens Johnson Syndrome (SJS)	Painful raw areas called erosions that resemble a severe hot-water burn	PD-1/PD-L1, CTLA-4	(18)
Toxic epidermal necrolysis (TEN)	Widespread skin pain, spreading rash, blisters and large areas of peeling skin, sores, swelling and crusting on the mucous membranes, including the mouth, eyes and vagina	PD-1/PD-L1, CTLA-4	(19, 20)
Drug reaction with eosinophilia and systemic symptoms (DRESS)	An extensive mucocutaneous rash, accompanied by fever, lymphadenopathy, hepatitis, hematologic abnormalities with eosinophilia and atypical lymphocytes	PD-1/PD-L1, CTLA-4	(6, 21)

TABLE 2 Some current biomarkers of irAEs.

Category	Biomarker	Specific irAE	Specific cancer type
Serum factors	IL-6 (32–34)	Non-specific	Non-specific
	IL-17 (25, 35)	ICIs-induced colitis,	Melanoma
	C reaction protein (36–38)	Non-specific	RCC, NSCLC
	Preexisting auto-antibody (39–41)	Endocrine irAEs	Non-specific
	Serum neurofilament light chain (42)	Neuro irAEs	Non-specific
Cells	Neutrophil to lymphocyte ratio (43)	Non-specific	Non-specific
	Platelet-to-lymphocyte ratio (44)	Non-specific	NSCLC
	$IgG4^+/PD\text{-}1^+$ MFI ratio (45)	Non-specific	Non-specific
	Tumor Infiltrating Lymphocytes (46)	Cutaneous irAEs	Melanoma
Others	TMB (47)	Non-specific	Non-specific
	Circulating tumor DNA (48, 49)	Non-specific	Non-specific
	Indoleamine 2,3-dioxygenase 1 (50)	Immune-mediated hepatotoxicity	Non-specific

RCC, renal cell carcinoma; NSCLC, non-small cell lung cancer; IL-6, interleukin-6; IL-17, interleukin-17; TMB, tumor mutation burden; MFI, mean fluorescence intensity.

events (51–53). From a systemic biology perspective, a macroscopic immune network has gradually been uncovered and additional molecules that were previously unknown have been identified as biomarkers for the prediction of both anti-tumor efficacy and irAEs.

2 Epidemiology and clinical manifestations

Cutaneous irAEs is one of the most common types of irAEs, with regards to morbidity. cirAEs arise in as many as 34% of patients receiving anti-PD-1/PD-L1 therapy and about 43% –45% of those on CTLA-4 inhibitors (54). The incidence of cirAEs varies among the patients suffering from different types of cancers, and even different pathological subtypes and different stages of certain cancers (55). Distinct types of ICIs can also lead to distinct incidence of cirAEs (56). Nevertheless, cirAEs commonly manifest as maculopapular rash, psoriasiform rash, bullous pemphigoid (BP), vitiligo, pruritus, eczema, and Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) less commonly (13). Cutaneous irAEs occur early, with the time to onset ranging from 3 to 4 weeks (57), compared to 12 weeks in the endocrine gland (58) and 22.2 weeks in the gastrointestinal tract (59). Therefore, for the common and early onset and suffering manifestations, there is an urgent need to investigate cirAEs, uncovering its mechanism, and identifying its predictive biomarkers. Such information will serve to relieve the pain of patients as well as contribute to cancer therapy.

3 Mechanisms

ICIs are agents that block the interaction between checkpoints and the associated ligands and thereby block the subsequent intracellular signaling. The most commonly used ICIs target PD-1/PD-L1, with others targeting of CTLA-4, Tim-3, and LAG-3. Although both CTLA-4 and PD-1/PD-L1 are negative checkpoints, they play different roles in regulating the immune response, thus leading to different adverse events once blocked. CTLA-4 is a competitive inhibitor of CD28, a co-stimulatory signal receptor that is essential for T cell activation (Figure 1A). CTLA-4 is considered to be the most important negative checkpoint, as murine animals lacking CTLA-4 will die at an early age due to severe lymphoproliferation (60). Moreover, regulatory T cells (Treg) also function *via* CTLA-4 expression, competitively binding to B7 expressed on antigen presenting cells (APCs), which blocks its co-stimulatory effects on naïve T cells (61). PD-1 is one of the inhibitory receptors that contain an immunoreceptor tyrosine-based inhibition motif (ITIM) or the related immunoreceptor tyrosine-based switch motif (ITSM), which could remove the phosphates once activated and thereby inhibit the signaling (Figure 1B). PD-1 is able to bind with PD-L1 and PD-L2, which are constitutively expressed by a variety of cells and inductively expressed on APCs during inflammation, respectively (62, 63). Regulating the expression of PD-1 can control the intensity of the immune response, as pro-inflammatory cytokines have been shown to down-regulate PD-1 expression and murine models lacking PD-1 tend to develop auto-immune diseases (64). Therefore, various checkpoints substantially contribute to the regulation of the immune response and tolerance. Medications that affect checkpoints may lead to a disorder in immune homeostasis.

Having established a macroscopic overview of the action of ICIs in the immune response, we will now discuss the mechanism of irAEs, especially cirAEs. In general, irAEs are primarily induced by the overactivation of the immune response due to a blockades of negative regulators, and auto-immune responses are activated as a result. As previously discussed, cirAEs manifest commonly and early, indicating that cirAEs have some distinct characteristics other than the common mechanism of irAEs. Here, we propose

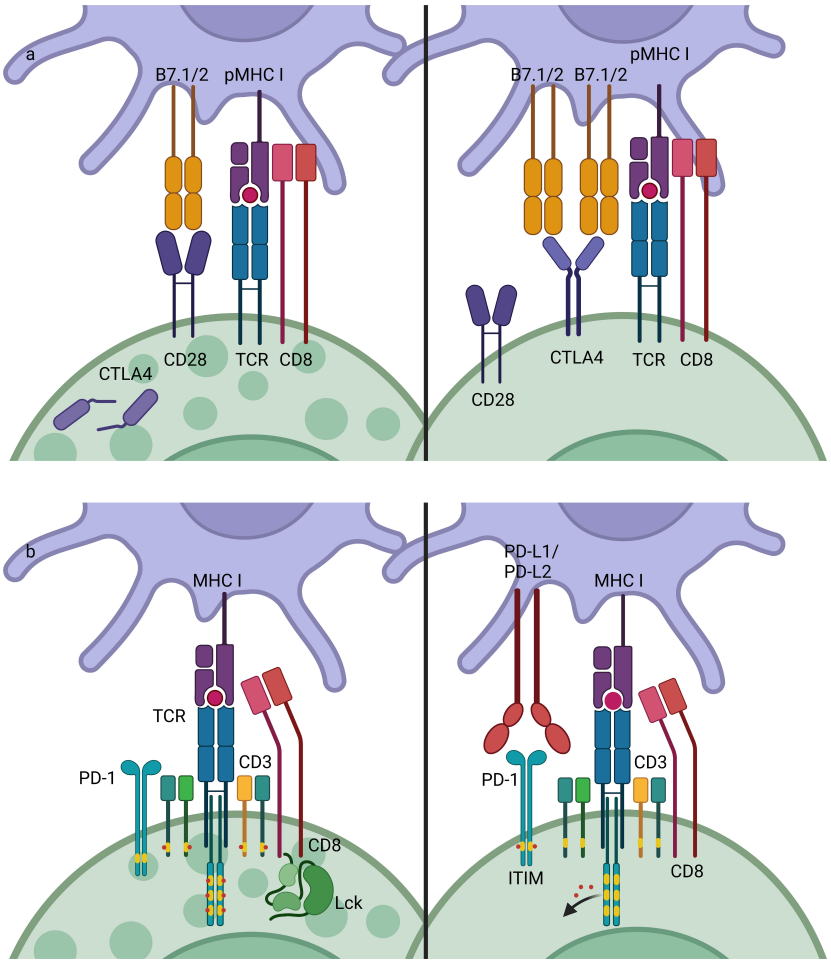


FIGURE 1
Mechanisms of CTLA-4 and PD-1/PD-L1.CTLA-4 and PD-1 are both negative checkpoints that inhibit the activation of lymphocytes. **(A)** T cells can be activated by APCs by pMHC-TCR (signal 1) and co-stimulatory molecules such as B7-CD28 (signal 2). CTLA-4 is competitive inhibitor of CD28, which has higher affinity to B7, thus inhibiting the co-stimulatory signaling in T cells activation. **(B)** PD-1 is an inhibitory receptor that contains an ITIM or ITSM, which mediate dephosphorylation reaction once activated, thus stopping the activation signaling transduction. CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; MHC, major histocompatibility complex; TCR, T cell receptor; ITIM, immunoreceptor tyrosine-based inhibition motif; ITSM, immunoreceptor tyrosine-based switch motif.

that the commensal microbiota and the distinct characteristics of cutaneous immune system may be the issue. Next, we will first demonstrate the role of auto-immune response in irAEs, followed by a discussion of the commensal microbiota and the characteristics of cutaneous immunity. Finally, we will discuss genetic factors.

3.1 Autoimmunity

An important mechanism of irAEs is the autoimmune response, which is the immune response that targets self-antigens. Many irAEs are considered to be or appear to mimic autoimmune diseases, including myocarditis (65), diabetes mellitus (66), hypothyroidism (67), pneumonitis (68), rheumatoid arthritis (69), vitiligo (70), BP (10) and psoriasis (71). The association between checkpoints and autoimmunity has previously been confirmed by the Genome-Wide Association Study (GWAS), in which mutations in the CTLA-4 and PD-1/PD-L1 genes were identified to be responsible for several autoimmune diseases, such as Grave's Disease and systemic lupus erythematosus (SLE) (72, 73). Other studies have also demonstrated that the IL-27-mediated priming of naïve T cells could upregulate the expression of PD-L1, which inhibited the differentiation of $CD4^+$ T cells into a Th17 phenotype, thereby exhibiting protection against autoimmune diseases (74). The mechanism of this protection also involved a blockade of the TCR from binding to dendritic cells (DCs) through the interaction of PD-1 and PD-L1 (75). Moreover, PD-L1 were found to be abundantly expressed on pancreatic β-cells to avoid autoimmune attack (76). Therefore, a PD-1/PD-L1 blockade may induce autoimmune diabetes (type 1 diabetes mellitus, T1DM) by destroying this tolerance. *Pdcd1*$^{-/-}$*Ctla4*$^{+/-}$ mice can be used as the model to study ICI-associated myocarditis (ICI-MC) (77). Moreover, the engineered expression of PD-1/PD-L1 have been used for the treatment of several immune diseases, including arthritis, colitis, and T1DM (78, 79). This indispensable role of PD-1/PD-L1 for preventing autoimmunity was also confirmed by a

clinical research in a patient with an inherited PD-1 deficiency, diagnosed with T1DM, hypothyroidism, and idiopathic arthritis, who was dying from severe pulmonary autoimmunity (80). In fact, although the mechanism of 'central tolerance' eliminates most of the lymphocytes which could be activated by self-antigens, self-reactive lymphocytes always exist in the natural immune repertoire but do not elicit remarkable autoimmune diseases, due partly to the lack of activation signal (also termed as 'second signal') and the action of negative checkpoints such as PD-1/PD-L1, termed 'peripheral tolerance', thus keeping a balance between preventing infection and preventing autoimmunity. In some contexts, infection is a common trigger of autoimmune diseases because it leads to an abundant release of pro-inflammatory cytokines, which act as activation signals towards self-reactive lymphocytes. The application of ICIs may also activate the autoimmune response by liberating self-reactive lymphocytes from the inhibitory control of negative checkpoints. Therefore, in this manner, irAEs of ICIs often appear to mimic classic autoimmune diseases. Since self-active T cells can induce the autoimmune response *via* two methods, exhibiting direct cytotoxicity and facilitating B cell-induced immune response, auto-antibodies are also involved in the irAEs, which is in line with previous literature. The hypophysitis and diabetes mellitus induced by anti-CTLA-4 and anti-PD-1/PD-L1, respectively, can serve as examples of cases in which auto-antibodies, while undetectable at baseline, developed significantly following treatment with ICIs (64, 81). Another important autoimmune disease is bullous pemphigoid (BP), which is associated with impaired basement membrane zone (BMZ) caused by auto-antibodies targeting BP180 and BP230. Trauma, burn or radiation may elicit BP by destroying the immune barrier which leads to the exposure of self-antigen to self-active lymphocytes, and application of some drugs also results in BP which may due to the immune-modulatory effects of these drugs. ICBs will also give rise to disturbance of immune responses. The increased risk of BP in patients receiving anti-PD-1/PD-L1 has been confirmed by series of clinic researches (11, 13, 82, 83), while the molecular mechanisms still need further researches to elucidate. A depletion of Tregs, which function depending on immune checkpoints, may play a role in the pathogenesis of BP, according to immunopathological results (84).

The relevance of anti-tumor efficacy and the irAEs of ICIs also implies the autoimmune mechanism of irAEs. While some studies did not confirm the association between the treatment efficacy and irAEs (29), others did find that the occurrence of irAEs was usually associated with a more robust response to ICI therapy and better prognosis (70, 85–88). GWAS studies also identified an IL-7 variant that can lead to increased irAEs incidence and a concomitant increase in overall survival in melanoma patients (89, 90). The failure of the immune system to eliminate tumors is partially due to a lack of a true 'onco-antigen', that is, the tumors do not present distinct antigens that can be recognized by the immune system rather than being tolerated. This is because tumors comprise part of our body and the mechanism of immune tolerance can prevent the body's response to them. The condition may differ with the application of ICIs, which interferes with immune homeostasis. Several studies have found that severe irAEs were associated with a longer overall survival, even while regarding irAEs as an indicator for predicting the prognosis of patients receiving ICIs. This finding may be partly explained by the fact that ICIs can promote the anti-tumor immune response by inhibiting immune tolerance, as PD-1/PD-L1 plays an important role in mediating the immune tolerance. An example is vitiligo, a common irAE in melanoma patients receiving anti-PD-1 therapy that is caused by an autoimmune attack to melanocytes (Figure 2). Research has proposed that this effect is due to the cross-reactivity between T cells directed against tumors and a related antigen expressed in normal tissues (27). Under normal physiological conditions, T cell targeting of antigens expressed on normal melanocytes will not be activated, nor will those that target related antigens expressed on tumors due to the immune tolerance. Therefore, neither the auto-immune response

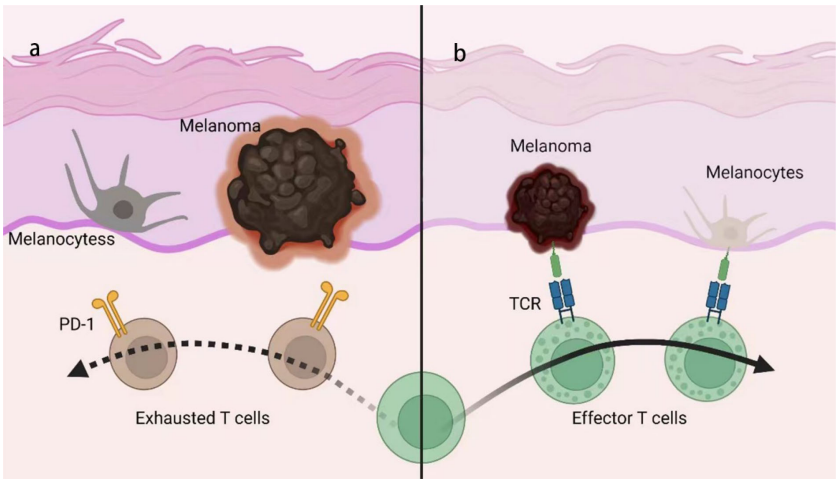


FIGURE 2
Mechanism of anti-PD-1/PD-L1-induced vitiligo. **(A)** Melanoma and melanocytes exhibit some shared antigen but are protected from immune attack by peripheral tolerance mechanisms, such as PD-1/PD-L1. **(B)** With PD-1/PD-L1 blocked, T cells will be activated by melanoma and initiate immune response targeting both tumors and normal tissue, due to the shared antigen on melanoma and melanocytes, termed 'cross-activation'. TCR, T cell receptor.

nor the anti-tumor response is intensely elicited. Once tolerance is destroyed by PD-1/PD-L1 blockade, these T cells will be activated by melanoma or by melanocytes, thus attacking melanoma cells as well as normal melanocytes, which may account for the relevance between the efficacy and irAEs of ICIs. Moreover, this theory may help explain why the irAEs vary among the different types of cancers, depending on the cross antigens between tumors and normal cells. Whether the PD-1/PD-L1 blockade could promote anti-tumors immunity *via* decreasing tolerance to tumors requires validation with further research. However, the role of checkpoints in preventing autoimmune diseases and the relationship between the severity of irAEs and better prognosis have been established by previous studies.

3.2 Targeting at commensal microbiota

The link between commensal microbiota and response to ICIs for the treatment of cancer has been revealed by a series of studies that investigated the heterogeneity of the patients' response to ICIs (91–98). Using 16S ribosome RNA gene sequencing, both preclinical and clinical studies have found distinct commensal microbiota between patients who are ICI-responsive and non-responsive (97, 99). There is increased concern that the commensal microbiota and its metabolites have a substantial influence on host homeostasis. For example, the interaction between the microbiota and host can 'shape' the immune system of the host. As a result, there is a heterogeneous response to ICIs due to the heterogeneity of the commensal microbiota to some extent. Although the association between the anti-tumor efficacy and the irAEs of ICIs remains conflicting (29, 85, 100–102), some studies have actually found a positive relationship (100–102), indicating that commensal microbiota may play a role in the pathogenesis of irAEs. It has been well established that the colon is the location in which there is the most abundant commensal microbiota, and the skin is another important residence. Epidemiological investigations have shown that irAEs most commonly involve the skin, GI tract, and endocrine system (5, 103). The microbiota abundance and irAE frequency in the skin and GI tract may indicate the potential relevance of commensal microbiota. One study confirmed an association between irAEs and several *Lachnospiraceae* spp. and indicated that the abundance of *Streptococcus* spp. substantially contributes to the distinction of irAEs (91). Additional studies have also supported the association between the commensal microbiota and irAEs (93, 95, 104). Reports researching the impact of PPIs have found that the application of PPIs has also had an impact on irAEs by influencing the microbiome (105, 106). The commensal microbiota profile may be used to predict irAEs (93) and the therapy targeting the commensal microbiota, such as fecal microbiota transplantation (FMT), may be used to cure irAEs (107).

Skin is the first-line barrier to protect the host from microbial invasion while maintaining a peaceful coexistence with resident microbiota (108), along with other barriers, such as the GI tract, respiratory tract and genital tract. A homeostatic state is formed under the complex microbiota-host interaction network and the intensity of immune response is controlled to a 'set point', which is suitable for the micro-ecosystem. Immune homeostasis is maintained by many immune regulators, including cytokines, regulatory receptors and regulatory immune cells. The application of ICIs makes great intervention for this control mechanism. Physiologically, within the action of checkpoints, T cells will not become activated to target commensal microbiota due to the lack of activation signals and presence of inhibition signals, plus some regulatory immune cells (e.g., Tregs) and cytokines (e.g., IL-10). Once CTLA-4 or PD-1/PD-L1 is blocked, however, $CD4^+$ and $CD8^+$ T cells may be activated and induce a subsequent immune response, which can lead to tissue damage. A recent study found that *Staphylococcus epidermidis* could only elicit inflammation in the context of a CTLA-4 blockade, the latter of which resulted in excessive activation of IL-17-producing commensal-specific T cells; thus inducing skin damage (109). Moreover, since the commensal microbiota itself also plays a crucial role in maintaining immunological homeostasis, an inappropriate immune response causes indirect damage by inhibiting commensal microbiota. Research into inflammatory bowel disease (IBD) has revealed that the failure to limit inappropriate inflammation contributes to ulcerative colitis and Crohn's disease (110–112), and other research about atopic dermatitis (AD) has found that microbiota diversity was decreased in inflamed AD skin (113) and reverted during the treatment and recovery (114). Moreover, epidermal barrier dysfunction represents a key factor associated with the pathogenesis of AD, which can be due to an over-release of pro-inflammatory cytokines and damage-associated molecular patterns (DAMPs) (115), such as that seen in inherited filaggrin deficiency (116). Further research into the influence of ICIs on the cutaneous micro-economy must be conducted. In summary, the cutaneous commensal microbiota is highly involved in the pathogenesis of cirAEs and the immune responses targeting commensal microbiota can lead to tissue damage by both direct and indirect methods, as a result of impaired immune tolerance.

3.3 The cutaneous immunity

In this section, we will aim to explore that why the skin is a common and early target of irAEs. The hallmark of the skin from an immunological perspective is the abundance of immune molecules and cells, as well as higher activity of the immune response. The immune profile is determined by and is suitable for the systemic role of the skin as a barrier for the entire body and its corresponding physiological functions. Our internal environment is separated from the external environment by the skin and mucosa, which covers the surface of body and the internal lumen, respectively, such that the skin is exposed to the most direct effects of various of physical, chemical and biological factors. The role of the skin to protect the internal environment from being affected by these disturbing agents, thereby helping to maintain internal homeostasis, so as to increase the active immunity of the skin. Similar to the colon, which also continuously makes contact with a wide range of foreign antigens and may lead to diarrhea, abdominal distension, and abdominal pain if the local immune response is induced (117–120), the skin also continuously faces a multitude of

foreign stimuli. Moreover, since the immune responses to these factors can occasionally be senseless and challenging, immune tolerance is of greater significance in the skin compared to other parts of the body. UV radiation will give rise to DNA damage (121, 122), contacting chemicals will also affect, and the commensal microbiota is an obvious source of foreign antigens. Using the immune response induced by UV radiation as an example, keratinocytes could be activated by UV radiation, initiating the formation of NLRP3 inflammasome and releasing IL-1β, which acts as an important pro-inflammatory cytokine (123, 124). By blocking the mechanisms used to limit the immune response, the persistent stimuli of UV radiation can over-activate the immune response in both intensity and duration, leading to cutaneous disorders. Therefore, the skin is a common target for the destruction of immune tolerance by ICIs. Moreover, the immune response in the skin is more readily initiated due to the abundance of the immune cells residing within the skin. Keratinocytes and melanocytes represent two major types of epidermal cells which generate keratin and melanin and act as crucial components of the skin barrier, respectively. In addition, both of these cell types express TLRs and NLRs and can initiate the immune response by secreting pro-inflammatory cytokines and chemokines to activate and recruit other immune cells (125, 126). Another important cell type that can induce an immune response is Langerhans cells (LCs), which can be regarded as a specific type of dendritic cell for its similar antigen-presenting function as a classic DC, whereas recent studies have shown that LCs are resident macrophages in the epidermis (127). Additionally, tissue-resident memory T cells (T_{RM}) also contribute substantially with their ability to rapidly recall the immune response by releasing cytokines or exhibiting cytotoxicity (128). In particular, $CD8^+$ T_{RM} have been shown to patrol the tissue or function as a local sentinel in both epidermal and dermal layers, providing a rapid and tissue-wide immune response (129). Significantly, there is a constitutive expression of negative checkpoints (e.g., PD-1, LAG-3, and Tim-3) on these T_{RM} in the skin (130, 131). Therefore, the application of ICIs may lead to the over-activation of T_{RM}. Taken together, these characteristics of cutaneous immunity indicate that the skin is more susceptible to the adverse events induced by drugs that affect immune homeostasis and the onset of cirAEs occurs swiftly due to the rapid responses of these immune cells.

In addition to inducing a local immune response, the skin is also responsible for transmitting invading signals to the brain; thus, the skin is largely innervated by sensory nerves. The role of inflammation on inducing sensations such as pain and itching is relatively clear (132). It has been shown that some neuropeptides, such as substance P (SP) and vasoactive intestinal peptide (VIP), can activate immune cells (e.g., mast cells), as confirmed by previous studies (133–135). Additionally, several studies have reported highly complex crosstalk or interactions between the immune response and these sensations. Moreover, the experimental application of imiquimod (IMQ) in murine skin could provoke inflammatory lesions that resemble human psoriasis. This effect was found to be blocked pharmacologically or through genetic ablation of nociceptors and could be restored by exogenous IL-23. A subsequent detailed study confirmed that the sensory neurons expressing the ion channels, TRPV1 and $Na_V1.8$, could regulate the production of IL-23/IL-17 by interacting with dermal dendritic cells to modulate the local immune response (136). Another subset of neurons expressing MrgprD was shown to inhibit the degranulation of mast cells and limit the cutaneous immune response *via* releasing glutamate. Indeed, the loss of these neurons may lead to immune disorders (137). There is also a subset of macrophages that have been identified to interact with sensory nerves, surveilling and trimming the myelin sheath (138). Due to the complicated interaction between sensory nerves and immune cells, such homeostasis appears to be susceptible to intervention, and some unpleasant sensations (e.g., chronic pain and itchiness) are commonly induced once the immune response is activated, as the manifestation of cirAEs.

3.4 Genetics

We have established that the irAEs are closely related to autoimmunity. Despite the unclear precise mechanism, epidemiological investigations have found that autoimmune diseases usually have a strong genetic component, which means some are easier to suffer from these diseases, whereas others are not. Psoriasis is a common disease that cirAEs appear to mimic (also termed 'psoriasiform rash') after using PD-1/PD-L1 (139, 140) and is considered to be an autoimmune disease to some extent (141, 142). Previous research has found that in people with parents suffering from psoriasis are easier to suffer from this disease (143), several psoriasis susceptibility genes have been identified, including HLA-Cw6, IL12B, IL23R, and LCE3B/3C (144). T1DM is another example which is also a classic autoimmune disease and one of the most common irAEs. The primary risk factor for β-cell immunity is confirmed as genetic, which mainly occurs in individuals with either HLA-DR3-DQ2 or HLA-DR4-DQ8 haplotypes, or both (145). Alopecia is the most common hair toxicity associated with ICIs and has a phenotype similar to alopecia areata (AA) (13). The GWAS study identified 139 SNPs associated with AA and demonstrated an autoimmune mechanism (146). Genomics-based and recent multi-omics-based approaches have shed light on the research into autoimmune diseases and irAEs. Some of these biomarkers may potentially be applied for the prediction and precise treatment of diseases in the future.

4 Prediction of cirAEs

Since cutaneous irAEs occur often and early, patients suffer and are forced to withdraw, and there is an urgent and unmet demand for seeking validated biomarkers to predict cirAEs due to its high morbidity and negative influence on cancer immunotherapy. This task can be conducted by traditional epidemiological methods, such as cross-sectional, cohort, or case-control studies (147–149). The probable biomarkers that have currently been identified are either general characteristics (e.g., age (150, 151), gender (152), and BMI (153)) or common serum molecules based on the current understanding of the immunological mechanisms of cirAEs (e.g.,

CRP (154), IFN-γ (155)). Regarding to the antigenicity, tumor mutation burden (TMB) (156–158) and microsatellite instability (MSI) (159, 160), which stand for the neoantigen or onco-antigen, are used to predict the efficacy of ICIs and the risk of irAEs. As for the strategies by which tumors suppress the immune response, the expression of PD-L1 was also considered as a predictive biomarker for the responsiveness of ICIs (161). However, these biomarkers do not provide appropriate predictions in clinical practice, and the results of studies identifying these biomarkers also remain conflicting. These discrepancies are partially due to the heterogeneity of the cirAEs. As previously discussed, cirAEs are closely related to cutaneous commensal microbiota and autoimmunity, both of which are highly heterogeneous among the population. Therefore, general characteristics alone may not be sufficient to induce cirAEs and those serum factors often play a common role in several pathways in the immune network, thereby lacking precision. Traditional research methods of molecular biology explore the role of a 'pathway' rather than dealing with the 'network', ignoring the crosstalk among the pathways which appear to be independent. In contrast, the technology of multi-omics screens for the whole genome, transcriptome, proteome and metabolome, analyzing the whole signaling network in different stages from gene to metabolites. It also helps to study commensal microbiota, which is unavoidable in cirAE research, as discussed previously.

Researchers have identified *LCP1* and *ADPGK* as irAE biomarkers by conducting a comprehensive screening across mRNA, miRNA, lncRNA, protein expression and non-silent gene mutations across 26 cancer types, in which lymphocyte cytosolic protein 1 (*LCP1*), involved in T cell activation, achieved the highest correlation coefficient. The addition of the adenosine diphosphate-dependent glucokinase (*ADPGK*), which can mediate a metabolic shift during T cell activation, to *LCP1*, led to a linear-regression model with the best accuracy among all the bivariate models. These two biomarkers were validated by a subsequent cohort study, which involved 28 cancer patients receiving anti-PD-1/PD-L1 therapy and found higher geometric mean and stronger immunohistochemistry staining in the irAEs group. The area under the receiver-operating characteristic curve (AUC) of *LCP1* and *ADPGK* to predict irAE was 0.78 and 0.78, whereas the combination of *LCP1* and *ADPGK* had a better AUC value at 0.80 (162). Another study established a tri-variate model composed of CDC42EP3-206, TMEM138-211, and IRX3-202 to predict irAEs by combining pharmacovigilance data and pan-cancer transcriptomic information (163). RNA and whole exon sequencing of tumors from 13 patients who developed ICI-induced diabetes mellitus (ICI-DM) showed significant overexpression of ORM1, PLG, G6PC and a missense mutation in NLRC5. The researcher proposed that NLRC5 mutation could be used to predict ICI-DM (164). The analysis of protein-protein interactions also helped to identify biomarkers, for which four immunogenetic variants were identified by genotyping 39 variants in 18 genes using a multiplex genotyping assay (165). Single-cells RNA sequencing revealed that patients with distinct T cells populations at baseline were under the risk of distinct types of irAEs and this could serve as biomarker for those irAEs. Fewer $CD8^+$ T_{CM} cells, more Th2 and Th17 cells were observed in patients with irAEs, and were associated with a higher risk of ICIs-induced arthritis, pneumonitis, and thyroiditis (166). Higher resolution human leucocyte antigen (HLA)-I typing on 179 patients with NSCLC treated with anti-PD-1/PD-L1 found that homozygosity at one or more HLA-I loci was associated with a reduced risk of irAE, including pruritus and rash (relative risk (RR) = 0.61, 95% CI 0.33 – 0.95, P = 0.035) and this could also serve as a biomarker (167). A variation in HLA-DRB1 was found to be associated with one or more types of cirAEs, and a more detailed association between HLA-DRB1*11:01 and pruritus was validated (168). This finding was in line with that of a previous study confirming an association between HLA-DRB1*11:01 and atopic dermatitis (AD) (169). The results of 16S rRNA gene amplification and multi-parallel sequencing also indicated that microbiota may serve as a potential biomarker (93, 104). Non-coding RNA (e.g., miR-146a) was found to be associated with irAEs in preclinical studies, and the predictive efficacy was validated by analyzing the effect of a SNP in the *MIR164A* gene on irAEs in 167 patients treated with ICIs. SNP rs2910164 led to reduced miR-164a expression and was associated with an increased risk of irAEs (170). Taken together, these studies via multi-omics technology have shed light on the discovery of biomarkers that can predict irAEs, although the efficacy should be validated using large number of clinical trials and the testing methods must be improved to be suitable for clinical practice.

There're also many biomarkers for the responsiveness to ICIs therapy being identified by means of multi-omics, with a potential role in predicting irAEs as well. In a rich resource of scRNA-seq and bulk mRNA-seq analysis, B cells and T follicular helper cells were found mediating the response to ICI in breast cancers, and a new predictive gene signature was identified (171). Based on the antigenicity of tumors, the analysis of self-immunopeptidome also served to predict the response of ICIs. This method calculated the ratio of nonsynonymous to synonymous mutation (dN/dS) to discriminate the 'escaped tumors' and 'edited tumors', with the former presenting neoantigens but escaping immune attack by immunosuppressive mechanisms such as over-expressing PD-L1, thus responsive to ICIs and under risk of irAEs; and the latter escaping by neoantigen-depletion that prevent tumors from being recognized by immune system, thus non-responsive to ICIs (172). A study of proteomics also identified leukemia inhibitory factor (LIF) as a novel predictive biomarker of resistance of ICIs (173). Moreover, a quantitative functional proteomics analysis[QF-Pro] found that functional engagement of the PD-1/PD-L1 complex but not PD-L1 expression alone is highly predictive to the response to ICIs in non-small-cell lung cancer (174). Another multi-omics study of 108 human papilloma virus (HPV)-negative head and neck squamous cell carcinomas (HNSCCs) identified three subtypes with responsiveness to CDK inhibitors, anti-EGFR antibody and immunotherapy, respectively, and an immune-proteogenomic analysis uncovered the mechanisms of immunosuppression and ICIs-resistance (175). Metabolomics studies found that hypoxanthine and histidine in early on-treatment serum (176), indoleamine-2,3-dioxygenase (IDO) (177) and very long-chain fatty acid-containing lipids (VLCFA-containing lipids) (178) were also predictive biomarkers for the response to ICIs. Still, these biomarkers need further validation for the predictive efficacy of irAEs, in addition to the anti-tumor efficacy.

Another important method is radiomics, which assess tumors based on the abundant images from computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT) (173, 174). The analysis of genomics, transcriptomics, proteomics and metabolomics, as previously discussed, need puncture or surgery for biopsy. Due to the spatial and temporal heterogeneity, however, it is not available to get whole information by sampling (175). As a widely used and non-invasive diagnosis method, radiographic examination serves as a repeatable and rapid approach for assessing the tumors. These traditional radiographic imaging, equipped with modern technologies such as high-resolution imaging, data mining algorithms and high-throughput analysis, provides global information about the biology of tumors and contributes to predicting the efficacy and adverse events of immunotherapy. Nowadays, radiomics studies seek for biomarkers mainly by analyzing the characteristics of tumor microenvironment (TME) (176), such as tumor-infiltrating lymphocytes (TIL), microcirculation, various signal molecules and extracellular matrix, tightly associated with immunotherapy. As known, TIL is a significant parameter to predict the response to immunotherapy, CT, PET/CT and MRI-based biomarkers to assess TIL have been identified by radiomics studies (4, 177, 178). There're also radiomics-based prediction models for assessing the PD-L1 expression being proposed, using the radiomics feature combined with clinical characteristics (5–9). Radiomics features that predict ICI-induced pneumonitis were identified by maximum relevance and minimum redundancy feature selection method, anomaly detection algorithm, and leave-one-out cross-validation, despite the predictive efficacy to other types of irAEs remaining unvalidated. Nevertheless, radiomics analysis, involving in the technology of multi-omics, will play an increasingly crucial role in the research of tumors.

5 Summary

In this review we discussed the application of ICI therapy to cancers and its adverse events in epidemiology, followed by a detailed discussion of its immunological mechanism and prediction. Cutaneous irAEs represents one of the most common types of irAE associated with ICI therapy and can lead to substantial suffering, as well as hinder the normal application of ICI, with a blockade of the normal role of checkpoints in the regulation of immune response being an initiating factor of irAEs. The immune response is a double-edge sword in that an appropriate immune response can serve as a defense against invading pathogenic microbes, eliminating damaged and aging cells and surveilling the oncogenic cells, whereas a disordered immune response will induce harmful effects. Checkpoints, including positive and negative checkpoints, play a crucial role in limiting the immune response and mediating immune tolerance. In this manner, these checkpoints contribute substantially to the maintenance of immune homeostasis, although it might be used by tumors to suppress immunity. From this perspective, ICIs may induce the non-specific enhancement of immune activity, including both increased cytotoxicity and broadened immune targets, thereby giving rise to an over-activated immune response. Such overactivation can manifest as irAE, and cutaneous irAEs commonly occur early for the distinctive immune signature of the skin as discussed above. For the broad use of ICIs in comprehensive cancer therapy, predicting and identifying irAEs is necessary, especially cirAEs. Previous studies have primarily conducted epidemiological investigations or measured the serum levels of some immune molecules, failing to identify satisfying biomarkers due to the heterogeneity of irAEs. Multi-omics analysis has shed light on the precise mechanism of irAEs and identify several genetic variants, non-coding RNAs and enzymes, which can potentially serve as biomarkers for predicting cirAEs; however, further clinical validation is required. Nevertheless, we believe that multi-omics research will continue to contribute more for both uncovering the mechanism and identifying of biomarkers.

Although various of PD-1/PD-L1 blockers have been applicated in clinical practice, the complete mechanisms of checkpoints such as TIM-3 and LAG-3 still remain unclear and the distinct mechanisms of irAEs induced by different types of ICBs need more researches to elucidate. The clinical manifestations of irAEs also provide a novel pathway to uncover the role of these immune checkpoints in regulating immune homeostasis. More precise understanding of cutaneous immunity and cutaneous immune diseases such as psoriasis and atopic dermatitis is also needed for exploring the mechanisms of cirAEs. The predictive biomarkers for cirAEs will be more precise, specific to certain type and severity of cirAEs. Finally, the developing multi-omics analysis technologies, especially single-cell and spatial multi-omics analysis, will provide more and more information which helps not only to find predictive biomarkers but also to uncover the mechanisms of cirAEs.

Author contributions

TC conducted the bulk of the writing and the crafting of the figures; XZ performed the formulation of the overarching research goal and the revision of the draft; XZ and XW retrieved literature; YZ critically revised the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This study was financially funded by the National Natural Science Foundation of China (NO. 81602757) and Technology Commission of Shanghai Municipality (No. 21Y11905200).

Acknowledgments

Figures were created with biorender.com.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Meissner TB, Schulze HS, Dale SM. Immune editing: overcoming immune barriers in stem cell transplantation. *Curr Stem Cell Rep* (2022) 8(4):206–18. doi: 10.1007/s40778-022-00221-0

2. Starling S. Mhc molecules: immune editing shapes the cancer landscape. *Nat Rev Immunol* (2017) 17(12):729. doi: 10.1038/nri.2017.129

3. Sundar R, Huang KK, Kumar V, Ramnarayanan K, Demircioglu D, Her Z, et al. Epigenetic promoter alterations in gi tumour immune-editing and resistance to immune checkpoint inhibition. *Gut* (2022) 71(7):1277–88. doi: 10.1136/gutjnl-2021-324420

4. Boutros C, Tarhini A, Routier E, Lambotte O, Ladurie F, Carbonnel F, et al. Safety profiles of anti-Ctla-4 and anti-Pd-1 antibodies alone and in combination. *Nat Rev Clin Oncol* (2016) 13(8):473–86. doi: 10.1038/nrclinonc.2016.58

5. Sibaud V. Dermatologic reactions to immune checkpoint inhibitors : skin toxicities and immunotherapy. *Am J Clin Dermatol* (2018) 19(3):345–61. doi: 10.1007/s40257-017-0336-3

6. Quach H, Johnson D, LeBoeuf N, Zwerner J, Dewan A. Cutaneous adverse events caused by immune checkpoint inhibitors. *J Am Acad Dermatol* (2021) 85(4):956–66. doi: 10.1016/j.jaad.2020.09.054

7. Capdevila J, Wirth L, Ernst T, Ponce Aix S, Lin C, Ramlau R, et al. Pd-1 blockade in anaplastic thyroid carcinoma. *J Clin Oncol Off J Am Soc Clin Oncol* (2020) 38 (23):2620–7. doi: 10.1200/JCO.19.02727

8. Schoenfeld J, Giobbie-Hurder A, Ranasinghe S, Kao K, Lako A, Tsuji J, et al. Durvalumab plus tremelimumab alone or in combination with low-dose or hypofractionated radiotherapy in metastatic non-Small-Cell lung cancer refractory to previous Pd(L)-1 therapy: an open-label, multicentre, randomised, phase 2 trial. *Lancet Oncol* (2022) 23(2):279–91. doi: 10.1016/s1470-2045(21)00658-6

9. Ueno M, Ikeda M, Morizane C, Kobayashi S, Ohno I, Kondo S, et al. Nivolumab alone or in combination with cisplatin plus gemcitabine in Japanese patients with unresectable or recurrent biliary tract cancer: a non-randomised, multicentre, open-label, phase 1 study. *Lancet Gastroenterol Hepatol* (2019) 4(8):611–21. doi: 10.1016/s2468-1253(19)30086-x

10. Asdourian MS, Shah N, Jacoby TV, Reynolds KL, Chen ST. Association of bullous pemphigoid with immune checkpoint inhibitor therapy in patients with cancer: a systematic review. *JAMA Dermatol* (2022) 158(8):933–41. doi: 10.1001/jamadermatol.2022.1624

11. Shalata W, Weissmann S, Itzhaki Gabay S, Sheva K, Abu Saleh O, Jama A, et al. A retrospective, single-institution experience of bullous pemphigoid as an adverse effect of immune checkpoint inhibitors. *Cancers (Basel)* (2022) 14(21):5451. doi: 10.3390/cancers14215451

12. Kawsar A, Edwards C, Patel P, Heywood RM, Gupta A, Mann J, et al. Checkpoint inhibitor-associated bullous cutaneous immune-related adverse events: a multicentre observational study. *Br J Dermatol* (2022) 187(6):981–7. doi: 10.1111/bjd.21836

13. Geisler AN, Phillips GS, Barrios DM, Wu J, Leung DYM, Moy AP, et al. Immune checkpoint inhibitor-related dermatologic adverse events. *J Am Acad Dermatol* (2020) 83(5):1255–68. doi: 10.1016/j.jaad.2020.03.132

14. Khoja L, Day D, Wei-Wu Chen T, Siu L, Hansen A. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review. *Ann Oncol Off J Eur Soc Med Oncol* (2017) 28(10):2377–85. doi: 10.1093/annonc/mdx286

15. Cutroneo P, Ingrasciotta Y, Isgrò V, Rullo E, Berretta M, Fiorica F, et al. Psoriasis and psoriasiform reactions secondary to immune checkpoint inhibitors. *Dermatol Ther* (2021) 34(2):e14830. doi: 10.1111/dth.14830

16. Chan L, Hwang S, Byth K, Kyaw M, Carlino M, Chou S, et al. Survival and prognosis of individuals receiving programmed cell death 1 inhibitor with and without immunologic cutaneous adverse events. *J Am Acad Dermatol* (2020) 82(2):311–6. doi: 10.1016/j.jaad.2019.06.035

17. Lee Y, Kim H, Won C, Chang S, Lee M, Choi J, et al. Characterization and prognostic significance of cutaneous adverse events to anti-programmed cell death-1 therapy. *J Korean Med Sci* (2019) 34(26):e186. doi: 10.3346/jkms.2019.34.e186

18. Zhang J, Zhang P, Xu Q, Zhu Y, Chen W, Ji C. Pembrolizumab associated stevens-Johnson syndrome with porokeratosis in a patient in the setting of primary hepatocellular carcinoma. *Australas J Dermatol* (2022) 63(1):e71–e4. doi: 10.1111/ajd.13704

19. Gong Y, Mao J, Liu M, Gao J. A case of toxic epidermal necrolysis associated with lenvatinib and sintilimab therapy for intrahepatic cholangiocarcinoma. *J Int Med Res* (2023) 51(5):3000605231173556. doi: 10.1177/03000605231173556

20. Yang H, Ma Q, Sun Y, Zhang K, Xing Y, Li H. Case report: toxic epidermal necrolysis associated with sintilimab in a patient with relapsed thymic carcinoma. *Front Oncol* (2022) 12:1065137. doi: 10.3389/fonc.2022.1065137

21. Criado PR, Avancini J, Santi CG, Medrado AT, Rodrigues CE, de Carvalho JF. Drug reaction with eosinophilia and systemic symptoms (Dress): a complex interaction of drugs, viruses and the immune system. *Isr Med Assoc J* (2012) 14(9):577–82.

22. Tivol EA, Borriello F, Schweitzer AN, Lynch WP, Bluestone JA, Sharpe AH. Loss of ctla-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of ctla-4. *Immunity* (1995) 3(5):541–7. doi: 10.1016/1074-7613(95)90125-6

23. Waterhouse P, Penninger JM, Timms E, Wakeham A, Shahinian A, Lee KP, et al. Lymphoproliferative disorders with early lethality in mice deficient in ctla-4. *Science* (1995) 270(5238):985–8. doi: 10.1126/science.270.5238.985

24. Esfahani K, Miller WHJr. Reversal of autoimmune toxicity and loss of tumor response by interleukin-17 blockade. *N Engl J Med* (2017) 376(20):1989–91. doi: 10.1056/NEJMc1703047

25. Tarhini AA, Zahoor H, Lin Y, Malhotra U, Sander C, Butterfield LH, et al. Baseline circulating il-17 predicts toxicity while tgf-B1 and il-10 are prognostic of relapse in ipilimumab neoadjuvant therapy of melanoma. *J Immunother Cancer* (2015) 3:39. doi: 10.1186/s40425-015-0081-1

26. Lo JA, Fisher DE, Flaherty KT. Prognostic significance of cutaneous adverse events associated with pembrolizumab therapy. *JAMA Oncol* (2015) 1(9):1340–1. doi: 10.1001/jamaoncol.2015.2274

27. Byrne EH, Fisher DE. Immune and molecular correlates in melanoma treated with immune checkpoint blockade. *Cancer* (2017) 123(S11):2143–53. doi: 10.1002/cncr.30444

28. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American society of clinical oncology clinical practice guideline. *J Clin Oncol* (2018) 36(17):1714–68. doi: 10.1200/jco.2017.77.6385

29. Horvat TZ, Adel NG, Dang TO, Momtaz P, Postow MA, Callahan MK, et al. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at memorial Sloan Kettering cancer center. *J Clin Oncol* (2015) 33 (28):3193–8. doi: 10.1200/jco.2015.60.8448

30. Carli L, Tani C, Querci F, Della Rossa A, Vagnani S, Baldini C, et al. Analysis of the prevalence of cataracts and glaucoma in systemic lupus erythematosus and evaluation of the rheumatologists' practice for the monitoring of glucocorticoid eye toxicity. *Clin Rheumatol* (2013) 32(7):1071–3. doi: 10.1007/s10067-013-2214-6

31. Huscher D, Thiele K, Gromnica-Ihle E, Hein G, Demary W, Dreher R, et al. Dose-related patterns of glucocorticoid-induced side effects. *Ann Rheum Dis* (2009) 68 (7):1119–24. doi: 10.1136/ard.2008.092163

32. Wang Y, Zou J, Li Y, Jiao X, Wang Y, Zhuo N, et al. Serological biomarkers predict immune-related adverse events and clinical benefit in patients with advanced gastrointestinal cancers. *Front Immunol* (2022) 13:987568. doi: 10.3389/fimmu.2022.987568

33. Shi Y, Liu X, Liu J, Zhang D, Liu X, Yue Y, et al. Correlations between peripheral blood biomarkers and clinical outcomes in advanced non-small cell lung cancer patients who received immunotherapy-based treatments. *Trans Lung Cancer Res* (2021) 10(12):4477–93. doi: 10.21037/tlcr-21-710

34. Muir C, Wood C, Clifton-Bligh R, Long G, Scolyer R, Carlino M, et al. Association of antithyroid antibodies in checkpoint inhibitor-associated thyroid immune-related adverse events. *J Clin Endocrinol Metab* (2022) 107(5):e1843–e9. doi: 10.1210/clinem/dgac059

35. Johnson D, Patel AB, Uemura MI, Trinh VA, Jackson N, Zobniw CM, et al. Il17a blockade successfully treated psoriasiform dermatologic toxicity from immunotherapy. *Cancer Immunol Res* (2019) 7(6):860–5. doi: 10.1158/2326-6066.Cir-18-0682

36. Koguchi Y, Iwamoto N, Shimada T, Chang S, Cha J, Curti B, et al. Trough levels of ipilimumab in serum as a potential biomarker of clinical outcomes for patients with advanced melanoma after treatment with ipilimumab. *J Immunother Cancer* (2021) 9 (10):e002663. doi: 10.1136/jitc-2021-002663

37. Kankkunen E, Penttilä P, Peltola K, Bono P. C-reactive protein and immune-related adverse events as prognostic biomarkers in immune checkpoint inhibitor treated metastatic renal cell carcinoma patients. *Acta Oncol (Stockholm Sweden)* (2022) 61(10):1240–7. doi: 10.1080/0284186X.2022.2104132

38. Zhou J, Wong A, Wang H, Tan F, Chen X, Jin S, et al. Elucidation of the application of blood test biomarkers to predict immune-related adverse events in atezolizumab-treated nsclc patients using machine learning methods. *Front Immunol* (2022) 13:862752. doi: 10.3389/fimmu.2022.862752

39. Tahir SA, Gao J, Miura Y, Blando J, Tidwell RSS, Zhao H, et al. Autoimmune antibodies correlate with immune checkpoint therapy-induced toxicities. *Proc Natl Acad Sci U.S.A.* (2019) 116(44):22246–51. doi: 10.1073/pnas.1908079116

40. Toi Y, Sugawara S, Sugisaka J, Ono H, Kawashima Y, Aiba T, et al. Profiling preexisting antibodies in patients treated with anti-Pd-1 therapy for advanced non-small cell lung cancer. *JAMA Oncol* (2019) 5(3):376–83. doi: 10.1001/jamaoncol.2018.5860

41. Gay S, Rossi G, Corica G, Graziani G, Genova C, Rijavec E, et al. Retracted article: can baseline endocrinological examination and thyroid ultrasound predict the development of thyroid disease in immunotherapy-treated patients? results from a prospective, single-center, open-label study. *Endocrine* (2020) 69(1):233. doi: 10.1007/s12020-019-01854-8

42. Möhn N, Mahjoub S, Duzzi L, Narten E, Grote-Levi L, Körner G, et al. Monocyte chemoattractant protein 1 as a potential biomarker for immune checkpoint inhibitor-associated neurotoxicity. *Cancer Med* (2023) 12(8):9373–83. doi: 10.1002/cam4.5695

43. Eun Y, Kim IY, Sun JM, Lee J, Cha HS, Koh EM, et al. Risk factors for immune-related adverse events associated with anti-Pd-1 pembrolizumab. *Sci Rep* (2019) 9 (1):14039. doi: 10.1038/s41598-019-50574-6

44. Pavan A, Calvetti L, Dal Maso A, Attili I, Del Bianco P, Pasello G, et al. Peripheral blood markers identify risk of immune-related toxicity in advanced non-small cell lung cancer treated with immune-checkpoint inhibitors. *Oncologist* (2019) 24 (8):1128–36. doi: 10.1634/theoncologist.2018-0563

45. Gazzano M, Parizot C, Psimaras D, Vozy A, Baron M, Abbar B, et al. Anti-Pd-1 immune-related adverse events are associated with high therapeutic antibody fixation on T cells. *Front Immunol* (2022) 13:1082084. doi: 10.3389/fimmu.2022.1082084

46. Stephens M, Asdourian M, Jacoby T, Shah N, Thompson L, Otto T, et al. Tumor-infiltrating lymphocytes as a predictive biomarker of cutaneous immune-related adverse events after immune checkpoint blockade in patients with advanced melanoma. *J Am Acad Dermatol* (2023) S0190-9622(23):00193–7. doi: 10.1016/j.jaad.2023.01.040

47. Sholl LM, Hirsch FR, Hwang D, Botling J, Lopez-Rios F, Bubendorf L, et al. The promises and challenges of tumor mutation burden as an immunotherapy biomarker: a perspective from the international association for the study of lung cancer pathology committee. *J Thorac Oncol* (2020) 15(9):1409–24. doi: 10.1016/j.jtho.2020.05.019

48. Ren S, Chen J, Xu X, Jiang T, Cheng Y, Chen G, et al. Camrelizumab plus carboplatin and paclitaxel as first-line treatment for advanced squamous nsclc (Camel-sq): a phase 3 trial. *J Thorac Oncol Off Publ Int Assoc Study Lung Cancer* (2022) 17(4):544–57. doi: 10.1016/j.jtho.2021.11.018

49. Jin Y, Chen D, Wang F, Yang C, Chen X, You J, et al. The predicting role of circulating tumor DNA landscape in gastric cancer patients treated with immune checkpoint inhibitors. *Mol Cancer* (2020) 19(1):154. doi: 10.1186/s12943-020-01274-7

50. Yoshimura K, Tamano Y, Nguyen Canh H, Zihan L, Le Thanh D, Sato Y, et al. A novel pathologic marker, indoleamine 2,3-dioxygenase 1, for the cholangiopathy of immune checkpoint inhibitors-induced immune mediated hepatotoxicity as adverse events and the prediction of additional ursodeoxycholic acid treatment. *Med Mol Morphol* (2023) 56(2):106–15. doi: 10.1007/s00795-022-00344-7

51. DePeaux K, Delgoffe GM. Metabolic barriers to cancer immunotherapy. *Nat Rev Immunol* (2021) 21(12):785–97. doi: 10.1038/s41577-021-00541-y

52. Pavlova NN, Thompson CB. The emerging hallmarks of cancer metabolism. *Cell Metab* (2016) 23(1):27–47. doi: 10.1016/j.cmet.2015.12.006

53. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* (2011) 144(5):646–74. doi: 10.1016/j.cell.2011.02.013

54. Muntyanu A, Netchiporouk E, Gerstein W, Gniadecki R, Litvinov I. Cutaneous immune-related adverse events (Iraes) to immune checkpoint inhibitors: a dermatology perspective on management [Formula: see text]. *J cutaneous Med Surg* (2021) 25(1):59–76. doi: 10.1177/1203475420943260

55. Nguyen N, Wan G, Ugwu-Dike P, Alexander N, Raval N, Zhang S, et al. Influence of melanoma type on incidence and downstream implications of cutaneous immune-related adverse events in the setting of immune checkpoint inhibitor therapy. *J Am Acad Dermatol* (2023) 88(6):1308–16. doi: 10.1016/j.jaad.2023.02.014

56. Puzanov I, Diab A, Abdallah K, Bingham CO3rd, Brogdon C, Dadu R, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the society for immunotherapy of cancer (Sitc) toxicity management working group. *J Immunother Cancer* (2017) 5(1):95. doi: 10.1186/s40425-017-0300-z

57. Lacouture ME, Wolchok JD, Yosipovitch G, Kähler KC, Busam KJ, Hauschild A. Ipilimumab in patients with cancer and the management of dermatologic adverse events. *J Am Acad Dermatol* (2014) 71(1):161–9. doi: 10.1016/j.jaad.2014.02.035

58. Chang LS, Barroso-Sousa R, Tolaney SM, Hodi FS, Kaiser UB, Min L. Endocrine toxicity of cancer immunotherapy targeting immune checkpoints. *Endocr Rev* (2019) 40(1):17–65. doi: 10.1210/er.2018-00006

59. Miyahara K, Noda T, Ito Y, Hidaka H, Fujimoto S, Takedomi H, et al. An investigation of nine patients with gastrointestinal immune-related adverse events caused by immune checkpoint inhibitors. *Digestion* (2020) 101(1):60–5. doi: 10.1159/000504647

60. Chambers C, Sullivan T, Allison J. Lymphoproliferation in ctla-4-Deficient mice is mediated by costimulation-dependent activation of Cd4+ T cells. *Immunity* (1997) 7 (6):885–95. doi: 10.1016/s1074-7613(00)80406-9

61. Marangoni F, Zhakyp A, Corsini M, Geels S, Carrizosa E, Thelen M, et al. Expansion of tumor-associated treg cells upon disruption of a ctla-4-Dependent feedback loop. *Cell* (2021) 184(15):3998–4015.e19. doi: 10.1016/j.cell.2021.05.027

62. Sun C, Mezzadra R, Schumacher TN. Regulation and function of the pd-L1 checkpoint. *Immunity* (2018) 48(3):434–52. doi: 10.1016/j.immuni.2018.03.014

63. Latchman Y, Wood C, Chernova T, Chaudhary D, Borde M, Chernova I, et al. Pd-L2 is a second ligand for pd-1 and inhibits T cell activation. *Nat Immunol* (2001) 2 (3):261–8. doi: 10.1038/85330

64. Chen L, Flies DB. Molecular mechanisms of T cell Co-stimulation and Co-inhibition. *Nat Rev Immunol* (2013) 13(4):227–42. doi: 10.1038/nri3405

65. Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, et al. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med* (2016) 375(18):1749–55. doi: 10.1056/NEJMoa1609214

66. Rui J, Deng S, Arazi A, Perdigoto AL, Liu Z, Herold KC. B cells that resist immunological attack develop during progression of autoimmune diabetes in nod mice. *Cell Metab* (2017) 25(3):727–38. doi: 10.1016/j.cmet.2017.01.005

67. Osorio JC, Ni A, Chaft JE, Pollina R, Kasler MK, Stephens D, et al. Antibody-mediated thyroid dysfunction during T-cell checkpoint blockade in patients with non-Small-Cell lung cancer. *Ann Oncol* (2017) 28(3):583–9. doi: 10.1093/annonc/mdw640

68. Sears C, Peikert T, Possick J, Naidoo J, Nishino M, Patel S, et al. Knowledge gaps and research priorities in immune checkpoint inhibitor-related pneumonitis. an official American thoracic society research statement. *Am J Respir Crit Care Med* (2019) 200 (6):e31–43. doi: 10.1164/rccm.201906-1202ST

69. Cappelli LC, Thomas MA, Bingham CO3rd, Shah AA, Darrah E. Immune checkpoint inhibitor-induced inflammatory arthritis as a model of autoimmune arthritis. *Immunol Rev* (2020) 294(1):106–23. doi: 10.1111/imr.12832

70. Teulings HE, Limpens J, Jansen SN, Zwinderman AH, Reitsma JB, Spuls PI, et al. Vitiligo-like depigmentation in patients with stage iii-iv melanoma receiving immunotherapy and its association with survival: a systematic review and meta-analysis. *J Clin Oncol* (2015) 33(7):773–81. doi: 10.1200/jco.2014.57.4756

71. Belzer A, Mortlock RD, Pach J, Cohen JM, Leventhal JS. The effect of baseline eczema or psoriasis on the morphology of cutaneous immune-related adverse events due to immune checkpoint inhibitor therapy. *J Am Acad Dermatol* (2023) 88 (5):1198–200. doi: 10.1016/j.jaad.2023.01.002

72. Farh KK, Marson A, Zhu J, Kleinewietfeld M, Housley WJ, Beik S, et al. Genetic and epigenetic fine mapping of causal autoimmune disease variants. *Nature* (2015) 518 (7539):337–43. doi: 10.1038/nature13835

73. Parkes M, Cortes A, van Heel DA, Brown MA. Genetic insights into common pathways and complex relationships among immune-mediated diseases. *Nat Rev Genet* (2013) 14(9):661–73. doi: 10.1038/nrg3502

74. Hirahara K, Ghoreschi K, Yang XP, Takahashi H, Laurence A, Vahedi G, et al. Interleukin-27 priming of T cells controls il-17 production in trans *Via* induction of the ligand pd-L1. *Immunity* (2012) 36(6):1017–30. doi: 10.1016/j.immuni.2012.03.024

75. Fife B, Pauken K, Eagar T, Obu T, Wu J, Tang Q, et al. Interactions between pd-1 and pd-L1 promote tolerance by blocking the tcr-induced stop signal. *Nat Immunol* (2009) 10(11):1185–92. doi: 10.1038/ni.1790

76. Osum KC, Burrack AL, Martinov T, Sahli NL, Mitchell JS, Tucker CG, et al. Interferon-gamma drives programmed death-ligand 1 expression on islet B cells to limit T cell function during autoimmune diabetes. *Sci Rep* (2018) 8(1):8295. doi: 10.1038/s41598-018-26471-9

77. Axelrod ML, Meijers WC, Screever EM, Qin J, Carroll MG, Sun X, et al. T Cells specific for A-myosin drive immunotherapy-related myocarditis. *Nature* (2022) 611 (7937):818–26. doi: 10.1038/s41586-022-05432-3

78. Hou M, Wei Y, Zhao Z, Han W, Zhou R, Zhou Y, et al. Immuno-engineered nanodecoys for the multi-target anti-inflammatory treatment of autoimmune diseases. *Adv Mater (Deerfield Beach Fla)* (2022) 34(12):e2108817. doi: 10.1002/adma.202108817

79. Zhang X, Kang Y, Wang J, Yan J, Chen Q, Cheng H, et al. Engineered pd-L1-Expressing platelets reverse new-onset type 1 diabetes. *Adv Mater (Deerfield Beach Fla)* (2020) 32(26):e1907692. doi: 10.1002/adma.201907692

80. Ogishi M, Yang R, Aytekin C, Langlais D, Bourgey M, Khan T, et al. Inherited pd-1 deficiency underlies tuberculosis and autoimmunity in a child. *Nat Med* (2021) 27 (9):1646–54. doi: 10.1038/s41591-021-01388-5

81. Gauci ML, Laly P, Vidal-Trecan T, Baroudjian B, Gottlieb J, Madjlessi-Ezra N, et al. Autoimmune diabetes induced by pd-1 inhibitor-retrospective analysis and pathogenesis: a case report and literature review. *Cancer Immunol Immunother* (2017) 66(11):1399–410. doi: 10.1007/s00262-017-2033-8

82. Guan S, Zhang L, Zhang J, Song W, Zhong D. A case report of steroid-refractory bullous pemphigoid induced by immune checkpoint inhibitor therapy. *Front Immunol* (2022) 13:1068978. doi: 10.3389/fimmu.2022.1068978

83. Wang T, Shao Q, Xiao C, Liu L. Case report: bullous pemphigoid associated with sintilimab therapy for Pmmr/Mss colorectal cancer. *Front Oncol* (2023) 13:1124730. doi: 10.3389/fonc.2023.1124730

84. Bowman C, Delrieu O. Immunogenetics of drug-induced skin blistering disorders. part I: perspective. *Pharmacogenomics* (2009) 10(4):601–21. doi: 10.2217/pgs.09.11

85. Hua C, Boussemart L, Mateus C, Routier E, Boutros C, Cazenave H, et al. Association of vitiligo with tumor response in patients with metastatic melanoma treated with pembrolizumab. *JAMA Dermatol* (2016) 152(1):45–51. doi: 10.1001/jamadermatol.2015.2707

86. Downey SG, Klapper JA, Smith FO, Yang JC, Sherry RM, Royal RE, et al. Prognostic factors related to clinical response in patients with metastatic melanoma treated by ctl-associated antigen-4 blockade. *Clin Cancer Res* (2007) 13(22 Pt 1):6681–8. doi: 10.1158/1078-0432.Ccr-07-0187

87. Haratani K, Hayashi H, Chiba Y, Kudo K, Yonesaka K, Kato R, et al. Association of immune-related adverse events with nivolumab efficacy in non-Small-Cell lung cancer. *JAMA Oncol* (2018) 4(3):374–8. doi: 10.1001/jamaoncol.2017.2925

88. Sanlorenzo M, Vujic I, Daud A, Algazi A, Gubens M, Luna SA, et al. Pembrolizumab cutaneous adverse events and their association with disease progression. *JAMA Dermatol* (2015) 151(11):1206–12. doi: 10.1001/jamadermatol.2015.1916

89. Groha S, Alaiwi SA, Xu W, Naranbhai V, Nassar AH, Bakouny Z, et al. Germline variants associated with toxicity to immune checkpoint blockade. *Nat Med* (2022) 28 (12):2584–91. doi: 10.1038/s41591-022-02094-6

90. Taylor CA, Watson RA, Tong O, Ye W, Nassiri I, Gilchrist JJ, et al. Il7 genetic variation and toxicity to immune checkpoint blockade in patients with melanoma. *Nat Med* (2022) 28(12):2592–600. doi: 10.1038/s41591-022-02095-5

91. McCulloch J, Davar D, Rodrigues R, Badger J, Fang J, Cole A, et al. Intestinal microbiota signatures of clinical response and immune-related adverse events in melanoma patients treated with anti-Pd-1. *Nat Med* (2022) 28(3):545–56. doi: 10.1038/s41591-022-01698-2

92. Simpson R, Shanahan E, Batten M, Reijers I, Read M, Silva I, et al. Diet-driven microbial ecology underpins associations between cancer immunotherapy outcomes and the gut microbiome. *Nat Med* (2022) 28(11):2344–52. doi: 10.1038/s41591-022-01965-2

93. Chaput N, Lepage P, Coutzac C, Soularue E, Le Roux K, Monot C, et al. Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab. *Ann Oncol Off J Eur Soc Med Oncol* (2017) 28(6):1368–79. doi: 10.1093/annonc/mdx108

94. Han K, Nam J, Xu J, Sun X, Huang X, Animasahun O, et al. Generation of systemic antitumour immunity *Via* the in situ modulation of the gut microbiome by an orally administered inulin gel. *Nat Biomed Eng* (2021) 5(11):1377–88. doi: 10.1038/s41551-021-00749-2

95. Andrews M, Duong C, Gopalakrishnan V, Iebba V, Chen W, Derosa L, et al. Gut microbiota signatures are associated with toxicity to combined ctla-4 and pd-1 blockade. *Nat Med* (2021) 27(8):1432–41. doi: 10.1038/s41591-021-01406-6

96. Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillère R, et al. Gut microbiome influences efficacy of pd-1-Based immunotherapy against epithelial tumors. *Science* (2018) 359(6371):91–7. doi: 10.1126/science.aan3706

97. Matson V, Fessler J, Bao R, Chongsuwat T, Zha Y, Alegre ML, et al. The commensal microbiome is associated with anti-Pd-1 efficacy in metastatic melanoma patients. *Science* (2018) 359(6371):104–8. doi: 10.1126/science.aao3290

98. Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC, Karpinets TV, et al. Gut microbiome modulates response to anti-Pd-1 immunotherapy in melanoma patients. *Science* (2018) 359(6371):97–103. doi: 10.1126/science.aan4236

99. Sivan A, Corrales L, Hubert N, Williams JB, Aquino-Michaels K, Earley ZM, et al. Commensal bifidobacterium promotes antitumor immunity and facilitates anti-Pd-L1 efficacy. *Science* (2015) 350(6264):1084–9. doi: 10.1126/science.aac4255

100. Das S, Johnson DB. Immune-related adverse events and anti-tumor efficacy of immune checkpoint inhibitors. *J Immunother Cancer* (2019) 7(1):306. doi: 10.1186/s40425-019-0805-8

101. Grangeon M, Tomasini P, Chaleat S, Jeanson A, Souquet-Bressand M, Khobta N, et al. Association between immune-related adverse events and efficacy of immune checkpoint inhibitors in non-Small-Cell lung cancer. *Clin Lung Cancer* (2019) 20 (3):201–7. doi: 10.1016/j.cllc.2018.10.002

102. Judd J, Zibelman M, Handorf E, O'Neill J, Ramamurthy C, Bentota S, et al. Immune-related adverse events as a biomarker in non-melanoma patients treated with programmed cell death 1 inhibitors. *Oncologist* (2017) 22(10):1232–7. doi: 10.1634/theoncologist.2017-0133

103. Weber JS, Hodi FS, Wolchok JD, Topalian SL, Schadendorf D, Larkin J, et al. Safety profile of nivolumab monotherapy: a pooled analysis of patients with advanced melanoma. *J Clin Oncol* (2017) 35(7):785–92. doi: 10.1200/jco.2015.66.1389

104. Dubin K, Callahan MK, Ren B, Khanin R, Viale A, Ling L, et al. Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-Blockade-Induced colitis. *Nat Commun* (2016) 7:10391. doi: 10.1038/ncomms10391

105. Horvath A, Rainer F, Bashir M, Leber B, Schmerboeck B, Klymiuk I, et al. Biomarkers for oralization during long-term proton pump inhibitor therapy predict survival in cirrhosis. *Sci Rep* (2019) 9(1):12000. doi: 10.1038/s41598-019-48352-5

106. Cortellini A, Tucci M, Adamo V, Stucci LS, Russo A, Tanda ET, et al. Integrated analysis of concomitant medications and oncological outcomes from pd-1/Pd-L1 checkpoint inhibitors in clinical practice. *J Immunother Cancer* (2020) 8(2): e001361. doi: 10.1136/jitc-2020-001361

107. Wang Y, Wiesnoski DH, Helmink BA, Gopalakrishnan V, Choi K, DuPont HL, et al. Fecal microbiota transplantation for refractory immune checkpoint inhibitor-associated colitis. *Nat Med* (2018) 24(12):1804–8. doi: 10.1038/s41591-018-0238-9

108. Belkaid Y, Tamoutounour S. The influence of skin microorganisms on cutaneous immunity. *Nat Rev Immunol* (2016) 16(6):353–66. doi: 10.1038/nri.2016.48

109. Ma B, Anandasabapathy N. Immune checkpoint blockade and skin toxicity pathogenesis. *J Invest Dermatol* (2022) 142(3 Pt B):951–9. doi: 10.1016/j.jid.2021.06.040

110. Kühn R, Löhler J, Rennick D, Rajewsky K, Müller W. Interleukin-10-Deficient mice develop chronic enterocolitis. *Cell* (1993) 75(2):263–74. doi: 10.1016/0092-8674(93)80068-p

111. Travis MA, Reizis B, Melton AC, Masteller E, Tang Q, Proctor JM, et al. Loss of integrin Alpha(V)Beta8 on dendritic cells causes autoimmunity and colitis in mice. *Nature* (2007) 449(7160):361–5. doi: 10.1038/nature06110

112. Sellon RK, Tonkonogy S, Schultz M, Dieleman LA, Grenther W, Balish E, et al. Resident enteric bacteria are necessary for development of spontaneous colitis and immune system activation in interleukin-10-Deficient mice. *Infect Immun* (1998) 66 (11):5224–31. doi: 10.1128/iai.66.11.5224-5231.1998

113. Byrd AL, Deming C, Cassidy SKB, Harrison OJ, Ng WI, Conlan S, et al. Staphylococcus aureus and staphylococcus epidermidis strain diversity underlying pediatric atopic dermatitis. *Sci Transl Med* (2017) 9(397):eaal4651. doi: 10.1126/scitranslmed.aal4651

114. Kong HH, Oh J, Deming C, Conlan S, Grice EA, Beatson MA, et al. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Res* (2012) 22(5):850–9. doi: 10.1101/gr.131029.111

115. Elias MS, Long HA, Newman CF, Wilson PA, West A, McGill PJ, et al. Proteomic analysis of filaggrin deficiency identifies molecular signatures characteristic of atopic eczema. *J Allergy Clin Immunol* (2017) 140(5):1299–309. doi: 10.1016/j.jaci.2017.01.039

116. Kezic S, O'Regan GM, Lutter R, Jakasa I, Koster ES, Saunders S, et al. Filaggrin loss-of-Function mutations are associated with enhanced expression of il-1 cytokines in the stratum corneum of patients with atopic dermatitis and in a murine model of filaggrin deficiency. *J Allergy Clin Immunol* (2012) 129(4):1031–9.e1. doi: 10.1016/j.jaci.2011.12.989

117. Shale M, Schiering C, Powrie F. Cd4(+) T-cell subsets in intestinal inflammation. *Immunol Rev* (2013) 252(1):164–82. doi: 10.1111/imr.12039

118. Peterson LW, Artis D. Intestinal epithelial cells: regulators of barrier function and immune homeostasis. *Nat Rev Immunol* (2014) 14(3):141–53. doi: 10.1038/nri3608

119. Zigmond E, Bernshtein B, Friedlander G, Walker CR, Yona S, Kim KW, et al. Macrophage-restricted interleukin-10 receptor deficiency, but not il-10 deficiency, causes severe spontaneous colitis. *Immunity* (2014) 40(5):720–33. doi: 10.1016/j.immuni.2014.03.012

120. Round JL, Mazmanian SK. Inducible Foxp3+ regulatory T-cell development by a commensal bacterium of the intestinal microbiota. *Proc Natl Acad Sci U.S.A.* (2010) 107(27):12204–9. doi: 10.1073/pnas.0909122107

121. Prinz JC. Melanocytes: target cells of an hla-C*06:02-Restricted autoimmune response in psoriasis. *J Invest Dermatol* (2017) 137(10):2053–8. doi: 10.1016/j.jid.2017.05.023

122. Boniface K, Taïeb A, Seneschal J. New insights into immune mechanisms of vitiligo. *G Ital Dermatol Venereol* (2016) 151(1):44–54.

123. Robinson ES, Werth VP. The role of cytokines in the pathogenesis of cutaneous lupus erythematosus. *Cytokine* (2015) 73(2):326–34. doi: 10.1016/j.cyto.2015.01.031

124. Tanaka K, Asamitsu K, Uranishi H, Iddamalgoda A, Ito K, Kojima H, et al. Protecting skin photoaging by nf-kappab inhibitor. *Curr Drug Metab* (2010) 11 (5):431–5. doi: 10.2174/138920010791526051

125. Tremante E, Ginebri A, Lo Monaco E, Benassi B, Frascione P, Grammatico P, et al. A melanoma immune response signature including human leukocyte antigen-e. *Pigment Cell Melanoma Res* (2014) 27(1):103–12. doi: 10.1111/pcmr.12164

126. Lai Y, Gallo RL. Toll-like receptors in skin infections and inflammatory diseases. *Infect Disord Drug Targets* (2008) 8(3):144–55. doi: 10.2174/187152651080803014

127. Doebel T, Voisin B, Nagao K. Langerhans cells - the macrophage in dendritic cell clothing. *Trends Immunol* (2017) 38(11):817–28. doi: 10.1016/j.it.2017.06.008

128. Gebhardt T, Palendira U, Tscharke DC, Bedoui S. Tissue-resident memory T cells in tissue homeostasis, persistent infection, and cancer surveillance. *Immunol Rev* (2018) 283(1):54–76. doi: 10.1111/imr.12650

129. Dijkgraaf FE, Matos TR, Hoogenboezem M, Toebes M, Vredevoogd DW, Mertz M, et al. Tissue patrol by resident memory Cd8(+) T cells in human skin. *Nat Immunol* (2019) 20(6):756–64. doi: 10.1038/s41590-019-0404-3

130. Ma JZ, Russell TA, Spelman T, Carbone FR, Tscharke DC. Lytic gene expression is frequent in hsv-1 latent infection and correlates with the engagement of a cell-intrinsic transcriptional response. *PloS Pathog* (2014) 10(7):e1004237. doi: 10.1371/journal.ppat.1004237

131. Mark KE, Wald A, Magaret AS, Selke S, Olin L, Huang ML, et al. Rapidly cleared episodes of herpes simplex virus reactivation in immunocompetent adults. *J Infect Dis* (2008) 198(8):1141–9. doi: 10.1086/591913

132. Baral P, Udit S, Chiu IM. Pain and immunity: implications for host defence. *Nat Rev Immunol* (2019) 19(7):433–47. doi: 10.1038/s41577-019-0147-2

133. Meixiong J, Anderson M, Limjunyawong N, Sabbagh MF, Hu E, Mack MR, et al. Activation of mast-Cell-Expressed mas-related G-Protein-Coupled receptors drives non-histaminergic itch. *Immunity* (2019) 50(5):1163–71. doi: 10.1016/j.immuni.2019.03.013

134. Talbot J, Hahn P, Kroehling L, Nguyen H, Li D, Littman D. Feeding-dependent vip neuron-Ilc3 circuit regulates the intestinal barrier. *Nature* (2020) 579(7800):575–80. doi: 10.1038/s41586-020-2039-9

135. Seillet C, Luong K, Tellier J, Jacquelot N, Shen R, Hickey P, et al. The neuropeptide vip confers anticipatory mucosal immunity by regulating Ilc3 activity. *Nat Immunol* (2020) 21(2):168–77. doi: 10.1038/s41590-019-0567-y

136. Riol-Blanco L, Ordovas-Montanes J, Perro M, Naval E, Thiriot A, Alvarez D, et al. Nociceptive sensory neurons drive interleukin-23-Mediated psoriasiform skin inflammation. *Nature* (2014) 510(7503):157–61. doi: 10.1038/nature13199

137. Zhang S, Edwards T, Chaudhri V, Wu J, Cohen J, Hirai T, et al. Nonpeptidergic neurons suppress mast cells *Via* glutamate to maintain skin homeostasis. *Cell* (2021) 184(8):2151–66. doi: 10.1016/j.cell.2021.03.002

138. Kolter J, Feuerstein R, Zeis P, Hagemeyer N, Paterson N, d'Errico P, et al. A subset of skin macrophages contributes to the surveillance and regeneration of local nerves. *Immunity* (2019) 50(6):1482–97. doi: 10.1016/j.immuni.2019.05.009

139. Ohtsuka M, Miura T, Mori T, Ishikawa M, Yamamoto T. Occurrence of psoriasiform eruption during nivolumab therapy for primary oral mucosal melanoma. *JAMA Dermatol* (2015) 151(7):797–9. doi: 10.1001/jamadermatol.2015.0249

140. Bonigen J, Raynaud-Donzel C, Hureaux J, Kramkimel N, Blom A, Jeudy G, et al. Anti-Pd1-Induced psoriasis: a study of 21 patients. *J Eur Acad Dermatol Venereol* (2017) 31(5):e254–e7. doi: 10.1111/jdv.14011

141. Ayala-Fontánez N, Soler DC, McCormick TS. Current knowledge on psoriasis and autoimmune diseases. *Psoriasis (Auckl)* (2016) 6:7–32. doi: 10.2147/ptt.S64950

142. Bowcock A, Krueger J. Getting under the skin: the immunogenetics of psoriasis. *Nat Rev Immunol* (2005) 5(9):699–711. doi: 10.1038/nri1689

143. Parisi R, Iskandar I, Kontopantelis E, Augustin M, Griffiths C, Ashcroft D. National, regional, and worldwide epidemiology of psoriasis: systematic analysis and modelling study. *BMJ (Clinical Res ed)* (2020) 369:m1590. doi: 10.1136/bmj.m1590

144. Ran D, Cai M, Zhang X. Genetics of psoriasis: a basis for precision medicine. *Precis Clin Med* (2019) 2(2):120–30. doi: 10.1093/pcmedi/pbz011

145. Pociot F, Lernmark Å. Genetic risk factors for type 1 diabetes. *Lancet* (2016) 387(10035):2331–9. doi: 10.1016/s0140-6736(16)30582-7

146. Rozin A, Schapira D, Bergman R. Alopecia areata and relapsing polychondritis or mosaic autoimmunity? the first experience of Co-trimoxazole treatment. *Ann Rheum Dis* (2003) 62(8):778–80. doi: 10.1136/ard.62.8.778

147. Head L, Gorden N, Gulick RV, Amato CM, Frazer-Abel A, Robinson W, et al. Biomarkers to predict immune-related adverse events with checkpoint inhibitors. *J Clin Oncol* (2019) 37(8_suppl):131–. doi: 10.1200/JCO.2019.37.8_suppl.131

148. Fujisawa Y, Yoshino K, Otsuka A, Funakoshi T, Fujimura T, Yamamoto Y, et al. Fluctuations in routine blood count might signal severe immune-related adverse events in melanoma patients treated with nivolumab. *J Dermatol Sci* (2017) 88(2):225–31. doi: 10.1016/j.jdermsci.2017.07.007

149. Diehl A, Yarchoan M, Hopkins A, Jaffee E, Grossman SA. Relationships between lymphocyte counts and treatment-related toxicities and clinical responses in patients with solid tumors treated with pd-1 checkpoint inhibitors. *Oncotarget* (2017) 8(69):114268–80. doi: 10.18632/oncotarget.23217

150. Isono T, Kagiyama N, Takano K, Hosoda C, Nishida T, Kawate E, et al. Outcome and risk factor of immune-related adverse events and pneumonitis in patients with advanced or postoperative recurrent non-small cell lung cancer treated with immune checkpoint inhibitors. *Thorac Cancer* (2021) 12(2):153–64. doi: 10.1111/1759-7714.13736

151. Marur S, Singh H, Mishra-Kalyani P, Larkins E, Keegan P, Sridhara R, et al. Fda analyses of survival in older adults with metastatic non-small cell lung cancer in controlled trials of pd-1/Pd-L1 blocking antibodies. *Semin Oncol* (2018) 45(4):220–5. doi: 10.1053/j.seminoncol.2018.08.007

152. Kartolo A, Sattar J, Sahai V, Baetz T, Lakoff JM. Predictors of immunotherapy-induced immune-related adverse events. *Curr Oncol* (2018) 25(5):e403–e10. doi: 10.3747/co.25.4047

153. Cortellini A, Bersanelli M, Santini D, Buti S, Tiseo M, Cannita K, et al. Another side of the association between body mass index (Bmi) and clinical outcomes of cancer patients receiving programmed cell death protein-1 (Pd-1)/ programmed cell death-ligand 1 (Pd-L1) checkpoint inhibitors: a multicentre analysis of immune-related adverse events. *Eur J Cancer* (2020) 128:17–26. doi: 10.1016/j.ejca.2019.12.031

154. Abolhassani AR, Schuler G, Kirchberger MC, Heinzerling L. C-reactive protein as an early marker of immune-related adverse events. *J Cancer Res Clin Oncol* (2019) 145(10):2625–31. doi: 10.1007/s00432-019-03002-1

155. Hirashima T, Kanai T, Suzuki H, Yoshida H, Matsusita A, Kawasumi H, et al. Significance of pre-treatment interferon-gamma release in patients with non-Small-Cell lung cancer receiving immune checkpoint inhibitors. *Anticancer Res* (2020) 40(12):6971–8. doi: 10.21873/anticanres.14721

156. Devarakonda S, Rotolo F, Tsao MS, Lanc I, Brambilla E, Masood A, et al. Tumor mutation burden as a biomarker in resected non-Small-Cell lung cancer. *J Clin Oncol* (2018) 36(30):2995–3006. doi: 10.1200/JCO.2018.78.1963

157. Bomze D, Hasan Ali O, Bate A, Flatz L. Association between immune-related adverse events during anti-Pd-1 therapy and tumor mutational burden. *JAMA Oncol* (2019) 5(11):1633–5. doi: 10.1001/jamaoncol.2019.3221

158. Nassar A, Adib E, Abou Alaiwi S, El Zarif T, Groha S, Akl E, et al. Ancestry-driven recalibration of tumor mutational burden and disparate clinical outcomes in response to immune checkpoint inhibitors. *Cancer Cell* (2022) 40(10):1161–72. doi: 10.1016/j.ccell.2022.08.022

159. Vikas P, Messersmith H, Compton C, Sholl L, Broaddus R, Davis A, et al. Mismatch repair and microsatellite instability testing for immune checkpoint inhibitor therapy: asco endorsement of college of American pathologists guideline. *J Clin Oncol Off J Am Soc Clin Oncol* (2023) 41(10):1943–8. doi: 10.1200/JCO.22.02462

160. Ciombor K, Eng C. Immunotherapy in localized microsatellite instability-High/Mismatch repair deficient solid tumors: are we ready for a new standard of care? *J Clin Oncol* (2023) 41(12):2138–40. doi: 10.1200/jco.22.02564

161. Patel SP, Kurzrock R. Pd-L1 expression as a predictive biomarker in cancer immunotherapy. *Mol Cancer Ther* (2015) 14(4):847–56. doi: 10.1158/1535-7163.Mct-14-0983

162. Petukhova L, Duvic M, Hordinsky M, Norris D, Price V, Shimomura Y, et al. Genome-wide association study in alopecia areata implicates both innate and adaptive immunity. *Nature* (2010) 466(7302):113–7. doi: 10.1038/nature09114

163. He X, Yu J, Shi H. Pan-cancer analysis reveals alternative splicing characteristics associated with immune-related adverse events elicited by checkpoint immunotherapy. *Front Pharmacol* (2021) 12:797852. doi: 10.3389/fphar.2021.797852

164. Caulfield J, Aizenbud L, Perdigoto A, Meffre E, Jilaveanu L, Michalek D, et al. Germline genetic variants are associated with development of insulin-dependent diabetes in cancer patients treated with immune checkpoint inhibitors. *J Immunother Cancer* (2023) 11(3):e006570. doi: 10.1136/jitc-2022-006570

165. Xin Z, You L, Na F, Li J, Chen M, Song J, et al. Immunogenetic variations predict immune-related adverse events for pd-1/Pd-L1 inhibitors. *Eur J Cancer (Oxford Engl 1990)* (2023) 184:124–36. doi: 10.1016/j.ejca.2023.01.034

166. Bukhari S, Henick BS, Winchester RJ, Lerrer S, Adam K, Gartshteyn Y, et al. Single-cell rna sequencing reveals distinct T cell populations in immune-related adverse events of checkpoint inhibitors. *Cell Rep Med* (2023) 4(1):100868. doi: 10.1016/j.xcrm.2022.100868

167. Abed A, Law N, Calapre L, Lo J, Bhat V, Bowyer S, et al. Human leucocyte antigen genotype association with the development of immune-related adverse events in patients with non-small cell lung cancer treated with single agent immunotherapy. *Eur J Cancer* (2022) 172:98–106. doi: 10.1016/j.ejca.2022.05.021

168. Hasan Ali O, Berner F, Bomze D, Fässler M, Diem S, Cozzio A, et al. Human leukocyte antigen variation is associated with adverse events of checkpoint inhibitors. *Eur J Cancer* (2019) 107:8–14. doi: 10.1016/j.ejca.2018.11.009

169. Horton R, Gibson R, Coggill P, Miretti M, Allcock RJ, Almeida J, et al. Variation analysis and gene annotation of eight mhc haplotypes: the mhc haplotype project. *Immunogenetics* (2008) 60(1):1–18. doi: 10.1007/s00251-007-0262-2

170. Marschner D, Falk M, Javorniczky NR, Hanke-Müller K, Rawluk J, Schmitt-Graeff A, et al. Microrna-146a regulates immune-related adverse events caused by immune checkpoint inhibitors. *JCI Insight* (2020) 5(6):e132334. doi: 10.1172/jci.insight.132334

171. Hollern D, Xu N, Thennavan A, Glodowski C, Garcia-Recio S, Mott K, et al. B cells and T follicular helper cells mediate response to checkpoint inhibitors in high mutation burden mouse models of breast cancer. *Cell* (2019) 179(5):1191–206. doi: 10.1016/j.cell.2019.10.028

172. Zapata L, Caravagna G, Williams MJ, Lakatos E, AbdulJabbar K, Werner B, et al. Immune selection determines tumor antigenicity and influences response to checkpoint inhibitors. *Nat Genet* (2023) 55(3):451–60. doi: 10.1038/s41588-023-01313-1

173. Loriot Y, Marabelle A, Guégan J, Danlos F, Besse B, Chaput N, et al. Plasma proteomics identifies leukemia inhibitory factor (Lif) as a novel predictive biomarker of immune-checkpoint blockade resistance. *Ann Oncol Off J Eur Soc Med Oncol* (2021) 32(11):1381–90. doi: 10.1016/j.annonc.2021.08.1748

174. Sánchez-Magraner L, Gumuzio J, Miles J, Quimi N, Martínez Del Prado P, Abad-Villar M, et al. Functional engagement of the pd-1/Pd-L1 complex but not pd-L1 expression is highly predictive of patient response to immunotherapy in non-Small-Cell lung cancer. *J Clin Oncol* (2023) 41(14):2561–70. doi: 10.1200/jco.22.01748

175. Huang C, Chen L, Savage S, Eguez R, Dou Y, Li Y, et al. Proteogenomic insights into the biology and treatment of hpv-negative head and neck squamous cell carcinoma. *Cancer Cell* (2021) 39(3):361–79. doi: 10.1016/j.ccell.2020.12.007

176. Nie X, Xia L, Gao F, Liu L, Yang Y, Chen Y, et al. Serum metabolite biomarkers predictive of response to pd-1 blockade therapy in non-small cell lung cancer. *Front Mol Biosci* (2021) 8:678753. doi: 10.3389/fmolb.2021.678753

177. Kocher F, Amann A, Zimmer K, Geisler S, Fuchs D, Pichler R, et al. High indoleamine-2,3-Dioxygenase 1 (Ido) activity is linked to primary resistance to immunotherapy in non-small cell lung cancer (Nsclc). *Trans Lung Cancer Res* (2021) 10(1):304–13. doi: 10.21037/tlcr-20-380

178. Mock A, Zschäbitz S, Kirsten R, Scheffler M, Wolf B, Herold-Mende C, et al. Serum very long-chain fatty acid-containing lipids predict response to immune checkpoint inhibitors in urological cancers. *Cancer Immunol Immunother CII* (2019) 68(12):2005–14. doi: 10.1007/s00262-019-02428-3

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 03 July 2023
DOI 10.3389/fonc.2023.1199195

OPEN ACCESS

EDITED BY
Maria-Ioanna (Marianna) Christodoulou,
European University Cyprus, Cyprus

REVIEWED BY
Sudhakar Tummala,
University of Texas MD Anderson Cancer Center, United States
Edwin Peguero,
Moffitt Cancer Center, United States

*CORRESPONDENCE
Ge Xiong
gexiong@ucdavis.edu

RECEIVED 03 April 2023
ACCEPTED 30 May 2023
PUBLISHED 03 July 2023

CITATION
Xiong G, Young RB, Chow H, Maverakis E, Maselli RA, Richman DP and Li T (2023) Intravenous immunoglobulin is safe and effective in controlling pre-existing paraneoplastic neuromuscular diseases in cancer patients treated with immune checkpoint inhibitors: two case reports and literature review.
Front. Oncol. 13:1199195.
doi: 10.3389/fonc.2023.1199195

Intravenous immunoglobulin is safe and effective in controlling pre-existing paraneoplastic neuromuscular diseases in cancer patients treated with immune checkpoint inhibitors: two case reports and literature review

Ge Xiong[1]*, Richard Benjamin Young[2], Helen Chow[2], Emanual Maverakis[3], Ricardo A. Maselli[1], David Paul Richman[1] and Tianhong Li[2]

[1]Department of Neurology, School of Medicine, University of California, Davis, Sacramento, CA, United States, [2]Division of Hematology/Oncology, Department of Internal Medicine, School of Medicine, University of California, Davis, Sacramento, CA, United States, [3]Department of Dermatology, School of Medicine, University of California, Davis, Sacramento, CA, United States

Immune checkpoint inhibitors cause rare but potentially fatal neuromuscular complications, leading to a concern to use these agents in cancer patients with pre-existing autoimmune or inflammatory neuromuscular diseases. We report two such patients with paraneoplastic dermatomyositis and "seronegative" paraneoplastic demyelinating neuropathy, respectively, who have been successfully treated with immune checkpoint inhibitor monotherapy as well as maintenance intravenous immunoglobulin. While controlling the paraneoplastic or autoimmune neuromuscular diseases, the use of intravenous immunoglobulin did not compromise the anti-cancer effect of immune checkpoint inhibitor.

KEYWORDS

immune checkpoint inhibitor, intravenous immune globulin (IVIg), safety and effectiveness, pre-existing, paraneoplastic neurologic disease

Introduction

Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy by activating immune responses through releasing the blockage to programmed cell death protein-1 (PD-1) or cytotoxic T lymphocyte associated antigen 4 (CTLA-4) signaling pathways. The unleashed immune responses can cause a variety of autoimmune syndromes in cancer

patients receiving ICIs. ICI-associated neuromuscular complications, which include polymyositis, dermatomyositis, myasthenia gravis, Guillain–Barre syndrome (GBS), and chronic inflammatory demyelinating neuropathy (CIDP), are rare but potentially fatal. These neuromuscular complications not only cause high mortality but also lead to significant morbidity including paralysis and imbalance (2.9%–4.2%) (1, 2). There is an unmet need for neurologists and oncologists to develop a clinical workflow for early recognition and effective treatment of these ICI-associated neuromuscular complications. Patients with preexisting autoimmune diseases have increased risks for developing cancers (3–5). It is unknown if patients with preexisting inflammatory myopathy/neuropathy can safely receive or continue immunomodulatory agents and if the immunomodulatory agents may compromise the efficacy of ICI against cancer. Here, we report two cases of preexisting autoimmune paraneoplastic myopathy/neuropathy that were successfully controlled with intravenous immunoglobulin (IVIG) while their cancers remained in clinical remission due to PD-1 inhibitors (Table 1).

Case description

Patient 1: A 66-year-old Asian man, former smoker (29 pack-year history of cigarette smoking, quit 15 years ago) with controlled hypertension and diabetes, presented with rash and muscle ache. The erythematous papular rash was first present in the extremities, head, and trunk, accompanied by pruritus and burning pain, which worsened after sun exposure (Figure 1D (a)). Over a 3-month period, the symptoms rapidly evolved into diffuse muscle pain, edema, and pain in wrists, elbows, and knees, along with weakness in the lower extremities, especially noticeable in climbing stairs. He was initially treated with hydrocortisone 2.5% lotion and ketoconazole 2% shampoo without improvement in his symptoms. Two months later, the patient noticed multiple lateral cervical masses, which enlarged over the subsequent 3 months, in association with sharp pain radiating from the neck to bilateral upper extremities. Over the next month, he noticed weakness progressing to bilateral arms, then difficulty swallowing dry food. Ultrasound of the neck revealed cervical lymphadenopathy. Positron emission tomography/computerized tomography (PET/CT) scan showed a subpleural right upper lobe bilobed primary tumor, scattered left upper lobe pulmonary nodules, too small to characterize by PET, and bilateral cervical and mediastinal lymphadenopathy consistent with metastatic lymph nodes. Brain magnetic resonance imaging (MRI) did not reveal any metastatic disease. Ultrasound-guided core needle biopsy of the left supraclavicular lymph node revealed metastatic poorly differentiated adenocarcinoma of lung primary with 100% expression of programmed death-ligand 1 (PD-L1) by immunohistochemistry stain. There was insufficient tumor specimen for tumor genomic profiling. Next-generation sequencing of plasma circulating tumor DNA did not identify any actionable mutation. The patient was started on pembrolizumab standard-of-care dose at 200 mg intravenously (IV) every 3 weeks and referred to neurology for the neck pain and extremity weakness, and dermatology for the rash. Neurological exam demonstrated weakness in bilateral proximal upper and lower extremities [Medical Research Council (MRC) grade 4/5 in deltoid, biceps, triceps, wrist extension/flexion, hip flexion, and knee extension/flexion], normal deep tendon reflexes, hyperesthesia to pinprick in bilateral upper extremities and thighs, normal vibration, and

TABLE 1 Summary of two cases of inflammatory neuromuscular diseases.

	Patient 1	Patient 2
Age at onset (years), sex	66, male	55, female
Initial lab results	Elevated CK (885 U/L), ESR (59 mm/h), positive TIF-1 gamma, anti-p155/140 antibodies Normal B12, TSH, SPEP, CRP, ANA, SSA, SSB, paraneoplastic antibody panel, A1C	Elevated ESR (85 mm/h) Normal B12, TSH, SPEP, ganglioside antibodies, MAG antibody, ANA, dsDNA antibody, rheumatoid factor, paraneoplastic antibody panel
Initial CSF results	Not performed	Elevated protein (275 mg/dl), normal white blood cell count (1/mm^3)
Initial electrophysiological study	Not performed	Chronic inflammatory demyelinating polyneuropathy (CIDP, meeting EFNS/PNS criteria)
IVIG treatment course **Response to IVIG treatment only**	0.4 g/kg/day × 5 days every 4–6 weeks for 11 months Not available	2 g/kg once then 1 g/kg every 4 weeks for 22 months, then 1 g/kg every 8 weeks for 21 months Worsening motor and sensory deficits
Interval between neurological symptoms and cancer diagnosis (months)	2 months	18 months
Cancer pathology	Metastatic poorly differentiated lung adenocarcinoma	Extraperitoneal malignant melanoma (M1a/metastatic melanoma)
Routine cancer treatment/duration	None	Dabrafenib 150 mg twice daily + Trametinib 2 mg daily for 10 months
ICI treatment	Pembrolizumab every 3 weeks for 21 cycles	Nivolumab every 4 weeks for 24 cycles

ANA, anti-nuclear antibody; CK, creatine kinase; CRP, C-reactive protein; CSF, cerebrospinal fluid; dsDNA, double-strand deoxyribonucleic acid; ESR, erythrocyte sedimentation rate; MAG, myelin-associated glycoprotein; SPEP, serum protein electrophoresis; SSA, Sjogren's syndrome-related antigen A autoantibody; SSB antibody, Sjogren's syndrome- related antigen B autoantibody; TIF-1, transcription intermediary factor-1; TSH, thyroid- stimulating hormone.

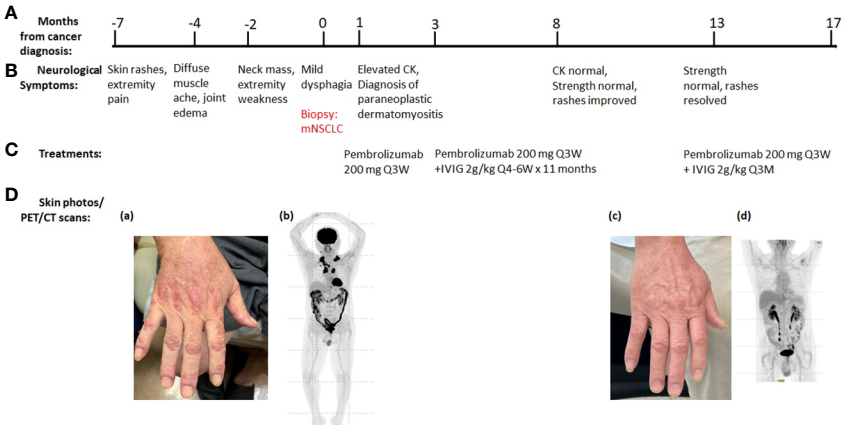


FIGURE 1
Summary of key events in the clinical course of patient 1. **(A)** Timeline from the cancer diagnosis. "0" is the time when metastatic non-small cell lung cancer (mNSCLC) was confirmed by the biopsy. **(B)** Timeline of neurological symptoms. **(C)** Summary of the systemic treatments. **(D)** Serial skin photos and PET images assess disease status. (a) Extensive Gottron's papules in hands before ICI treatment. (b) PET before ICI treatment showed increased radiotracer uptakes in lung, cervical, and mediastinal lymph nodes. (c) Resolution of skin rash after ICI and IVIG treatment. (d) Resolution of all FDG-avid tumor lesions after ICI treatment.

temperature sensation. Dermatological evaluation showed extensive erythematous, lichenified plaques and papules on extremities, trunk, and scalp. He had positive Gottron's papules, Shawl's sign, and V neck erythema (Figure 1D). Further testing revealed elevated creatine kinase (CK, 885 U/L), high positive anti-transcription intermediary factor 1 gamma (TIF 1-γ) antibody (154 units), and myositis-specific anti-p155/140 antibody (Table 1). Magnetic resonance imaging (MRI) of cervical spine showed mild to moderate degenerative changes at multiple levels without abnormal cord signal or root impingement. The patient refused electromyography/nerve conduction study (EMG/NCS) and muscle biopsy. The neurological diagnosis was paraneoplastic dermatomyositis. He was started on clobetasol 0.05% ointment twice daily that helped his pruritus and burning pain. Two months later, he started IVIG 2 g/kg every 4–6 weeks for the autoimmune disease while taking PD-1 inhibitor pembrolizumab 200 mg IV every 3 weeks (Figure 1). After 11 months of combined treatment, the rash resolved (Figure 1D), muscle strength returned to normal (MRC grade 5/5), and neck pain resolved. CK level became normal. TIF-γ antibody became low positive (26 units). PET/CT scan demonstrated resolution of essentially all previously active tumor lesions while his neurological symptoms were controlled, so the IVIG was reduced to maintenance dose at 2 g/kg every 3 months while pembrolizumab was maintained at 200 mg IV every 3 weeks (Figure 1). At the 24-month evaluation, he remained in clinical remission with metastatic lung cancer with normal muscle strength and no rash. Based on common terminology criteria for adverse events (CTCAE) grading, his function level was grade 3 initially. It improved to grade 0 after combined treatment of IVIG and pembrolizumab.

Patient 2: A 55-year-old Caucasian woman with past medical history of resected cutaneous melanoma of right leg 27 years ago developed symmetrical ascending numbness that progressed from feet and hands to the thighs and elbows over 3 months. She also complained of intermittent joint pain and fatigue. Neurological examination showed normal strength (MRC grading 5/5), decreased reflexes throughout (1+), decreased vibration sensation at bilateral ankles, and decreased pinprick sensation below bilateral mid-shins. The initial EMG study showed features consistent with an acquired demyelinating sensorimotor polyneuropathy with active denervation in right tibialis anterior muscle. Cerebrospinal fluid (CSF) studies demonstrated albuminocytological dissociation [elevated protein 275 mg/dl and normal white blood cell (WBC) count 1/mm^3]. Additional tests were normal, including vitamin B12, thyroid-stimulating hormone (TSH), serum protein electrophoresis, ganglioside antibodies, anti-myelin-associated glycoprotein (MAG) antibody, paraneoplastic antibody panel [including anti-Hu, collapsing response mediator protein-5 (CV2/CRMP-5), ganglionic acetylcholine receptor, amphiphysin antibody, glial nuclear antibody, voltage-gated potassium channel antibody, P/Q-type calcium channel antibody, and Purkinje cell cytoplasmic antibody], antinuclear antibodies (ANA), anti-double-stranded DNA antibody, and rheumatoid factor, except for elevated erythrocyte sedimentation rate (ESR) (85 mm/h). Her clinical presentation, EMG/NCS study, and CSF findings led to a diagnosis of CIDP based on European Federation of Neurological Societies/Peripheral Nerve Society EFNS/PNS criteria (Table 1). She received IVIG infusions, 1 g/kg every 4 weeks for 6 months after an initial dose of 0.4 g/kg/day for 5 days. Although the patient reported improvement of fatigue at follow-up, her neuropathy progressed based on the neurological exam. Examination at 14 months after symptom onset demonstrated mild weakness in toe extension and flexion (MRC grading 4/5), complete areflexia, decreased pinprick in bilateral fingers, and below bilateral mid-shins. Repeat EMG/NCS study (Table 2) also demonstrated interval progression of demyelinating sensorimotor polyneuropathy with partial conduction block, decreased amplitudes, and active and chronic denervation in distal extremities. Because the patient did not respond to the standard treatment of CIDP, alternative underlying etiologies were explored, including paraneoplastic

TABLE 2 Serial nerve conduction/EMG tests of patient 2.

Category	Item	Location	Baseline	6 months after IVIG monotherapy	10 months after IVIG+ chemotherapy	12 months after IVIG +ICI	
Sensory nerve action potentials (SNAPs)	Amplitude (μV)	Median	No response	No response	4.2	7.5	
		Ulnar	No response	No response	No response	4.2	
		Sural	No response	No response	No response	6.2	
	Conduction velocity (m/s)	Median	No response	No response	31	40	
		Ulnar	No response	No response	No response	36	
		Sural	No response	No response	No response	37	
Compound muscle action potentials (CMAPs)	Distal latency (ms)	Median	6.35	7.45	4.69	4.32	
		Ulnar	6.56	6.72	4.69	3.75	
		Peroneal	11.67	13.59	7.71	4.84	
		Tibial	10.89	9.53	9.22	4.27	
	Amplitude (mV)	Median	5.2	5.3	6.6	6.6	
		Ulnar	7.6	6.1 (conduction block at forearm)	12	14.1	
		Peroneal	2.1	1.3	1.9	4.1	
		Tibial	2.0	0.6	0.9	5.0	
	Conduction velocity (m/s)	Median	19	18	28	32	
		Ulnar	25	19	28	34	
		Peroneal	23	19	25	30	
		Tibial	33	22	26	32	
F wave Latencies		Median	64.7	ND	26.0	40.9	
		Ulnar	66.4	ND	50.7	40.4	
		Tibial	89.6	ND	ND	62.2	
Needle EMG			First dorsal interosseus	Normal	1+ positive sharp wave Decreased recruitment, prolonged duration	Decreased recruitment, prolonged duration	Decreased recruitment
			Tibialis anterior	1+ fibrillation Decreased recruitment	Decreased recruitment, prolonged duration	Decreased recruitment, prolonged duration	Decreased recruitment, prolonged duration
			Gastrocnemius	Normal	1+ positive sharp wave Decreased recruitment, prolonged duration	1+ fibrillation Decreased recruitment, prolonged duration	Decreased recruitment

All the nerve conduction studies and needle sampling were performed in right upper and lower extremities. Very abnormal nerve conduction studies were labeled in red color; mildly abnormal nerve conduction studies were labeled in blue color; normal nerve conduction studies were labeled in black color. Active denervation changes (fibrillations or positive sharp waves) in needle EMG were labeled in red color to suggest active neuropathy.

EMG, electromyography; SNAPs, sensory nerve action potentials; CMAPs, compound muscle action potentials; ND, not done; μV, microvolt; mV, millivolt; m/s, meters/second; ms, milliseconds.

neuropathy given her prior history of melanoma. At 18 months after initial onset of these symptoms, she developed right hip and back pain. Pelvic CT scan revealed a large pelvic wall mass and intra-abdominal lymphadenopathy. PET/CT scan showed a hypermetabolic right retroperitoneal soft tissue mass of 8.4 × 3.5 × 8.7 cm and several hypermetabolic right retroperitoneal and iliac/inguinal lymph nodes suggestive of nodal metastasis (Figure 2). There were also multiple focal regions of increased radiotracer uptake within the axial and appendicular muscles, which are nonspecific but might represent melanoma metastasis or, atypically, inflammatory changes or sites of subcutaneous lesions. Biopsy of the right retroperitoneal mass confirmed recurrent melanoma, and tumor genomic profiling revealed BRAF V600E mutation. The patient was treated with targeted therapy dabrafenib 150 mg twice daily and trametinib 2 mg daily (Table 1, Figure 2). She had partial tumor response by PET scan after three cycles of treatment, and the paresthesias were improved as well. Her strength remained stable with mild weakness in toe extension and flexion

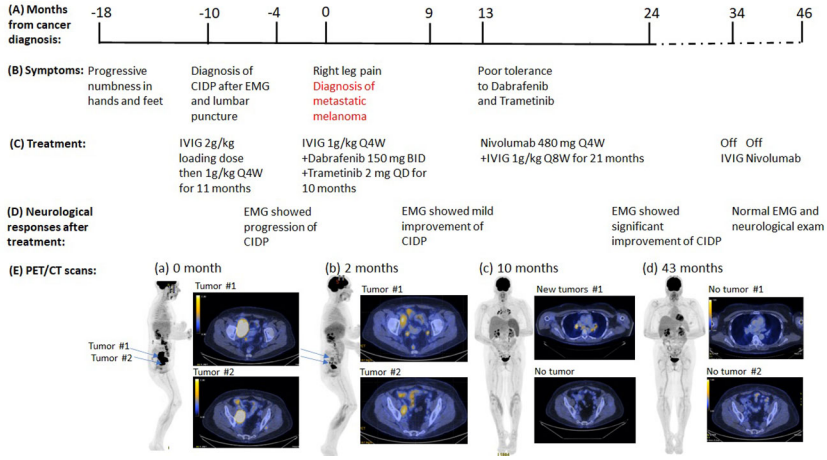


FIGURE 2
Summary of key events in the clinical course of patient 2. **(A)** Timeline from the cancer diagnosis. "0" is the time when metastatic melanoma was confirmed by the biopsy. **(B)** Timeline of neurological symptoms. **(C)** Summary of the systemic treatments. **(D)** Serial neurological responses after treatments. **(E)** Serial PET images assess disease status. (a) Right pelvic mass (8.5 x 5.4 cm), hypermetabolic right retroperitoneal and iliac/inguinal lymph nodes. (b) to (c), Continued improvement in pelvic lymphadenopathy, but new mediastinal and bilateral hilar lymphadenopathy (d) No evidence of residual, recurrent, or metastatic tumor.

(MRC grading 4/5). EMG/NCS study after 10 months of targeted therapeutics together with monthly IVIG treatment also demonstrated mild improvement of neuropathy (Figure 2, Table 2). At that time, dabrafenib/trametinib treatment was discontinued after 10 cycles due to mixed tumor response and poor tolerance. The oncologic treatment was switched to PD-1 inhibitor nivolumab 480 mg IV every 4 weeks. Simultaneously, the frequency of maintenance IVIG was reduced from every 4 weeks to every 8 weeks for 21 months due to the concern that frequent IVIG infusions might reduce the anti-tumor effect of the PD-1 inhibitor nivolumab (Figure 2). Repeat EMG testing, after 12 months of dual treatment with nivolumab and IVIG, demonstrated significant improvement. After 21 months of double therapy, neurological examination improved to normal strength (MRC grading 5/5) in all extremities, with normal sensation, and IVIG was discontinued. Surveillance PET/CT scans showed that the patient achieved complete remission (CR) after 19 cycles of nivolumab and has remained in CR since then (Figure 2). Nivolumab treatment was discontinued after 24 cycles. At the time of this submission, the patient has been in remission from both melanoma and neuropathy for 12 months (Figure 2). Based on CTCAE grading, she was at grade 2 before nivolumab treatment and it improved to grade 0 after the combined treatment of IVIG and nivolumab.

Discussion

The risk of progression of an inflammatory neuromuscular disease with ICI treatment is unknown. ICI targets PD-1 or CTLA-4 signaling pathways to disrupt immune regulation, thereby enhancing the anti-tumor immune response by both T cell- and B cell-mediated processes (6, 7). It is possible that the ICI may also activate a subgroup of regulatory T cells that could play a role in the immune-mediated paraneoplastic processes. For the autoimmune disorder myasthenia gravis (MG), the 2020 international consensus guidance considered the potential for exacerbation with ICI treatment—given the propensity for this treatment to induce autoimmunity (8, 9). The authors concluded, however, that pre-existing MG is not an absolute contraindication for ICI treatment (10).

For paraneoplastic neurological diseases, cancer can be diagnosed within 2 years of the onset of the neurological disorder (11). Paraneoplastic syndromes are present in more than 8% of cancer patients. The incidence has increased over time, which is likely associated with better diagnostic approaches and longer survival of these patients (12). Many paraneoplastic neurological syndromes are immune-mediated and associated with circulating autoantibodies to a number of known antigens. For paraneoplastic dermatomyositis, they include TIF1-γ (present in patient 1) and nuclear matrix protein-2 (NXP-2, also known as anti-MJ or p140). For paraneoplastic neuropathies, the following antibodies have been identified: Hu (also known as anti-neuronal nuclear antibody type 1, ANNA-1), CV2/CRMP-5, ganglionic acetylcholine receptor, and MAG (8–10). For other neuromuscular diseases, common autoantibodies associated with paraneoplastic syndromes include amphiphysin antibody, glial nuclear antibody, voltage-gated potassium channel antibody, P/Q-type calcium channel antibody, and Purkinje cell cytoplasmic antibody. For many cases, CSF results are positive when serum results are negative and are more readily interpretable because CSF generally lacks the interfering nonorgan-specific antibodies that are common in the serum of patients with cancer. The cancers may be new or recurrent, are usually limited in metastatic volume, and are often occult by standard imaging procedures. Detection of the informative marker autoantibodies allows early diagnosis and treatment of the cancer, which may lessen neurological morbidity and improve patient survival. However, up to 30% of the cases may not have any of the previously identified paraneoplastic autoantibodies, the so-called

seronegative paraneoplastic cases, making the diagnosis of paraneoplastic syndrome challenging. For involvement of the peripheral nerves or muscles, the clinical presentations may be similar to GBS (an acute inflammatory polyneuropathy), CIDP, autoimmune autonomic ganglionopathy, and inflammatory myopathy (11–14). A population-based cohort study in Denmark suggested that GBS patients had a three fold increased risk of cancer diagnosis in the first year of follow-up with an absolute cancer risk of 2.7% (15). Some cases with paraneoplastic neuromuscular disorders respond to immunosuppressants or immune modulators including IVIG (12). In these cases, when treatment with ICI is considered, there is concern that the immunosuppressants/immunomodulators will reduce the effectiveness of the ICI, making the treatment of cancer patients with pre-existing paraneoplastic syndromes even more complicated.

In the patients reported here, we had concluded, given the temporal association with the onset of underlying neoplasm, that each had paraneoplastic neuromuscular diseases because the cancers were diagnosed within 2 years of the onset of the neurological symptoms and the improvements of neuromuscular diseases correlated with the reduction of the tumors (11). Case 1 had paraneoplastic dermatomyositis and patient 2 had "seronegative" paraneoplastic demyelinating neuropathy (11, 12). The first case had clinical characteristics of dermatomyositis with positive TIF1-γ antibody, which has high specificity for cancer-associated dermatomyositis in adults. TIF1-γ is involved in the TGF-β signaling pathway, which is important for tumorigenesis and metastasis (16). The patient experienced the rash before the rapidly growing neck mass appeared. The dual treatment with PD-1 inhibitor and IVIG for 11 months resulted in the clearing of the clinical findings of dermatomyositis and normalization of the elevated serum CK, along with resolution of all the previously metabolic avid tumor lesions by PET scan, all of which support the diagnosis of paraneoplastic dermatomyositis.

The second case had been in remission from melanoma since surgical excision 27 years earlier and was found to have recurrent melanoma 1 year after the onset of demyelinating neuropathy. After 6 months of IVIG treatment alone, she had worsening neurological examination and EMG findings of polyneuropathy. Both her objective neurological exam and EMG studies improved along with the reduction in tumor size that followed combined ICI treatment and low-dose IVIG infusion for 12 months. The IVIG was discontinued at 52 months after the onset of initial neurological symptoms at which time the patient's neurological exam had returned to normal and PET showed no evidence of cancer. Even after the patient had been off IVIG for 12 months, her neurological exam remained normal and the surveillance PET scan did not show any evidence of cancer.

Both patients received dual ICI and IVIG treatment without exacerbation of myopathy or neuropathy. Moreover, in each, the neurological symptoms/examination improved in conjunction with tumor reduction. The first patient had significant improvements of the rash and proximal extremity weakness at 15 months of symptom onset while the metastatic lung cancer lesions decreased in size. The second patient had continued progression of the neuropathy at 14 months after symptom onset, by neurological exam and EMG findings, despite standard IVIG treatment (initial dose 2 g/kg every 4 weeks followed by maintenance dose of 1 g/kg every 4 weeks). In contrast to the response to IVIG alone, addition of the ICI to treat the tumor resulted in improvement of the neuropathy by both neurological examination and electrodiagnostic parameters.

With the increasing use of ICI in cancer treatments, ICI-associated neuromuscular complications have been more frequently encountered in clinical practice (1, 2). Thus, the early detection of ICI-associated neuromuscular complications has been the recent focus of both oncologists and neurologists. However, the early diagnosis of ICI-associated neuromuscular complications has been challenging. The wide spectrum of ICI-associated neuromuscular complications overlaps with paraneoplastic neuromuscular diseases, including myositis, myasthenia syndromes, and CIDP-like neuropathy. Careful attention to the time course of the illness and serial comprehensive physical examinations are very important to help differentiate paraneoplastic neuromuscular disorders from ICI-associated neuromuscular complications. As we know, the onset of neuromuscular symptoms frequently precedes the diagnosis of cancers in paraneoplastic neuromuscular disorders. On the other hand, the onset of neuromuscular symptoms follows the ICI treatment in cancer patients with ICI-associated neuromuscular complications. The differentiation between these two different categories of neuromuscular diseases will be very important for clinicians to decide if the patients should continue ICI or immunosuppressants or not.

The two patients presented here had excellent tumor responses to ICI along with improvement of the neuromuscular diseases. Our results support the view that ICI is not contraindicated in cancer patients with pre-existing immune-mediated neuromuscular diseases. In both cases, the neuromuscular disorders presented as paraneoplastic manifestations of the underlying neoplasm. Combined treatment with ICI and immunomodulator IVIG helped control the neuromuscular disease in each case, without compromising the anti-tumor effect of ICI. However, we recommend close monitoring of both the neuromuscular disease and the cancer during such treatment.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the IRB committee of the University of California, Davis (IRB ID 1784252-1) with the waiver of patients' consent. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

GX: Initiate the draft of the manuscript, summarize the two cases, contribute to the figures, Tables 1, 2 and part of discussion. RY: Contribute to the figures, case history and managements of patient 1. HC: Contribute to the case history and management of patient 2, part of Table 1. EM: Contribute to the case history and management of patient 1, part of the Figure 1. RM: Contribute to part of the case history and management of patient 2. DR: Contribute to part of case summaries and discussion. TL, MD: Contribute to the figures, introduction and part of discussion, Figures 1, 2. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Kao JC, Liao B, Markovic SN, Klein CJ, Naddaf E, Staff NP, et al. Neurological complications associated with anti-programmed death 1 (PD-1) antibodies. *JAMA Neurol* (2017) 74(10):1216–22. doi: 10.1001/jamaneurol.2017.1912

2. Chompoopong P, Zekeridou A, Shelly S, Ruff M, Dyck PJ, Klein CJ, et al. Comparison of immune checkpoint inhibitor-related neuropathies among patients with neuroendocrine and non-neuroendocrine tumours. *J Neurol Neurosurg Psychiatry* (2021) 93(1):112–4. doi: 10.1136/jnnp-2021-326369

3. Collins L, Quinn A, Stasko T. Skin cancer and immunosuppression. *Dermatol Clin* (2019) 37(1):83–94. doi: 10.1016/j.det.2018.07.009

4. Dias Lopes NM, Mendonça Lens HH, Armani A, Marinello PC, Cecchini AL. Thyroid cancer and thyroid autoimmune disease: a review of molecular aspects and clinical outcomes. *Pathol Res Pract* (2020) 216(9):153098. doi: 10.1016/j.prp.2020.153098

5. Zhou Z, Liu H, Yang Y, Zhou J, Zhao L, Chen H, et al. The five major autoimmune diseases increase the risk of cancer: epidemiological data from a large-scale cohort study in China. *Cancer Commun (Lond).* (2022) 42(5):435–46. doi: 10.1002/cac2.12283

6. Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD.. Cancer immunoediting: from immunosurveillance to tumor escape. *Nat Immunol* (2002) 3:991–8. doi: 10.1038/ni1102-991

7. Liu X, Hogg GD, DeNardo DG. Rethinking immune checkpoint blockade: 'Beyond the T cell'. *J Immunother Cancer.* (2021) 9(1):e001460. doi: 10.1136/jitc-2020-001460

8. Ramos-Casals M, Brahmer JR, Callahan MK, Flores-Chávez A, Keegan N, Khamashta MA, et al. Immune-related adverse events of checkpoint inhibitors. *Nat Rev Dis Primers.* (2020) 6(1):38. doi: 10.1038/s41572-020-0160-6

9. Khan S, Gerber DE. Autoimmunity, checkpoint inhibitor therapy and immune-related adverse events: a review. *Semin Cancer Biol* (2020) 64:93–101. doi: 10.1016/j.semcancer.2019.06.012

10. Narayanaswami P, Sanders DB, Wolfe G, Benatar M, Cea G, Evoli A, et al. International consensus guidance for management of myasthenia gravis: 2020 update. *Neurology* (2021) 96(3):114–22. doi: 10.1212/WNL.0000000000011124

11. Graus F, Delattre JY, Antoine JC, Dalmau J, Giometto B, Grisold W, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. *J Neurol Neurosurg Psychiatry* (2004) 75(8):1135–40. doi: 10.1136/jnnp.2003.034447

12. Pelosof LC, Gerber DE. Paraneoplastic syndromes: an approach to diagnosis and treatment. *Mayo Clin Proc* (2010) 85(9):838–54. doi: 10.4065/mcp.2010.0099

13. Koike H, Tanaka F, Sobue G. Paraneoplastic neuropathy: wide-ranging clinicopathological manifestations. *Curr Opin Neurol* (2011) 24(5):504–10. doi: 10.1097/WCO.0b013e32834a87b7

14. Baijens LW, Manni JJ. Paraneoplastic syndromes in patients with primary malignancies of the head and neck: four cases and a review of the literature. *Eur Arch Otorhinolaryngol* (2006) 263:32–6. doi: 10.1007/s00405-005-0942-1

15. Girma B, Farkas DK, Laugesen K, Skajaa N, Henderson VW, Boffetta P, et al. Cancer diagnosis and prognosis after Guillain-Barré syndrome: a population-based cohort study. *Clin Epidemiol.* (2022) 14:871–8. doi: 10.2147/CLEP.S369908

16. De Vooght J, Vulsteke JB, De Haes P, Bossuyt X, Lories R, De Langhe E. Anti-TIF1-γ autoantibodies: warning lights of a tumour autoantigen. *Rheumatol (Oxford).* (2020) 59(3):469–77. doi: 10.1093/rheumatology/kez572

frontiers | Frontiers in Immunology

TYPE Case Report
PUBLISHED 13 September 2023
DOI 10.3389/fimmu.2023.1150128

OPEN ACCESS

EDITED BY
Maria-Ioanna (Marianna) Christodoulou,
European University Cyprus, Cyprus

REVIEWED BY
Rahul Ravilla,
University of Arkansas for Medical Sciences, United States
Stergios Tsitos,
Ludwig Maximilian University of Munich, Germany

*CORRESPONDENCE
Alberto Torres-Zurita
albertotorreszurita@gmail.com

RECEIVED 23 January 2023
ACCEPTED 29 August 2023
PUBLISHED 13 September 2023

CITATION
Torres-Zurita A, Vázquez-Montero L, Gallego-López L, Mediano-Rambla MD and de la Cruz-Merino L (2023) Sarcoidosis-like reaction induced by immune checkpoint inhibitor in a patient with hepatocellular carcinoma: a case report.
Front. Immunol. 14:1150128.
doi: 10.3389/fimmu.2023.1150128

Sarcoidosis-like reaction induced by immune checkpoint inhibitor in a patient with hepatocellular carcinoma: a case report

Alberto Torres-Zurita[1]*, Lucía Vázquez-Montero[1], Laura Gallego-López[2], María Dolores Mediano-Rambla[1] and Luis de la Cruz-Merino[1]

[1]Department of Clinical Oncology, Virgen Macarena University Hospital, Seville, Spain, [2]Department of Internal Medicine, Virgen Macarena University Hospital, Seville, Spain

Nowadays, immune checkpoint inhibitors (ICI) have become the cornerstone of treatment for many tumors, either as monotherapy or in combination with other therapies. However, these drugs are associated with several new side effects that need early detection. We present the case of a 41-year-old male patient who has been diagnosed with advanced hepatocellular carcinoma (HCC) with metastatic retroperitoneal lymph nodes and a subdiaphragmatic metastatic lesion, undergoing second-line treatment with a combination of nivolumab and ipilimumab. After completing four cycles, the patient was admitted to the hospital due to intermittent fever and profuse sweating. A CT scan showed multiple pathologically enlarged lymph nodes in several locations, raising suspicion of disease progression. The patient's clinical progress was favorable after symptomatic treatment (antipyretics) and was discharged one week after admission. Several days later, the patient complained about painful bilateral ocular redness and was diagnosed with bilateral anterior uveitis. Further blood tests showed elevated angiotensin-converting enzyme (ACE) levels of 67 U/L (normal range: 8 – 52) and decreasing alpha-fetoprotein (AFP) levels of 698 ng/mL (previously 1210 ng/mL), indicative of non-progression of the oncological disease. Finally, an excisional biopsy confirmed the presence of non-necrotizing granulomatous lymphadenitis, leading to the diagnosis of sarcoidosis-like reaction (SLR) induced by immunotherapy as the etiology of the polyadenopathy syndrome. SLR, although uncommon, is an adverse effect of ICI treatment resulting from immune system dysregulation, which can mimic disease progression. It is crucial to be aware of this adverse event and to understand the optimal management approach.

KEYWORDS

hepatocellular carcinoma, immune-checkpoint inhibitor, nivolumab plus ipilimumab combination therapy, immune related adverse event (irAE), sarcoidosis

Introduction

The advent of immunotherapy has revolutionized the field of cancer treatment, transforming the trajectory of several tumor types. Notably, humanized monoclonal antibodies such as nivolumab and ipilimumab have emerged as prime examples. These antibodies target the programmed death receptor (PD-1) and cytotoxic T lymphocyte antigen-4 (CTLA-4) respectively, both of which are located on the cell membrane of T lymphocytes.

By exerting their therapeutic effects, these drugs have successfully intercepted one of the cancer cell's evasion mechanisms: immune response suppression. As a result, they have demonstrated clinical efficacy in malignancies such as melanoma, kidney cancer, and lung cancer. In the case of hepatocellular carcinoma (HCC), the combination of nivolumab and ipilimumab has shown significant activity, leading to its approval for this patient population based on the findings of the CheckMate 040 trial (1).

Immunotherapy has introduced new immune-related adverse events and clinical management challenges, including pseudoprogression and hyperprogression. These circumstances can sometimes be mistaken for immunotherapy-associated side effects, such as sarcoidosis-like reactions (SLRs) (2). To the best of our knowledge, we present the first published clinical case of SLR in a patient undergoing treatment with nivolumab plus ipilimumab for advanced HCC.

Case report

We present the case of a 41-year-old male patient with an unremarkable medical history who was diagnosed with stage C HCC according to the Barcelona Clinic Liver Cancer classification in October 2020. The carcinoma was located in a non-cirrhotic liver with metastatic retroperitoneal lymph nodes.

In January 2021, treatment with sorafenib 400 mg twice a day was started. However, after nine months, in October 2021, sorafenib was discontinued due to disease progression, characterized by the emergence of a new subdiaphragmatic metastatic lesion and by an increase in alpha-fetoprotein (AFP) levels to 1210 ng/mL (normal range: 0.1 – 10). Subsequently, second-line treatment with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg was started based on the findings of the CheckMate 040 trial. The patient received four cycles of this regimen until January 2022.

One week after completing the fourth cycle, the patient was admitted to the hospital due to intermittent fever and profuse sweating. A chest and abdominal CT scan performed during the admission showed multiple pathologically enlarged lymph nodes in several locations (cervical, bilateral hilar, axillary, and inguinal) and hepatosplenomegaly, but it also showed stability in the size of the retroperitoneal lymph nodes and the left subdiaphragmatic lesion. This was further confirmed by positron emission tomography (PET-CT). Consequently, an excisional biopsy of an inguinal lymph node was performed to obtain a histological diagnosis. Considering the patient's favorable clinical condition and the absence of a definitive diagnosis, it was decided to closely monitor the patient and administer symptomatic treatment with antipyretics. After one week, the fever subsided, and the patient was discharged from the hospital.

A week later, during a follow-up visit at our clinic, the patient complained about bilateral ocular redness accompanied by pain. Ophthalmology consultation lead to the diagnosis of bilateral anterior uveitis. After starting corticosteroids in eye drops, ocular symptoms disappeared in the following days. Given the distribution of the newly appeared lymph nodes, the stability of the previously known disease, and the anterior uveitis, we suspected that we were dealing with a SLR due to immune checkpoint inhibitors. Consequently, a comprehensive blood test, including autoimmunity markers and angiotensin-converting enzyme (ACE) levels, was requested while awaiting the results of the inguinal node biopsy. Given the possibility of disease progression as an alternative diagnosis, repeat alpha-fetoprotein levels were also requested. The immunotherapy was not resumed at this point.

Eventually, the biopsy results showed non-necrotizing granulomatous lymphadenitis (Figure 1). The blood test revealed increased ACE levels of 67 U/L (normal range: 8 – 52), decreasing AFP levels of 698 ng/mL (previously 1210 ng/mL), and negative results for autoimmunity markers. Together with the patient's symptoms, these findings were consistent with SLR following ICI.

Taking into account the disease control achieved with the treatment and the relatively mild symptoms experienced by the patient, it was decided to continue with maintenance nivolumab. After 3 months, a follow-up CT scan was performed, which showed the disappearance of the previously identified lymph nodes observed in the January 2022 CT scan. Furthermore, stability was observed in the retroperitoneal lymph nodes and the left subdiaphragmatic lesion. Consequently, the disease was classified as stable, and the treatment was continued. Currently, the patient remains on nivolumab and has not experienced any new episodes of SLR or disease progression.

Discussion

Sarcoidosis is a multisystemic granulomatous disease of uncertain etiology characterized by an aberrant immune response mediated by CD4 T lymphocytes. Upon interaction with antigen-presenting cells, these lymphocytes differentiate into helper T lymphocytes type 1 (Th1) and begin to secrete interleukin 2 (IL-2) and interferon gamma (IFN-γ), thereby increasing the production of tumor necrosis factor alpha (TNF-α) by macrophages. Cytokine activation results in the development of organized clusters of epithelioid histiocytes and macrophages surrounded by giant multinucleated cells and lymphocytes (non-necrotizing granulomas). Additionally, helper T lymphocytes type 17 (Th17) have also been involved in the pathogenesis of sarcoidosis (3).

Clinical manifestations vary depending on the affected body part, with pulmonary involvement, mediastinal lymphadenopathy, and cutaneous manifestations being the most characteristic ones. Common associated symptoms include fatigue, fever, night sweats, and weight loss. Extrapulmonary disease can be widespread and

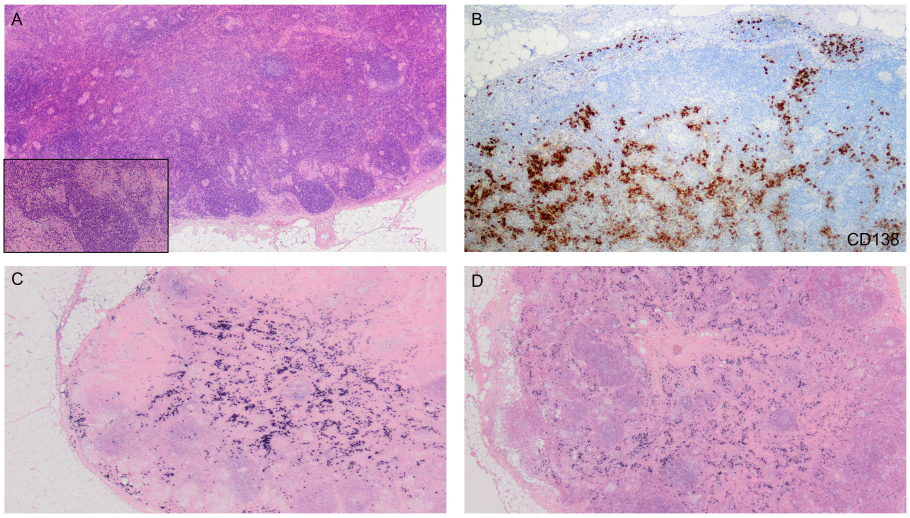


FIGURE 1
(A) Lymph node with the presence of non-epithelioid granulomas adjacent to peripheral primary lymphoid follicles. At higher magnification, confluent granulomas are better visualized, along with the presence of giant cells. (H&E; 2x and 10x). **(B)** Proliferation of plasma cells showing positive immunoreactivity to CD138. (CD138; 4x). **(C, D)** No restriction of kappa or lambda light chains observed. (Kappa and lambda; 2x).

affect several organs, such as the eyes (anterior uveitis), the nervous, cardiac, or renal systems and cause hepatosplenomegaly (3).

SLR as an adverse effect of immunotherapy is uncommon but increasingly reported due to the rising use of immune checkpoint inhibitors (ICIs). CTLA-4 blockade has been observed to elevate levels of Th17 lymphocytes in the bloodstream, leading to the increased production of proinflammatory cytokines such as interleukin 17 (IL-17) and TNF-α (4). Furthermore, the PD-1/PD-L1 pathway is associated with the balance of T helper lymphocytes/Th17 lymphocytes, and its blockade enhances Th17 lymphocyte activity and IL-17 expression (5). The blockade of the PD-1/PD-L1 pathway can also activate the mTOR pathway, which is involved in the spontaneous formation of granulomas (6).

The first case-control study of patients with SLR treated with immunotherapy reported 28 cases, mostly in melanoma patients (2). The majority of SLRs were mild to moderate (92.9% grade I-II). Symptoms, especially cough and dyspnea, were present in 53.6% of patients, with radiological findings predominantly in the mediastinal lymph nodes and lung parenchyma, while extrathoracic involvement was less frequent. Elevated ACE levels were observed in 40% of patients. This adverse event was more common when administering the combination of anti-PD1 and anti-CTLA4 therapy (46.4% with nivolumab and ipilimumab combination). The study also showed that patients with SLR had a longer survival. However, due to the heterogeneous population and retrospective nature of the study, drawing conclusions at this stage would be premature. Management of this adverse event varies based on severity, with systemic corticosteroids required in 17.9% of patients in this study, and up to 44% in other series (7). No patients needed immunosuppressive therapy for sarcoidosis management. Immunotherapy was temporarily interrupted in 10.7% of patients and permanently discontinued in 67.9% of patients, with 12 cases attributed to sarcoidosis. The use of corticosteroids should be considered in patients with SLR related to immunotherapy, depending on clinical severity, although it may reduce the efficacy of immunotherapy.

One of the main challenges in patients treated with immunotherapy with SLR is the ability of SLR to mimic disease progression, particularly due to lymph node involvement. In the context of immunotherapy, pseudoprogression and hyperprogression must also be considered. Essential clues in our case included the patient's good performance status, the abnormal distribution of lymph nodes compared to the previously known disease, the decrease in alpha-fetoprotein levels alongside an increase in ACE levels, and the clinical suspicion of SLR, which was further supported by the presence of typical non-necrotizing granulomas observed in the lymph node histopathological study.

The most notable aspect of our clinical case is the atypical presentation of this SLR due to immunotherapy, with predominantly extrapulmonary involvement (polyadenopathy syndrome, anterior uveitis and hepatosplenomegaly), emphasizing the importance of understanding the full clinical spectrum of this adverse event, which could potentially lead to the discontinuation of oncological treatment due to confusion with disease progression. It is also important to note that this adverse event can arise in various tumor types, including HCC. Our case represents the first clinical report in literature of an advanced HCC patient presenting with SLR induced by ICI.

Conclusion

SLRs due to immunotherapy are infrequent side effects; however, it is imperative to remain vigilant regarding their occurrence as they may mimic tumor recurrence or progression, leading to treatment discontinuation. Therefore, it is crucial to consider this adverse event and, if suspected, perform a histological study for definitive confirmation.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

AT-Z, LV-M and LG-L wrote the first draft of the manuscript. AT-Z did the bibliography review. MM-R and LC-M corrected the latest version of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

Author AT-Z has received honoraria from Daiichi-Sankyo for invited speaker. Author LC-M reports institutional grants from Celgene, Roche and MSD, as well as personal fees advisory boards and speakers contribution from Bristol Myers Squibb, MSD-Merck, AstraZeneca, Roche, Gilead, and Incyte.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Yau T, Kang Y, Kim T, El-Khoueiry A, Santoro A, Sangro B, et al. Efficacy and safety of nivolumab plus ipilimumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib. *JAMA Oncol* (2020) 6(11):e204564. doi: 10.1001/jamaoncol.2020.4564

2. Cabanié C, Ammari S, Hans S, Pobel C, Laparra A, Danlos F, et al. Outcomes of patients with cancer and sarcoid-like granulomatosis associated with immune checkpoint inhibitors: A case–control study. *Eur J Cancer.* (2021) 156:46–59. doi: 10.1016/j.ejca.2021.07.015

3. Iannuzzi M, Rybicki B, Teirstein A. Sarcoidosis. *New Engl J Med* (2007) 357 (21):2153–65. doi: 10.1056/NEJMra071714

4. Vogel WV, Guislain A, Kvistborg P, Schumacher TN, Haanen JB, Blank CU. Ipilimumab-induced sarcoidosis in a patient with metastatic melanoma undergoing complete remission. *J Clin Oncol* (2012) 30:e7–e10. doi: 10.1200/JCO.2011.37.9693

5. Facco M, Cabrelle A, Teramo A, Olivieri V, Gnoato M, Teolato S, et al. Sarcoidosis is a Th1/Th17 multisystem disorder. *Thorax* (2010) 66:144–50. doi: 10.1136/thx.2010.140319

6. Celada LJ, Rotsinger JE, Young A, Shaginurova G, Shelton D, Hawkins C, et al. Programmed death-1 inhibition of phosphatidylinositol 3-kinase/AKT/mechanistic target of rapamycin signaling impairs sarcoidosis CD4+ T cell proliferation. *Am J Respir Cell Mol Biol* (2017) 56(1):74–82. doi: 10.1165/rcmb.2016-0037OC

7. Tetzlaff M, Nelson K, Diab A, Staerkel G, Nagarajan P, Torres-Cabala C, et al. Granulomatous/sarcoid-like lesions associated with checkpoint inhibitors: a marker of therapy response in a subset of melanoma patients. *J ImmunoTher Cancer* (2018) 6 (1):14. doi: 10.1186/s40425-018-0323-0

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 31 October 2023
DOI 10.3389/fphar.2023.1213608

OPEN ACCESS

EDITED BY
Aysin Tulunay Virlan,
University of Glasgow, United Kingdom

REVIEWED BY
Tayfur Toptas,
School of Medicine, Marmara University, Türkiye
Justin Arnall,
Atrium Health Carolinas Medical Center (CMC), United States

*CORRESPONDENCE
Na Li,
171772958@qq.com

RECEIVED 28 April 2023
ACCEPTED 17 October 2023
PUBLISHED 31 October 2023

CITATION
Li N, Feng Y, Chen X, Li Y, Zhang C and Yin Y (2023), Hematologic and lymphatic system toxicities associated with immune checkpoint inhibitors: a real-world study. *Front. Pharmacol.* 14:1213608. doi: 10.3389/fphar.2023.1213608

Hematologic and lymphatic system toxicities associated with immune checkpoint inhibitors: a real-world study

Na Li[1]*, Yong Feng[2], XiaoLing Chen[3], Ye Li[1], Chengmiao Zhang[1] and Yin Yin[1]

[1]Department of Central Laboratory, Shenyang Tenth People's Hospital, Shenyang Chest Hospital, Shenyang, China, [2]Department of Thoracic Surgery, Shenyang Tenth People's Hospital, Shenyang Chest Hospital, Shenyang, China, [3]Department of Pathology, Shenyang Tenth People's Hospital, Shenyang Chest Hospital, Shenyang, China

Introduction: Immune checkpoint inhibitors (ICIs) exert antitumor responses in many types of cancer but may also induce serious or fatal toxicities that affect all organ systems, including the hematologic and lymphatic systems. However, the risk of hematologic and lymphatic system toxicities following different ICI treatments remains unknown. This study aimed to describe the hematologic and lymphatic system toxicities associated with different ICI regimens and the impact of combining ICIs with anti-vascular endothelial growth factor drugs using the United States Food and Drug Administration Adverse Event Reporting System pharmacovigilance database.

Methods: The reporting odds ratio (ROR) and information component (IC) indices were used to identify disproportionate reporting of ICI-associated hematologic and lymphatic adverse events (AEs).

Results: We extracted 10,971 ICI-associated hematologic and lymphatic AEs from 35,417,155 reports. These AEs were more frequently reported in female patients (ROR: 1.04 95% confidence interval [CI]: 1.01–1.07) and younger patients (ROR: 1.05 95% CI: 1.01–1.09). The disseminated intravascular coagulation fatality rate (63.97%) was the highest among the reported preferred terms, despite its low incidence (3.32%). The time to onset of ICI-related hematologic and lymphatic AEs was relatively short, with 77.44% reported within 3 months. Disproportionate analysis showed that most ICIs were associated with significant overreporting of hematologic and lymphatic AEs (IC_{025}: 0.34 and ROR_{025}: 2.10). Hematologic and lymphatic system AEs were more frequently reported in patients treated with anti-programmed cell death protein 1/programmed cell death ligand 1 monotherapy than in those treated with anti-cytotoxic T-lymphocyte-associated protein 4 monotherapy (ROR: 1.54, 95% CI: 1.38–1.71), with atezolizumab showing the strongest signal (ROR_{025}: 4.19, IC_{025}: 1.00). In patients receiving combined treatment, ICIs plus bevacizumab exerted a higher disproportion signal than monotherapy (ROR: 161, 95% CI: 1.75–1.88).

Discussion: The spectrum of hematologic and lymphatic AEs differed according to the ICI regimen. Early recognition and management of ICI-related hematologic and lymphatic AEs are vital in clinical practice.

KEYWORDS

immune checkpoint inhibitors, hematologic and lymphatic toxicities, FDA adverse event reporting system, programmed cell death protein 1/programmed cell death ligand 1, cytotoxic T-lymphocyte-associated protein, monotherapy, bevacizumab, combination therapy

1 Introduction

Immune checkpoint inhibitors (ICIs) targeting the programmed cell death protein 1/programmed cell death ligand 1 (PD-1/PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) have revolutionized the treatment landscape for a wide range of cancers, demonstrating significant efficacy and favorable responses and pioneering a new therapeutic paradigm for many types of solid tumors (Ribas and Wolchok, 2018; Tang et al., 2018). Compared with monotherapy, combined ICI blockade can further improve clinical outcomes (Hammers et al., 2017; Hellmann et al., 2019; Wolchok et al., 2022). To date, three main types of ICIs have been approved by the United States Food and Drug Administration (FDA): PD-1 inhibitors such as cemiplimab, nivolumab, and pembrolizumab; PD-L1 inhibitors such as atezolizumab, avelumab, and durvalumab; and CTLA-4 inhibitors such as ipilimumab and tremelimumab (Ribas and Wolchok, 2018).

Although clinically effective, ICIs can be accompanied by severe and sometimes fatal organ system toxicities, including hematologic and lymphatic toxicities (Kennedy and Salama, 2020; Ghanem et al., 2022). Frequently reported ICI-related hematologic and lymphatic system complications include anemia (Chambers et al., 2022), thrombocytopenia (Xie et al., 2021), and pure red cell aplasia (Wright and Brown, 2017; Kroll et al., 2022). ICI-induced hematologic and lymphatic adverse events (AEs) are rare, with an incidence of 3.6% for all grades and 0.7% for grades III–IV (Michot et al., 2019; Petrelli et al., 2018). However, ICIs can lead to serious and life-threatening AEs, which are reported less frequently than common AEs and have not been extensively characterized.

Vascular endothelial growth factor (VEGF)-dependent angiogenesis plays a critical role in tumorigenesis and progression (Goel and Mercurio, 2013; Ferrara and Adamis, 2016). Bevacizumab, a recombinant humanized immunoglobulin (Ig) G1 monoclonal antibody targeting VEGF, was the first angiogenesis inhibitor approved by the United States FDA for treating a wide range of tumors (Viallard and Larrivée, 2017). VEGF can attenuate the antitumor immune response by reprogramming the tumor immune microenvironment; thus, anti-VEGF combined with immunotherapy has a potential synergistic antitumor effect (Bejarano et al., 2021). However, in combination therapy, the clinical benefits and overlapping toxicity of the drugs must be carefully considered. Although rare, bevacizumab can also cause some hematological complications, such as thrombocytopenia. A phase III randomized trial of bevacizumab for glioblastoma showed a higher incidence of thrombocytopenia than the placebo (34.1% vs. 27.3%) (Saran et al., 2016). According to a case report, a 59-year-old male patient with colon adenocarcinoma developed thrombocytopenia after treatment with bevacizumab (Kumar et al., 2012). Owing to the complex biological effects of combined ICI and VEGF inhibitor use, whether this combination enhances or reduces the toxicities of the hematologic and lymphatic systems remains unclear.

Given the increase in the use of ICIs in clinical practice, the potential risk to the hematologic and lymphatic systems should be considered. Herein, we report the results of a systematic analysis using real-world pharmacovigilance data to investigate the association of hematologic and lymphatic system toxicities of different ICI treatment regimens and further consider the effect of bevacizumab to provide evidence for clinical practice.

2 Materials and methods

2.1 Data sources and study design

This retrospective, observational pharmacovigilance study was conducted using the FDA Adverse Event Reporting System (FAERS) database, which is a collection of reports of AEs that allows for signal detection and quantification of the association between drugs and reporting of AEs (Min et al., 2018). All variables for each record, including age, sex, outcomes, drug name, reporting year, and reporting country, can be extracted from the FAERS database. AEs were coded using preferred terms (PTs) according to the international Medical Dictionary for Regulatory Activities (MedDRA). A specific PT was assigned to high-level terms and system-organ classes. In addition, we removed duplicate records using FDA's recommended method by choosing the latest FDA_DT if the CASEID was the same and choosing the higher PRIMARYID if the CASEID and FDA_DT were the same. In this analysis, the coverage period was from 1 January 2014 to 31 December 2022. The studied drugs included anti-PD-1 (nivolumab, cemiplimab, and pembrolizumab), anti-PD-L1 (atezolizumab, avelumab, and durvalumab), anti-CTLA-4 (ipilimumab and tremelimumab), and anti-VEGF antibodies. As FAERS does not use a uniform coding system for medications, both generic and brand-name drugs were used to identify study drug-associated records. The details of the drug names are listed in Supplementary Table S1. This study included both monotherapy and combination therapy. Toxicity was attributed to monotherapy if one drug was reported as the "primary suspect" and to combination therapy if one drug was reported as the "primary suspect" and other drugs were reported as "secondary suspects." This study included all blood and lymphatic system disorders (MedDRA code: 10005329) according to MedDRA version 25.0.

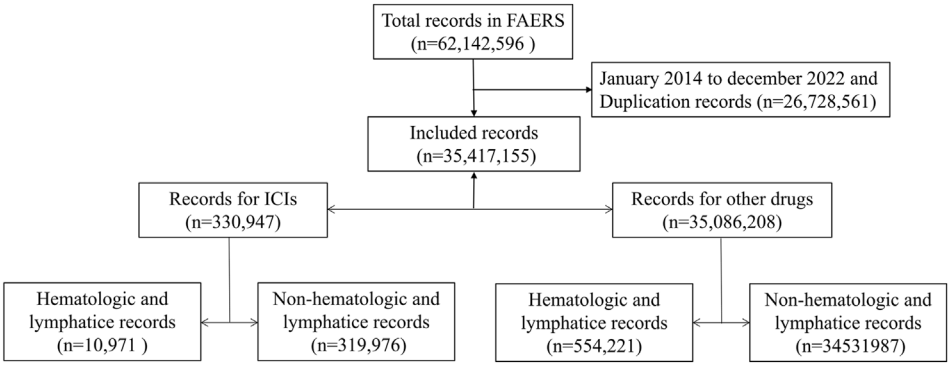


FIGURE 1
Screening process for adverse event records in the FAERS database.

2.2 Statistical analysis

Descriptive analysis was performed to summarize clinical features. Disproportionality analysis was used to evaluate specific AEs associated with a given drug (Ali et al., 2021). Reporting odds ratios (RORs) and information components (ICs) were used as indicators of disproportionality (Ang et al., 2016; Gatti et al., 2021). A significant signal was defined if the lower limit of the 95% confidence interval (CI) of ROR (ROR_{025}) was >1 in at least three cases or the lower limit of the 95% CI of the IC (IC_{025}) was >0. The equations for the two algorithms are provided in Supplementary Table S2. In our analysis, ICIs were compared with all other drugs in the full database. We did not consider ICIs in combination with chemotherapy owing to the limitations of chemotherapy drug screening. We performed disproportionality analyses for different subgroups, including sex, age, and different therapies (ROR only). Data were analyzed using SAS version 9.4 (SAS Institute Inc., Cary, NC, United States) and Microsoft Office Excel version 2023 (Microsoft Corp., Redmond, WA, United States).

3 Results

3.1 Identifying hematologic and lymphatic AEs from FAERS

To date, 62,142,596 records have been deposited in the FAERS database. After excluding duplicate records, 35,417,155 records were selected from 1 January 2014 to 31 December 2022, of which 330,947 were associated with ICI-related AEs. Subsequently, 10,971 records were screened for hematologic and lymphatic AEs associated with ICIs. In addition, 554,221 records on hematologic and lymphatic AEs associated with other drugs were included in the analytic dataset (Figure 1).

3.2 Descriptive analysis from FAERS

The clinical characteristics of patients with ICI-induced hematologic and lymphatic AEs are listed in Table 1. We found that 83.38% of the cases were reported in 2018–2022, reflecting a substantial increase in the use of ICIs in recent years. Most reports were from Japan (3,045, 27.75%), the United States (2,267, 20.66%), and France (1,143, 10.42%). There were more reports on men (55.37%) than on women (37.00%) and on patients aged ≥65 years (44.11%) than on those aged <65 years (36.25%).

In the analysis of deaths due to the 10 most frequently reported PTs in class-specific hematologic and lymphatic AEs, 2,180 (19.87%) were associated with ICIs (Table 1). Further analyses revealed that the severity of these events varied. In general, anemia, thrombocytopenia, febrile neutropenia, neutropenia, pancytopenia, myelosuppression, disseminated intravascular coagulation, lymphadenopathy, leukopenia, and autoimmune hemolytic anemia were the 10 most frequently reported PTs in class-specific hematologic and lymphatic systems. Although the incidence of disseminated intravascular coagulation (358/10,791%, 3.32%) was low, its case fatality rate (229/358%, 63.97%) was the highest among the 10 most frequently reported PTs. Anemia had the highest incidence (2,071/10,791%, 19.19%) and the second highest case fatality rate (542/2,071%, 26.17%; Figure 2).

3.3 Time to onset (TTO)

Figure 3 shows the TTO of the 10 most frequently reported PTs in the ICI-related hematologic and lymphatic systems. After excluding records with no event times, 5,417 records were included. A higher cumulative proportion of ICI-related hematologic and lymphatic AE records occurred 1 month after administration (51.36%, 2,782/5,417) than at any other time point. Of the ICI-related hematologic and lymphatic AEs, 77.44% (4,195/5,417) occurred within 3 months. Overall, the data for myelosuppression showed a relatively short median onset time (13 days), whereas those for lymphadenopathy and autohemolytic anemia had relatively long median onset times of 55 and 51 days, respectively (Figure 3).

3.4 Disproportionality analysis

The signal values and associations between hematologic and lymphatic AEs and different ICI regimens are summarized in

10.3389/fphar.2023.1213608

TABLE 1 Clinical characteristics of patients with ICI- and other drug-induced hematological and lymphatic system toxicity.

Characteristics	Hematological and lymphatic system AEs with ICIs (*n* = 10971)	Hematological and lymphatic system AEs with other drugs (*n* = 554221)
Sex		
Female	4059 (37.00%)	262811 (47.42%)
Male	6075 (55.37%)	217088 (39.17%)
Missing	837 (7.63%)	74321 (13.41%)
Age, years		
<65	3977 (36.25%)	240865 (43.46%)
≥65	4839 (44.11%)	164826 (29.74%)
Missing	2155 (19.64%)	148529 (26.80%)
Reporting year		
2014	110 (1.00%)	19398 (3.50%)
2015	299 (2.73%)	23832 (4.30%)
2016	507 (4.62%)	43783 (7.90%)
2017	907 (8.27%)	36024 (6.50%)
2018	1242 (11.32%)	55422 (10.00%)
2019	1583 (14.43%)	65952 (11.90%)
2020	1740 (15.86)	92001 (16.60%)
2021	2094 (19.09%)	104194 (18.80%)
2022	2489 (22.69%)	113615 (20.50%)
Reporting country		
United states	2267 (20.66%)	212322 (38.31%)
Japan	3045 (27.75%)	42120 (7.60%)
France	1143 (10.42%)	46665 (8.42%)
Germany	769 (7.01%)	30371 (5.48%)
China	638 (5.82%)	19397 (3.50%)
Italy	476 (4.34%)	23831 (4.30%)
Others	2017 (18.38%)	135728 (24.49%)
Missing	616 (5.61%)	101533 (18.32%)
Outcome		
Death	2180 (19.87%)	49935 (9.01%)
Hospitalization	4519 (41.19%)	189710 (34.23%)
Other serious events	3643 (33.20%)	271900 (49.06%)
Life threatening	203 (1.85%)	33807 (6.10%)
Disability	160 (1.46%)	6816 (1.23%)
Required	5 (0.05%)	1109 (0.20%)
Missing	189 (1.72%)	943 (0.17%)

ICIs, immune checkpoint inhibitors.
Data are presented as *n* (%).

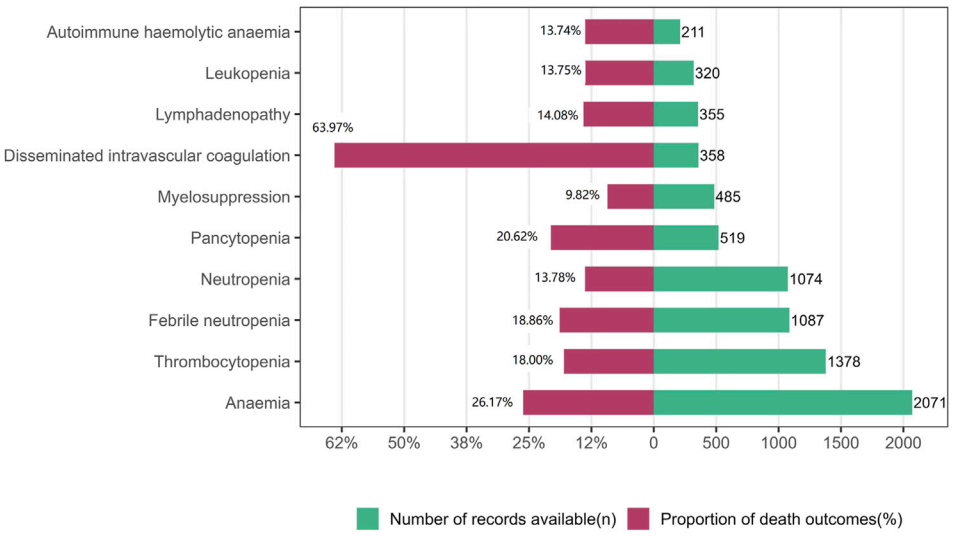


FIGURE 2
Records and proportions of deaths in class-specific hematological and lymphatic system adverse events.

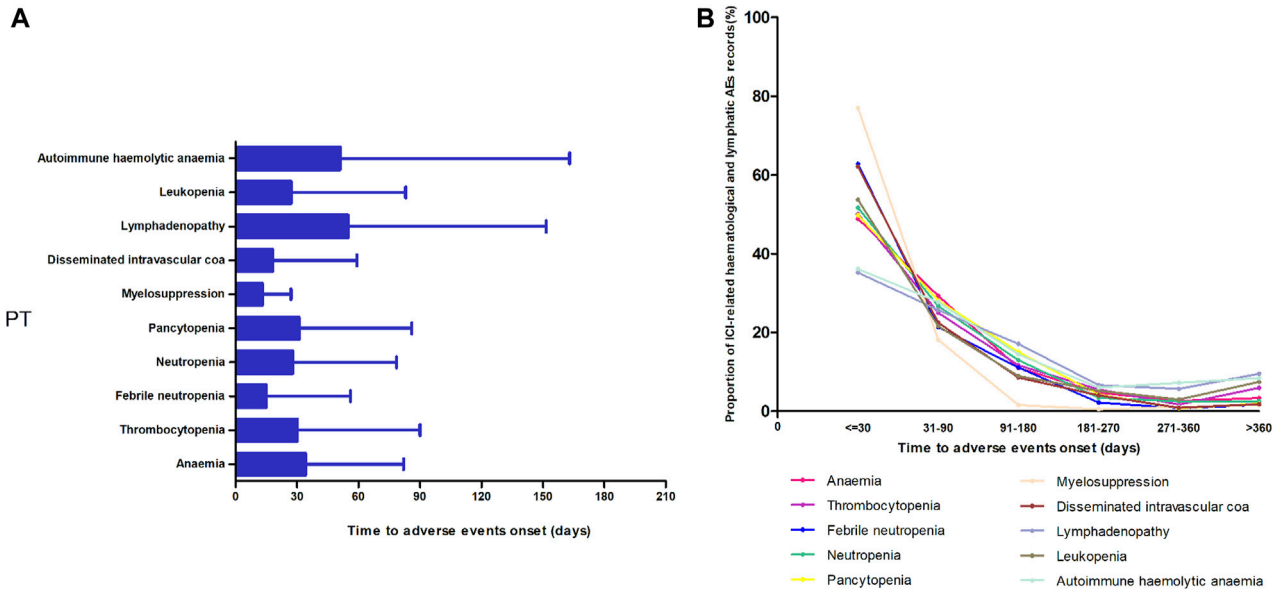


FIGURE 3
Time of onset of the top 10 most frequently reported preferred terms in the hematological and lymphatic systems. **(A)** Time of onset and **(B)** the cumulative proportion at different periods.

Table 2. In general, higher reporting frequencies of hematologic and lymphatic AEs were observed for most ICI regimens. The ROR_{025} was 2.10 and IC_{025} was 0.35 for ICIs, compared to the whole database. AEs were reported more frequently in female patients than in male patients (ROR: 1.05, 95% CI: 1.01–1.08, Supplementary Table S3) and in patients aged <65 years than in those aged ≥65 years (ROR: 1.05, 95% CI: 1.01–1.09, Supplementary Table S3). Regarding monotherapy, most hematologic and lymphatic AEs were reported for anti-PD-1 agents (N = 6407, 58.40%), whereas anti-PD-L1 drugs contributed to a lower proportion of AEs (N = 1975, 18.00%) but had stronger signal values (ROR_{025}: 7.68, IC_{025}: 2.84), especially atezolizumab, which had the strongest signal values (ROR_{025}: 4.19, IC_{025}: 1.00) among the monotherapies reported.

Hematologic and lymphatic toxicities were more frequently reported in patients treated with anti-PD-1/PD-L1 than in those treated with anti-CTLA-4 (ROR_{025}: 1.38). Among the combination therapies, nivolumab plus ipilimumab was the most common (N = 1476, 13.45%), but only its ROR was significant (ROR_{025}: 1.59, IC_{025}: −0.25). Durvalumab plus tremelimumab showed a stronger

TABLE 2 Signal value of hematological and lymphatic system AEs associated with different immunotherapy regimens.

Strategy	a (N)	b	c	d	ROR	ROR_{025}	ROR_{975}	IC	IC_{025}	IC_{975}
Total	10971	319976	554221	34531987	2.14	**2.10**	2.18	1.05	**0.35**	1.75
ICIs										
Nivolumab	3343	108806	561849	34743157	1.90	**1.84**	1.97	0.9	**0.05**	1.75
Pembrolizumab	2961	87965	562231	34763998	2.08	**2.00**	2.16	1.03	**0.16**	1.90
Cemiplimab	103	3024	565089	34848939	2.10	**1.73**	2.56	1.04	−0.48	2.56
Atezolizumab	1379	20329	563813	34831634	4.19	**3.97**	4.43	1.99	**1.00**	2.98
Durvalumab	508	11878	564684	34840085	2.64	**2.41**	2.88	1.36	**0.19**	2.53
Avelumab	88	3109	565104	34848854	1.75	**1.42**	2.16	0.78	−0.78	2.34
Ipilimumab	372	16050	564820	34835913	1.43	**1.29**	1.58	0.50	−0.73	1.73
Polytherapy1	1476	54518	563716	34797445	1.67	**1.59**	1.769	0.72	−0.25	1.64
Polytherapy2	36	1430	565156	34850533	1.55	**1.12**	2.16	0.61	−1.20	2.42
Polytherapy3	73	1206	565119	34850757	3.73	**2.95**	4.73	1.81	**0.20**	3.41
ICIs + bevacizumab	753	12615	564439	34839348	3.68	**3.42**	3.96	1.81	**0.72**	2.90
Anti-PD-1/PD-L1 vs. anti-CTLA-4	8382	235111	372	16050	1.54	**1.38**	1.71			
Polytherapy vs. monotherapy	1559	57489	8754	251161	0.77	0.74	0.82			
ICIs + bevacizumab vs. ICIs	753	12615	10971	319976	1.74	**1.61**	1.88			

Note: Bold text denotes significant signals.

ICIs, immune checkpoint inhibitors; Polytherapy1, nivolumab + ipilimumab; Polytherapy2, nivolumab + pembrolimab + ipilimumab; Polytherapy3, durvalumab + tremelimumab; CI, confidence interval; ROR, reporting odds ratio; ROR_{025}, lower limit of the 95% two-sided CI, of the ROR; ROR_{075}, upper limit of the 95% two-sided CI, of the ROR. a(N), the number of reports containing both ICIs, and hematological and lymphatic system AEs, in one subgroup; b, the number of reports containing both ICIs, and all other adverse events (except hematological and lymphatic system AEs) in one subgroup; c, the number of reports containing both ICIs, and hematological and lymphatic system AEs, in another subgroup; and d, the number of reports containing both ICIs, and all other adverse events in another subgroup.

signal (ROR_{025}: 2.95, IC_{025}: 0.20) than the above group, despite contributing a very small proportion of reported AEs (N = 73, 0.06%). Furthermore, ICIs plus anti-VEGF therapy showed the highest signal value among the combined therapies (ROR_{025}: 3.42, IC_{025}: 0.72). Disproportionate reporting was also found in combination therapy compared with monotherapy: hematologic and lymphatic AEs were more frequently reported in patients treated with ICI plus anti-VEGF combination therapy than in those treated with ICI monotherapies (ROR: 1.74, 95% CI: 1.61–1.88).

3.5 Spectrum of hematologic and lymphatic AEs in different ICI regimens

Figure 4 shows the hematologic and lymphatic system toxicity profiles of the different ICI monotherapy regimens. A total of 59 class-specific signals were significant in the anti-PD-1/PD-L1 classes compared with 15 signals in the anti-CTLA-4 class. Among the PD-1 inhibitors, pembrolizumab showed the broadest spectrum of hematologic and lymphatic AEs, with 41 PTs detected as signals, ranging from aplastic anemia (ROR_{025}: 1.06) to immune-mediated cytopenia (ROR_{025}: 131.29). There were 40 PTs significantly associated with nivolumab treatment, ranging from bone marrow failure (ROR_{025}: 1.10) to acquired amegakaryocytic thrombocytopenia (ROR_{025}: 20.58). There were six PTs significantly associated with cemiplimab treatment, ranging from febrile neutropenia (ROR_{025}: 1.06) to lymphadenopathy (ROR_{025}: 2.81). These six PTs overlapped with those of pembrolizumab and nivolumab therapy and included lymphadenopathy, eosinophilia, thrombocytopenia, anemia, pancytopenia, and febrile neutropenia.

The hematologic and lymphatic system spectra of anti-PD-L1 drugs varied substantially, with 24 PTs significantly associated with the atezolizumab treatment, ranging from agranulocytosis (ROR_{025}: 1.11) to myelosuppression (ROR_{025}: 13.20). There were 14 PTs associated with durvalumab, ranging from anemia (ROR025: 1.21) to myelosuppression (ROR025: 18.71). The following PTs were uniquely associated with atezolizumab: pure red cell aplasia, aplastic anemia, and lymphadenopathy. For the anti-PD-L1 group, myelosuppression was the most significant signal associated with atezolizumab (ROR_{025}: 13.20) and durvalumab (ROR_{025}: 18.71), followed by febrile neutropenia (ROR_{025}: 10.93 and 9.59, respectively). The four PT signals detected by avelumab all overlapped with atezolizumab and durvalumab. Anti-CTLA-4 treatment had 15 PTs significantly associated with ipilimumab, with 13 PTs overlapping with anti-PD-1 and 12 PTs with anti-PD-L1 (Figure 4).

Compared with the immune-monotherapy group, the double-ICI blockade group had relatively few PTs: 33 class-specific signals were detected, of which 4 were newly generated, namely, hemolysis, pseudolymphoma, thrombotic microangiopathy, and splenic hemorrhage. Notably, splenic hemorrhage had a relatively high signal for the durvalumab plus tremelimumab treatment (ROR_{025}: 11.82). Nivolumab plus ipilimumab, the most common tumor treatment, showed the broadest spectrum of hematologic and lymphatic system diseases, ranging from lymphadenitis (ROR_{025}:

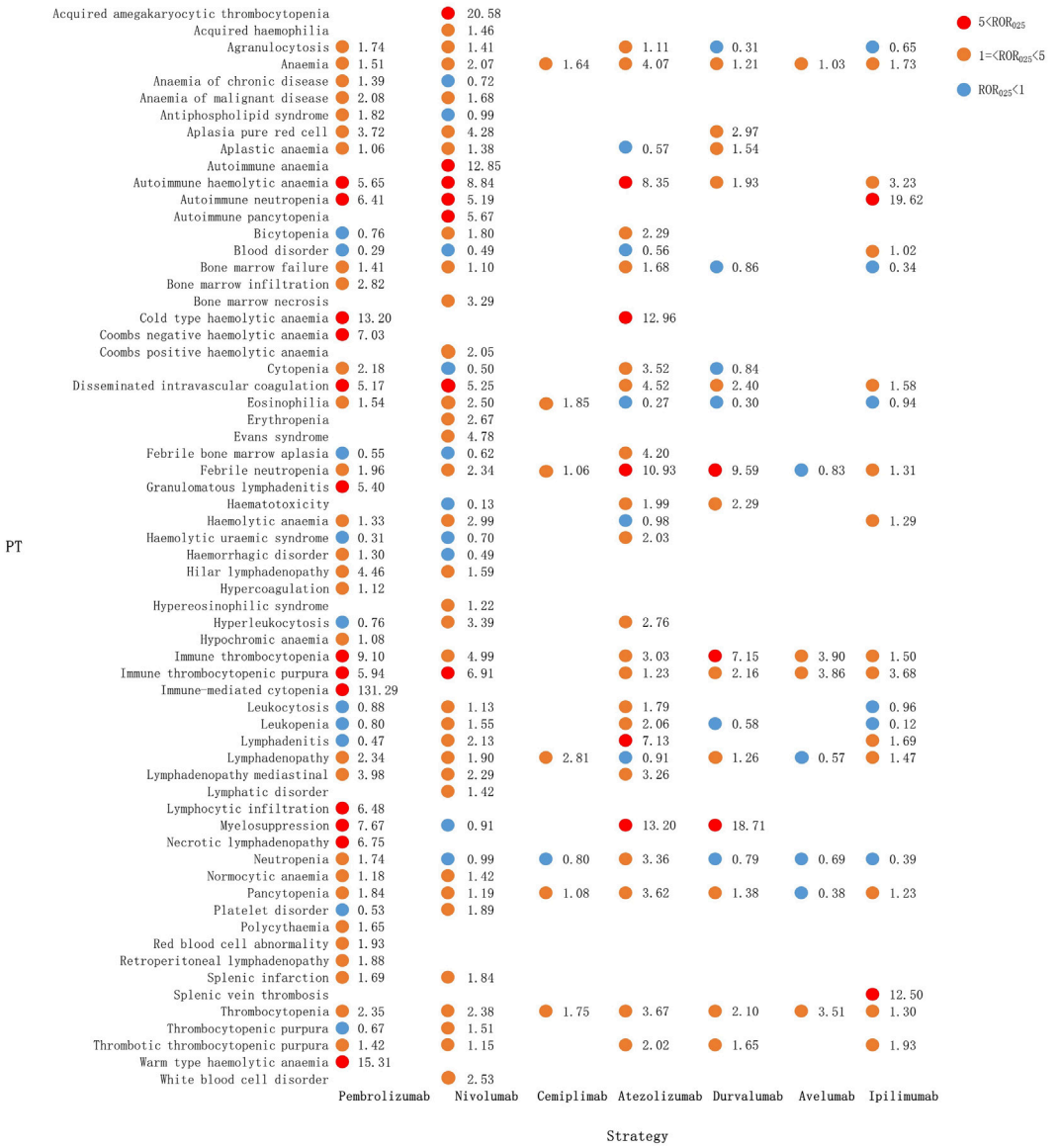


FIGURE 4
Hematological and lymphatic system toxicities for different ICI monotherapy strategies. PT, preferred term; IC, information component; IC_{025}, lower limit of the 95% confidence interval of IC; IC_{025}, greater than 0 was deemed a signal; ICI, immune checkpoint inhibitor.

1.07) to immune-mediated cytopenia (ROR_{025}: 45.05). As mentioned above, immune-mediated cytopenia was also the strongest signal in pembrolizumab monotherapy. In ICI plus bevacizumab treatment, 19 PT signals were detected, 5 of which were not present in the other combination regimens (Figure 5).

Overall, anemia (n = 207, 19.19%), thrombocytopenia (n = 1378, 12.77%), febrile neutropenia (n = 1078, 10.07%), and neutropenia (n = 1074, 9.95%) were the four most common hematologic and lymphatic system complications in patients who received ICIs. However, their correlation with different ICI therapies varied. Anemia and thrombocytopenia appeared to be associated with the most regimens except polytherapy2 (Figure 6). Febrile neutropenia was strongly associated with atezolizumab plus tremelimumab and ICI plus bevacizumab combination regimens but showed no correlation with avelumab. Similarly, neutropenia was associated with pembrolizumab, atezolizumab, and ICI plus bevacizumab combination regimens only.

4 Discussion

ICIs have remarkable clinical benefits against multiple tumor types. Although complications are rare, ICIs can induce various hematologic and lymphatic complications (Delanoy et al., 2019). However, the risk of experiencing hematologic and lymphatic AEs following ICI use has not been clearly quantified. To the best of our knowledge, this is the largest and most comprehensive pharmacovigilance study of ICI-induced hematologic and lymphatic system toxicities to date. In this study, several key findings were noted, and the combination of ICIs with anti-VEGF therapy was considered.

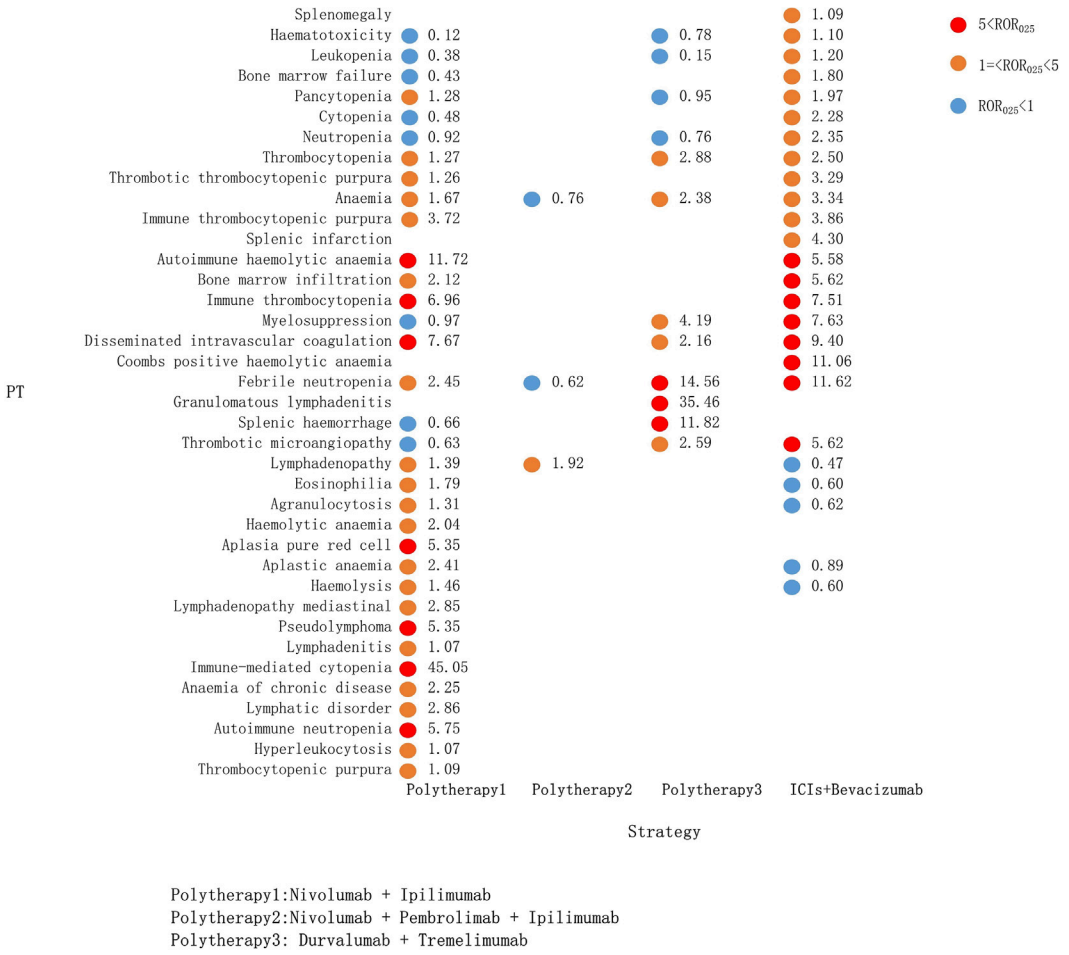


FIGURE 5
Hematological and lymphatic system toxicities for different ICI combination therapy strategies. PT, preferred term; IC, information component; IC_{025}, the lower end of the 95% confidence interval of IC; IC_{025}, greater than 0 was deemed a signal; ICI, immune checkpoint inhibitor.

The reporting frequency of ICI-related hematologic and lymphatic AEs was higher in female patients than in male patients. This result is consistent with that of a previous study by Ye et al. (2020). We attribute this to the fact that women tend to have stronger triggered and sustained immune responses against infections and have an increased propensity to develop autoimmune diseases compared to men (Grassadonia et al., 2018). Moreover, in the general population, there are differences in physiological factors, hormone levels, and hemoglobin levels between men and women, and women may be more susceptible to hematologic disorders (Rushton and Barth, 2010). However, the precise factors responsible for sex-related differences remain unclear and require further verification.

The reporting frequency of ICI-related hematologic and lymphatic AEs was also higher in younger patients than in older patients. A correlation between immune-related AEs (irAEs) and age has been hypothesized; however, different studies have yielded conflicting evidence. Conversely, immune senescence increases the risk of serious irAEs in older patients with cancer through an inflammatory process. In 2018, 23,586 FDA safety reports for ICI drugs were analyzed, and data were grouped according to age (<65, 67–75, and >75 years old). In patients with cancer, the incidence of irAEs was higher in those aged ≥65 years than in those aged <65 years for all single agents except atezolizumab (Elias et al., 2018). Another study reported that lower immunity in older patients may result in a lower effect of ICIs and may reduce the occurrence of immune-related AEs (Marur et al., 2018). Therefore, age should be considered in future studies, especially in studies of AEs related to the hematologic system.

The reported case fatality rate due to ICI-related hematologic and lymphatic AEs was higher owing to other drug-induced hematologic and lymphatic AEs, indicating that ICI-related hematologic and lymphatic AEs substantially affect patient mortality. Further analysis showed that the incidence of disseminated intravascular coagulation (DIC) was low, but the case fatality rate was high. DIC is a clinicopathological syndrome and is the most common pathway for the development of many disorders that cause a coagulation dysfunction. Multi-organ dysfunction syndrome is the leading cause of death in patients with DIC, and the death rate due to DIC is 31%–80% (Levi and Sivapalaratnam, 2018). Several cases of DIC associated with ICI therapy have been reported (Alberti et al., 2020; Maiorano et al., 2022). Although rare, in view of the high case fatality rate, it is important to pay close attention to the signs and symptoms of DIC during ICI therapy. In addition, unexpectedly, anemia had the second

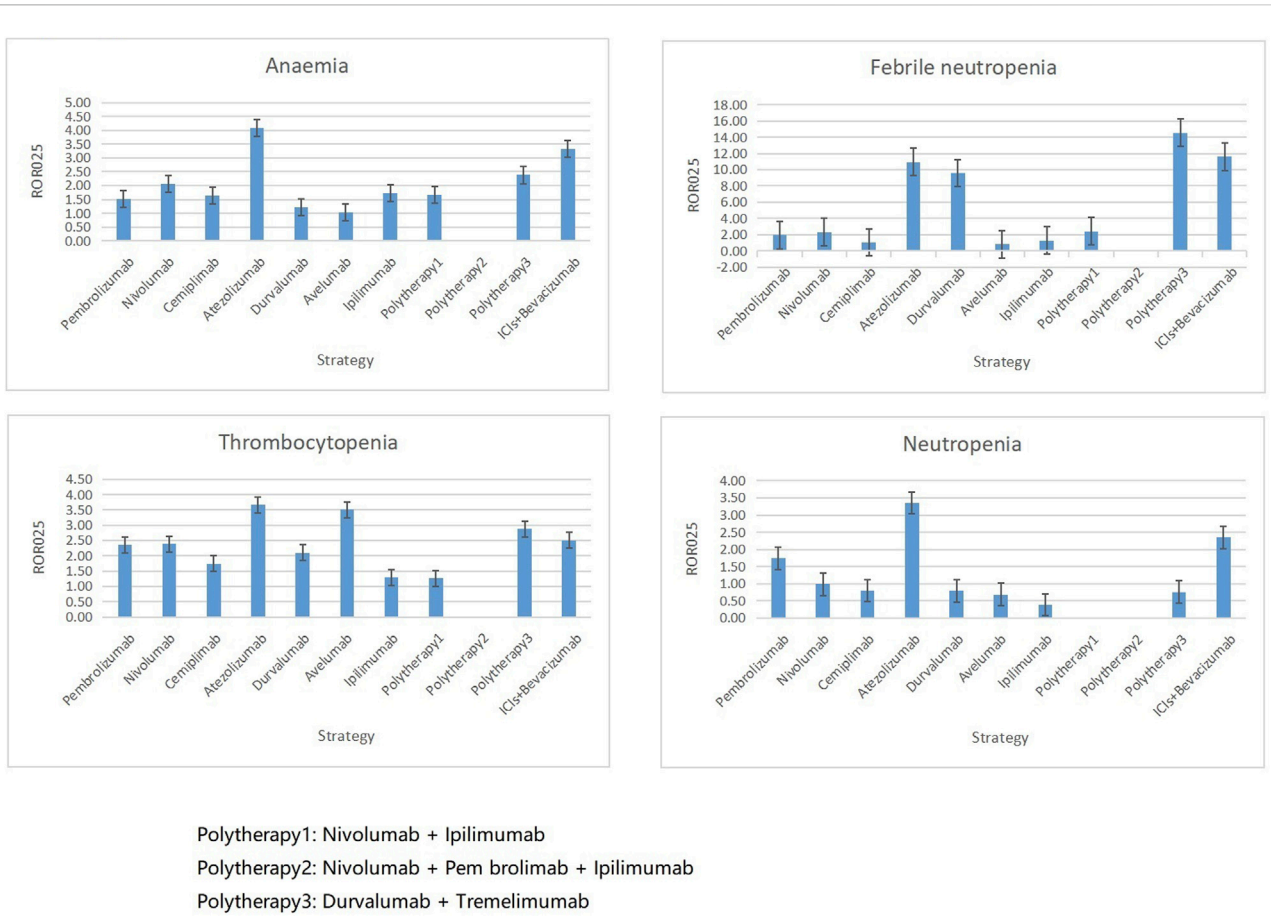


FIGURE 6
Associations between four top ranked PTs and different ICI strategies. PT, preferred term; IC, information component; ROR_{025}, greater than 0 was deemed a signal; ICI, immune checkpoint inhibitor.

highest fatality rate. In fact, the high fatality of anemia is associated with the fatal events that it causes. For example, it can lead to anemic heart disease (Goel et al., 2021), heart failure (Chopra and Anker, 2020; Loncar et al., 2021) and acute kidney failure (Locatelli et al., 2021). Furthermore, anemia exacerbates tumor hypoxia, which not only produces proteomic alterations that affect tumor dissemination and lead to malignant progression but also affects the efficacy of various antitumor therapies (Gilreath et al., 2014). Studies have shown that tumor-associated anemia increases the overall risk of death in cancer patients by 65%. Therefore, although anemia is a common complication, clinicians should not ignore it in their practice.

In the TTO analysis, the median TTO of ICI-related hematologic and lymphatic AEs was 28 days, and 77.44% of the events occurred within 3 months. Patients with myelosuppression had the shortest median TTO, and those with lymphadenopathy had the longest. Myelosuppression is the most common side effect of traditional chemotherapy drugs and can also be caused by newer antitumor drugs, such as targeted and immune drugs. Furthermore, more than 80% of chemotherapeutic drugs can lead to myelosuppression, which is mainly caused by central granulocytopenia and thrombocytopenia (Barreto et al., 2014; Fan et al., 2017; Weycker et al., 2019). The incidence of myelosuppression caused by targeted therapy and immunotherapy is significantly lower than that caused by chemotherapy. In addition, there are differences in the mechanisms of action. The onset of myelosuppression due to chemotherapeutic agents usually begins 5–7 days after the end of chemotherapy, peaks at 11–12 days, and then decreases (Wu et al., 2010). This is approximately the same as the time in our study using immunosuppressive agents to cause myelosuppression, suggesting that blood cell levels should be monitored timely, regardless of the treatment regimen used.

Lymphadenopathy is a common disease that can occur at any age and can be benign or malignant. Most cases of superficial lymph node enlargement are caused by non-specific acute/chronic inflammation, reactive hyperplasia, and specific infections. In general, tumors cause only a minority of lymphadenopathies (Maini and Nagalli, 2023). In cancer patients, lymph node enlargement may indicate the presence of local metastasis or disease progression. Meanwhile, pseudoprogression with ICIs may also show lymph node enlargement, which is mainly due to the activation of lymphocytes by ICIs, which causes a large number of lymphocytes to gather in the lymph node area to fight against tumor cells (Borcoman et al., 2019; Guan et al., 2022). Therefore, it is particularly important to clarify the nature of lymph node enlargement in oncological treatment, which is also the key for further selection of treatment options.

Our study assessed and compared the signal intensities of hematologic and lymphatic AEs associated with different ICI regimens. First, we compared ICI regimens with high-frequency AEs reported from the whole database. ICI treatment strategies are associated

with a high incidence of toxicity in multiple organ systems, which are not limited to hematologic and lymphatic systems but also include the endocrine (Zhai et al., 2019), respiratory (Cui et al., 2022), hepatic (Remash et al., 2021), and renal systems (Hu et al., 2021). In our study, hematologic and lymphatic AEs were reported more frequently in patients treated with anti-PD-1/PD-L1 monotherapy than in those treated with anti-CTLA-4 monotherapy, with atezolizumab showing the strongest risk signal. Notably, similar trends have been observed in neurological (Haugh et al., 2020) and renal AEs (Hu et al., 2021). A previous study (Michot et al., 2019) reviewed hematologic immune-related AEs with ICIs and reported that the frequency of hematologic AEs of all grades was higher with PD-1 (4.1%) and PD-L1 (4.7%) than with CTLA-4 (0.5%), consistent with our results. However, the precise mechanisms underlying these differences remain unclear and require further investigation.

Our study also provides information on the spectrum of hematologic and lymphatic AEs induced by different ICI regimens and found that the spectra differed according to the treatment regimen. Immune-mediated cytopenia showed the strongest disproportionate signal with pembrolizumab. In 2018, four cases of cytopenia following treatment with ICIs were reported in Texas (Sun et al., 2018). All four cases responded to conventional steroid therapy. Lymphadenopathy, eosinophilia, thrombocytopenia, anemia, pancytopenia, and febrile neutropenia were common to all three PD-1 drugs. Moreover, febrile neutropenia has been linked with pembrolizumab (Tozuka et al., 2018) and nivolumab (Ramchandren et al., 2019) immunotherapy; however, none of the disproportionality signals were statistically significant. In addition, we were unable to find any previous report of an association between cemiplimab and febrile neutropenia. Anemia is a common AE. A systematic review of AEs associated with PD-1 and PD-L1 inhibitor therapy in clinical trials showed that the incidence of anemia as a grade 3 or higher AE was 0.78% (Wang et al., 2019). Myelosuppression showed the most significant disproportionality in PD-L1 monotherapy; however, we were unable to find any published clinical case reports. In the analysis of ICI combination therapy, we identified four signals that have not been reported in the literature previously: hemolysis, pseudolymphoma, thrombotic microangiopathy, and splenic hemorrhage. These findings highlight the importance of signal detection in FAERS.

Studies have shown that VEGF may reprogramme the tumour immune microenvironment through multiple mechanisms. The combination of bevacizumab therapy with ICI therapy has good antitumor effects, especially in non-small-cell lung (Socinski et al., 2021), hepatocellular (Finn et al., 2020), and colorectal (Mettu et al., 2022) cancers. Our study showed that ICIs plus bevacizumab had the highest signal of disproportionality with respect to hematologic and lymphological AEs and was reported more frequently than for ICIs alone. Bai et al. (2021) found that PD-L1 checkpoint inhibitors combination bevacizumab therapy reduced the risk of pneumonia, respiratory failure and disease progression, while increasing the risk of fever, peripheral neuropathy, nephritis and bone marrow failure. The current data are limited to small prospective studies, and a real-world study with a large sample size is still lacking, especially studies of hematologic complications. The most recent pharmacovigilance analysis of ICIs in combination with bevacizumab showed that bevacizumab was an independent risk factor for interstitial lung disease, hypertension, and gastrointestinal bleeding (Gu et al., 2023), but there was no analysis of hematologic AEs. Thus, our results provide novel evidence for informing clinical practice.

This study had some limitations. First, FAERS is a spontaneous reporting system with multiple sources of data, thus suffering from inconsistent formats, duplication, and missing data. Second, the baseline data in the FAERS database are incomplete. Lastly, we did not consider combination chemotherapy regimens in this study, which may have introduced bias into the results. Nevertheless, our study is a systematic and an in-depth quantification of the potential risks to the hematologic and lymphatic systems for both all ICIs and their specific categories, in combination with bevacizumab. These results could provide valuable evidence for further research and clinical practice.

Overall, hematologic and lymphatic system toxicities were more frequently reported in ICI regimens than in other drug regimens, especially among patients treated with anti-PD-1/anti-PD-L1 agents. Compared with ICI monotherapy, ICI plus bevacizumab was associated with a higher incidence of hematologic and lymphatic AEs. Treatment with different ICI immunotherapies may result in unique and distinct profiles of hematologic and lymphatic AEs, depending on the agents used. Therefore, early recognition and management of ICI-related hematologic and lymphatic AEs are vital in clinical practice.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

NL designed and supervised the study; YF, YY, and XC downloaded the data; YL and CZ performed the statistical analysis; NL drafted and revised the manuscript. All authors participated in the interpretation of the results. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1213608/full#supplementary-material

References

Alberti, A., Mancin, M., Cortinovis, D., Bidoli, P., and Sala, L. (2020). Disseminated intravascular coagulation in advanced lung adenocarcinoma during first-line pembrolizumab. *Immunotherapy* 12, 629–633. doi:10.2217/imt-2020-0018

Ali, Z., Ismail, M., Khan, F., and Sajid, H. (2021). Association of H1-antihistamines with torsade de pointes: a pharmacovigilance study of the food and drug administration adverse event reporting system. *Expert Opin. Drug Saf.* 20, 101–107. doi:10.1080/14740338.2021.1846717

Ang, P. S., Chen, Z., Chan, C. L., and Tai, B. C. (2016). Data mining spontaneous adverse drug event reports for safety signals in Singapore - A comparison of three different disproportionality measures. *Expert Opin. Drug Saf.* 15, 583–590. doi:10.1517/14740338.2016.1167184

Bai, S., Tian, T., Pacheco, J. M., Tachihara, M., Hu, P., and Zhang, J. (2021). Immune-related adverse event profile of combination treatment of PD-(L)1 checkpoint inhibitors and bevacizumab in non-small cell lung cancer patients: data from the FDA adverse event reporting system. *Transl. Lung Cancer Res.* 10 (6), 2614–2624. doi:10.21037/tlcr-21-464

Barreto, J. N., McCullough, K. B., Ice, L. L., and Smith, J. A. (2014). Antineoplastic agents and the associated myelosuppressive effects: a review. *J. Pharm. Pract.* 27, 440–446. doi:10.1177/0897190014546108

Bejarano, L., Jordão, M. J. C., and Joyce, J. A. (2021). Therapeutic targeting of the tumor microenvironment. *Cancer Discov.* 11, 933–959. doi:10.1158/2159-8290.CD-20-1808

Borcoman, E., Kanjanapan, Y., Champiat, S., Kato, S., Servois, V., Kurzrock, R., et al. (2019). Novel patterns of response under immunotherapy. *Ann. Oncol.* 30, 385–396. doi:10.1093/annonc/mdz003

Chambers, B. S., Ward, D., Webster, R., Tunnard, V., and Hill, Q. A. (2022). Atezolizumab-induced autoimmune haemolytic anaemia caused by drug-independent antibodies. *Eur. J. Cancer.* 162, 158–160. doi:10.1016/j.ejca.2021.11.031

Chopra, V. K., and Anker, S. D. (2020). Anaemia, iron deficiency and heart failure in 2020: facts and numbers. *Esc. Heart Fail* 7, 2007–2011. doi:10.1002/ehf2.12797

Cui, C., Deng, L., Wang, W., Ren, X., Wang, Y., and Cui, W. (2022). Respiratory system toxicity induced by immune checkpoint inhibitors: a real-world study based on the FDA adverse event reporting system database. *Front. Oncol.* 12, 941079. doi:10.3389/fonc.2022.941079

Delanoy, N., Michot, J. M., Comont, T., Kramkimel, N., Lazarovici, J., Dupont, R., et al. (2019). Haematological immune-related adverse events induced by anti-PD-1 or anti-PD-L1 immunotherapy: a descriptive observational study. *Lancet Haematol.* 6, e48–e57. doi:10.1016/S2352-3026(18)30175-3

Elias, R., Giobbie-Hurder, A., McCleary, N. J., Ott, P., Hodi, F. S., and Rahma, O. (2018). Efficacy of PD-1 & PD-L1 inhibitors in older adults: a meta-analysis. *J. Immunother. Cancer* 6, 26. doi:10.1186/s40425-018-0336-8

Fan, K., Dai, L., Wu, Z., Yang, G., and Yang, M. (2017). Research progress of myelosuppression due to radiotherapy. *Chin. J. Traditional Chin. Med.* 32 (1), 5.

Ferrara, N., and Adamis, A. P. (2016). Ten years of anti-vascular endothelial growth factor therapy. *Nat. Rev. Drug Discov.* 15, 385–403. doi:10.1038/nrd.2015.17

Finn, R. S., Qin, S., Ikeda, M., Galle, P. R., Ducreux, M., Kim, T. Y., et al. (2020). Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N. Engl. J. Med.* 382, 1894–1905. doi:10.1056/NEJMoa1915745

Gatti, M., Antonazzo, I. C., Diemberger, I., De Ponti, F., and Raschi, E. (2021). Adverse events with sacubitril/valsartan in the real world: emerging signals to target preventive strategies from the FDA adverse event reporting system. *Eur. J. Prev. Cardiol.* 28, 983–989. doi:10.1177/2047487320915663

Ghanem, P., Marrone, K., Shanbhag, S., Brahmer, J. R., and Naik, R. P. (2022). Current challenges of hematologic complications due to immune checkpoint blockade: a comprehensive review. *Ann. Hematol.* 101, 1–10. doi:10.1007/s00277-021-04690-x

Gilreath, J. A., Stenehjem, D. D., and Rodgers, G. M. (2014). Diagnosis and treatment of cancer-related anemia. *Am. J. Hematol.* 89, 203–212. doi:10.1002/ajh.23628

Goel, H., Hirsch, J. R., Deswal, A., and Hassan, S. A. (2021). Anemia in cardiovascular disease: marker of disease severity or disease-modifying therapeutic target? *Curr. Atheroscler. Rep.* 23, 61. doi:10.1007/s11883-021-00960-1

Goel, H. L., and Mercurio, A. M. (2013). VEGF targets the tumour cell. *Nat. Rev. Cancer.* 13, 871–882. doi:10.1038/nrc3627

Grassadonia, A., Sperduti, I., Vici, P., Iezzi, L., Brocco, D., Gamucci, T., et al. (2018). Effect of gender on the outcome of patients receiving immune checkpoint inhibitors for advanced cancer: a systematic review and meta-analysis of Phase III randomized clinical trials. *J. Clin. Med.* 7, 542. doi:10.3390/jcm7120542

Gu, T., Jiang, A., Zhou, C., Lin, A., Cheng, Q., Liu, Z., et al. (2023). Adverse reactions associated with immune checkpoint inhibitors and bevacizumab: a pharmacovigilance analysis. *Int. J. Cancer* 80, 92–155. doi:10.1002/ijc.34332

Guan, Y., Feng, D., Yin, B., Li, K., and Wang, J. (2022). Immune-related dissociated response as a specific atypical response pattern in solid tumors with immune checkpoint blockade. *Ther. Adv. Med. Oncol.* 14, 17588359221096877. doi:10.1177/17588359221096877

Hammers, H. J., Plimack, E. R., Infante, J. R., Rini, B. I., McDermott, D. F., Lewis, L. D., et al. (2017). Safety and efficacy of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma: the CheckMate 016 study. *J. Clin. Oncol.* 35, 3851–3858. doi:10.1200/JCO.2016.72.1985

Haugh, A. M., Probasco, J. C., and Johnson, D. B. (2020). Neurologic complications of immune checkpoint inhibitors. *Expert Opin. Drug Saf.* 19, 479–488. doi:10.1080/14740338.2020.1738382

Hellmann, M. D., Paz-Ares, L., Bernabe Caro, R., Zurawski, B., Kim, S. W., Carcereny Costa, E., et al. (2019). Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N. Engl. J. Med.* 381, 2020–2031. doi:10.1056/NEJMoa1910231

Hu, F., Zhai, Y., Yuan, L., Liang, J., Xu, J., Guo, X., et al. (2021). Renal toxicities in immune checkpoint inhibitors with or without chemotherapy: an observational, retrospective, pharmacovigilance study leveraging US FARES database. *Cancer Med.* 10, 8754–8762. doi:10.1002/cam4.4343

Kennedy, L. B., and Salama, A. K. S. (2020). A review of cancer immunotherapy toxicity. *CA Cancer J. Clin.* 70, 86–104. doi:10.3322/caac.21596

Kroll, M. H., Rojas-Hernandez, C., and Yee, C. (2022). Hematologic complications of immune checkpoint inhibitors. *Blood* 139, 3594–3604. doi:10.1182/blood.2020009016

Kumar, J., Bhargava, M., and Aggarwal, S. (2012). Bevacizumab-induced reversible thrombocytopenia in a patient with adenocarcinoma of colon: rare adverse effect of bevacizumab. *Case Rep. Oncol. Med.* 2012, 695430. doi:10.1155/2012/695430

Levi, M., and Sivapalaratnam, S. (2018). Disseminated intravascular coagulation: an update on pathogenesis and diagnosis. *Expert Rev. Hematol.* 11, 663–672. doi:10.1080/17474086.2018.1500173

Locatelli, F., Del Vecchio, L., Minutolo, R., and De Nicola, L. (2021). Anemia: a connection between heart failure and kidney failure. *Cardiol. Clin.* 39, 319–333. doi:10.1016/j.ccl.2021.04.003

Loncar, G., Obradovic, D., Thiele, H., von Haehling, S., and Lainscak, M. (2021). Iron deficiency in heart failure. *Esc. Heart Fail* 8, 2368–2379. doi:10.1002/ehf2.13265

Maini, R., and Nagalli, S. (2023). "Lymphadenopathy," in *StatPearls* (Treasure Island, FL: StatPearls Publishing).

Maiorano, S., Gulden-Sala, W., Gerber, B., and Ghilardi, G. (2022). Anti-PD-L1 monoclonal antibody for the management of chronic disseminated intravascular coagulation secondary to a urothelial carcinoma: a case report. *J. Med. Case Rep.* 16, 113. doi:10.1186/s13256-022-03338-2

Marur, S., Singh, H., Mishra-Kalyani, P., Larkins, E., Keegan, P., Sridhara, R., et al. (2018). FDA analyses of survival in older adults with metastatic non-small cell lung cancer in controlled trials of PD-1/PD-L1 blocking antibodies. *Semin. Oncol.* 45, 220–225. doi:10.1053/j.seminoncol.2018.08.007

Mettu, N. B., Ou, F. S., Zemla, T. J., Halfdanarson, T. R., Lenz, H. J., Breakstone, R. A., et al. (2022). Assessment of capecitabine and bevacizumab with or without atezolizumab for the treatment of refractory metastatic colorectal cancer: a randomized clinical trial. *JAMA Netw. Open* 5, e2149040. doi:10.1001/jamanetworkopen.2021.49040

Michot, J. M., Lazarovici, J., Tieu, A., Champiat, S., Voisin, A. L., Ebbo, M., et al. (2019). Haematological immune-related adverse events with immune checkpoint inhibitors, how to manage? *Eur. J. Cancer.* 122, 72–90. doi:10.1016/j.ejca.2019.07.014

Min, J., Osborne, V., Kowalski, A., and Prosperi, M. (2018). Reported adverse events with painkillers: data mining of the US Food and Drug Administration adverse events reporting system. *Drug Saf.* 41, 313–320. doi:10.1007/s40264-017-0611-5

Petrelli, F., Ardito, R., Borgonovo, K., Lonati, V., Cabiddu, M., Ghilardi, M., et al. (2018). Haematological toxicities with immunotherapy in patients with cancer: a systematic review and meta-analysis. *Eur. J. Cancer.* 103, 7–16. doi:10.1016/j.ejca.2018.07.129

Ramchandren, R., Domingo-Domènech, E., Rueda, A., Trněný, M., Feldman, T. A., Lee, H. J., et al. (2019). Nivolumab for newly diagnosed advanced-stage classic Hodgkin lymphoma: safety and efficacy in the Phase II CheckMate 205 study. *J. Clin. Oncol.* 37, 1997–2007. doi:10.1200/JCO.19.00315

Remash, D., Prince, D. S., McKenzie, C., Strasser, S. I., Kao, S., and Liu, K. (2021). Immune checkpoint inhibitor-related hepatotoxicity: a review. *World J. Gastroenterol.* 27, 5376–5391. doi:10.3748/wjg.v27.i32.5376

Ribas, A., and Wolchok, J. D. (2018). Cancer immunotherapy using checkpoint blockade. *Science* 359, 1350–1355. doi:10.1126/science.aar4060

Rushton, D. H., and Barth, J. H. (2010). What is the evidence for gender differences in ferritin and haemoglobin? *Crit. Rev. Oncol. Hematol.* 73, 1–9. doi:10.1016/j.critrevonc.2009.03.010

Saran, F., Chinot, O. L., Henriksson, R., Mason, W., Wick, W., Cloughesy, T., et al. (2016). Bevacizumab, temozolomide, and radiotherapy for newly diagnosed glioblastoma: comprehensive safety results during and after first-line therapy. *Neuro. Oncol.* 18, 991–1001. doi:10.1093/neuonc/nov300

Socinski, M. A., Nishio, M., Jotte, R. M., Cappuzzo, F., Orlandi, F., Stroyakovskiy, D., et al. (2021). IMpower150 final overall survival analyses for atezolizumab plus

bevacizumab and chemotherapy in first-line metastatic nonsquamous NSCLC. *J. Thorac. Oncol.* 16, 1909–1924. doi:10.1016/j.jtho.2021.07.009

Sun, Y., Lee, S. K., Oo, T. H., and Rojas-Hernandez, C. M. (2018). Management of immune-mediated cytopenias in the era of cancer immunotherapy: a report of 4 cases. *J. Immunother.* 41, 32–34. doi:10.1097/CJI.0000000000000194

Tang, J., Hubbard-Lucey, V. M., Pearce, L., O'Donnell-Tormey, J., and Shalabi, A. (2018). The global landscape of cancer cell therapy. *Nat. Rev. Drug Discov.* 17, 465–466. doi:10.1038/nrd.2018.74

Tozuka, T., Sugano, T., Noro, R., Takano, N., Hisakane, K., Takahashi, S., et al. (2018). Pembrolizumab-induced agranulocytosis in a pulmonary pleomorphic carcinoma patient who developed interstitial lung disease and ocular myasthenia gravis. *Oxf. Med. Case Rep.* 2018, omy094. doi:10.1093/omcr/omy094

Viallard, C., and Larrivée, B. (2017). Tumor angiogenesis and vascular normalization: alternative therapeutic targets. *Angiogenesis* 20, 409–426. doi:10.1007/s10456-017-9562-9

Wang, Y., Zhou, S., Yang, F., Qi, X., Wang, X., Guan, X., et al. (2019). Treatment-related adverse events of PD-1 and PD-L1 inhibitors in clinical trials: a systematic review and meta-analysis. *JAMA Oncol.* 5, 1008–1019. doi:10.1001/jamaoncol.2019.0393

Weycker, D., Hatfield, M., Grossman, A., Hanau, A., Lonshteyn, A., Sharma, A., et al. (2019). Risk and consequences of chemotherapy-induced thrombocytopenia in US clinical practice. *BMC Cancer* 19, 151. doi:10.1186/s12885-019-5354-5

Wolchok, J. D., Chiarion-Sileni, V., Gonzalez, R., Grob, J. J., Rutkowski, P., Lao, C. D., et al. (2022). Long-term outcomes with nivolumab plus ipilimumab or nivolumab alone versus ipilimumab in patients with advanced melanoma. *J. Clin. Oncol.* 40, 127–137. doi:10.1200/JCO.21.02229

Wright, Z., and Brown, A. (2017). High-grade neutropenia in a patient successfully treated with nivolumab for refractory primary mediastinal B-cell lymphoma. *Blood Adv.* 1, 1306–1308. doi:10.1182/bloodadvances.2017008607

Wu, Y., Cui, X., Yuan, Y., and Zhao, Z. (2010). Prevention and treatment of myelosuppression caused by antitumour drugs. *Drug Eval.* 14, 7. doi:10.3969/j.issn.1672-2809.2010.14.007

Xie, W., Hu, N., and Cao, L. (2021). Immune thrombocytopenia induced by immune checkpoint inhibitrs in lung cancer: case report and literature review. *Front. Immunol.* 12, 790051. doi:10.3389/fimmu.2021.790051

Ye, X., Hu, F., Zhai, Y., Qin, Y., Xu, J., Guo, X., et al. (2020). Hematological toxicities in immune checkpoint inhibitors: a pharmacovigilance study from 2014 to 2019. *Hematol. Oncol.* 38, 565–575. doi:10.1002/hon.2743

Zhai, Y., Ye, X., Hu, F., Xu, J., Guo, X., Zhuang, Y., et al. (2019). Endocrine toxicity of immune checkpoint inhibitors: a real-world study leveraging US Food and Drug Administration adverse events reporting system. *J. Immunother. Cancer.* 7, 286. doi:10.1186/s40425-019-0754-2

frontiers | Frontiers in Immunology

TYPE Case Report
PUBLISHED 11 January 2024
DOI 10.3389/fimmu.2023.1291564

OPEN ACCESS

EDITED BY
Aysin Tulunay Virlan,
University of Glasgow, United Kingdom

REVIEWED BY
Manish Barvaliya,
Indian Council of Medical Research, India
Sebastian Yu,
Kaohsiung Medical University, Taiwan

*CORRESPONDENCE
Zhuangli Tang
tangzhuangli@zju.edu.cn

RECEIVED 09 September 2023
ACCEPTED 26 December 2023
PUBLISHED 11 January 2024

CITATION
Wang Q, Cao H, Zhang X, Wu H and Tang Z (2024) Case report: Apalutamide-induced severe lethal cutaneous adverse effects in China.
Front. Immunol. 14:1291564.
doi: 10.3389/fimmu.2023.1291564

Case report: Apalutamide-induced severe lethal cutaneous adverse effects in China

Qi Wang[1,2], Huali Cao[1], Xuetong Zhang[1], Huifeng Wu[3] and Zhuangli Tang[1*]

[1]Department of Dermatology, Second Affiliated Hospital of Zhejiang University, Hangzhou, China, [2]Department of Dermatology, Changxing People's Hospital, Huzhou, China, [3]Department of Urology, Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China

Introduction: Apalutamide is a novel agent for castration-resistant prostate cancer while skin rashes are the most common untoward reactions. Up to now, most of the reported dermatologic adverse events (dAEs) allocated to mild and moderate with a fair prognosis. Herein, we report a case series of severe dAEs in China caused by apalutamide.

Case presentation: The four patients all developed severe and lethal drug eruptions including Stevens-Johnson syndrome and toxic epidermal necrolysis with a mean incubation period of 40 days. On the basis of the medical condition, all the patients were suggested to withdraw apalutamide and three of them recovered. Of note, attempts of rechallenges of apalutamide may be fatal.

Discussion: The incidence of dAEs in previously conducted clinical trials exceeded 20%, with maculopapular rashes being the most common feature. However, the incidence and severity varied in different geographic regions and ethnicities. Inadequate attention was paid to severe cutaneous adverse reactions. Long latency may easily lead to the misdiagnosis of dAEs, and immediate withdrawal of apalutamide is the cornerstone of therapies.

Conclusion: Special and adequate attention should be paid to apalutamide-attributed severe cutaneous adverse effects. Besides, the prognosis of severe drug eruptions may be disappointing, and in-time withdrawal is vital.

KEYWORDS

apalutamide, severe dermatologic adverse events, long incubation period, prognosis, withdrawal

Introduction

Apalutamide, an androgen receptor antagonist, has recently been approved for the treatment of metastatic, castration-sensitive and non-metastatic, castration-resistant prostate cancer (PC) (1). On the basis of previous literature, dermatologic adverse events (dAEs) remain the most reported side effects of apalutamide. Up to now, 15 case reports and 3 retrospective analyses of apalutamide-related drug eruptions have been published, with a divergent geographic distribution indicating the Japanese most vulnerable to dAEs of apalutamide (2–15). However, most of the dAEs remain mild and moderate with a fair prognosis (16, 17). Globally, only five patients have been recorded as having experienced fatal outcomes due to a severe drug rash, i.e., Stevens-Johnson syndrome (SJS) and toxic epidermal syndrome (TEN), the most life-threatening conditions, which are relatively rare with the estimated incidence fluctuating around 0.94 to 5.76 per million persons per year (18–20), induced by apalutamide—four in Japan and one solitary case in China. Reports of severe dAEs or fatalities associated with apalutamide in China remained extremely rare. In this report, we documented four cases of severe dAEs including SJS and TEN and depicted the overall prognosis.

Case description

Case 1

One 77-year-old male patient with PC developed crimson maculopapular rashes on his trunk and limbs with buccal mucosal ulcers and ran a low-grade fever approximately 40 days after the initiation of apalutamide (240mg/day). His previous medical history included diabetes, chronic hepatitis B virus infection, which were treated with sitagliptin phosphate/metformin hydrochloride, tenofovir disoproxil fumarate and traditional Chinese medicine. These drugs were prescribed for more than 3 years without changes. The Naranjo adverse drug reaction probability scale score for apalutamide was 6 whereas that for other medications was 0, which indicated that apalutamide was the most probable drug to be blamed. Although the patient immediately withdrew apalutamide, the diffuse erythema continued spreading. Physical examination revealed numerous erythematosus scattering on the trunk; besides, hemorrhagic crusts and erosions were noticed on bilateral buccal mucosa and lips (Body Surface Area (BSA) about 26%) (Figures 1A, B). Biopsy was performed indicating interface dermatitis with whole-layer epidermal necrosis and dermal-epidermal fissure along with superficial perivascular infiltration of lymphocytes (Figure 2A). A diagnosis of SJS was made, and we initiated intravenous methylprednisolone (60mg/day, tapered to 30mg/day after improvement of conditions) and human serum albumin, TNF-α inhibitor (Adalimumab, 80mg the first dose followed by 40mg one week later), as well as topical ointments and other symptomatic treatments, the skin lesions thereafter improved rapidly (Figure 3A).

Case 2

One 69-year-old male patient who denied any allergies or previous medical history, developed florid papules and plaque on the dorsum of both feet for three months. The cutaneous lesions gradually increased, spreading to the whole body with intolerable pruritus (BSA, 34%) (Figure 1C). He started apalutamide (240mg/day) four months ago and he denied any other suspicious medication history even if the resident physician asked repeatedly. The Naranjo scale score for apalutamide was 6 which indicated that apalutamide was the probable cause. Of note, the rash worsened when he underwent COVID-19 infection. Histopathological findings were consistent with the diagnosis of drug eruptions including epidermal necrosis and perivascular infiltrated lymphocytes and eosinophils in the upper dermis (Figure 2B). Once he was hospitalized, a diagnosis of SJS was made and apalutamide was quit, thereafter, intravenous methylprednisolone (40mg/day) and oral thalidomide (25mg/day), as well as topical ointments were prescribed subsequently. Within two weeks, the skin lesions were better off and no relapse was heard (Figure 3B).

Case 3

One 72-year-old male patient with PC developed maculopapular erythema on his whole-body excluding head, neck and mucosa for around 45 days after the start of oral apalutamide (240 mg/day). He refused to discontinue apalutamide, hence erythema progressed by degrees and pruritus intensified. Scratches and lichenification were obvious (BAS about 66%) (Figure 1D). He had no comorbidities and negated any other drug history or anaphylactic conditions. The Naranjo scale score for apalutamide was 6 which indicated that apalutamide was the probable cause of the drug eruption. SJS was diagnosed and systemic methylprednisolone (40mg/day) were given and the skin rashes were better off. However, the patient requests discharge hence systemic corticosteroids were altered to oral tablets. On regular visits, oral medrol was tapered gradually and luckily, he reported steady improvement (Figure 3C).

Case 4

One 74-year-old male patient started apalutamide (240<no></no> mg/day) after the diagnosis of castration-resistant prostate cancer. His previous medical history included hypertension, diabetes, chronic kidney disease stage 5, renal anemia, chronic hepatitis B virus infection, hepatic insufficiency. No other newly-added drugs other than apalutamide were prescribed 3 months prior to such the condition. Shortly after the initiation of the drug (some 2 days, the patient cannot recall exactly), he experienced nausea and late-onset erythema on his trunk. He denied any adjustments of other daily drugs. Apalutamide was immediately discontinued and regular systemic treatments were prescribed subsequently and the rashes were on the mend. Unfortunately, owing to the rapid improvement of

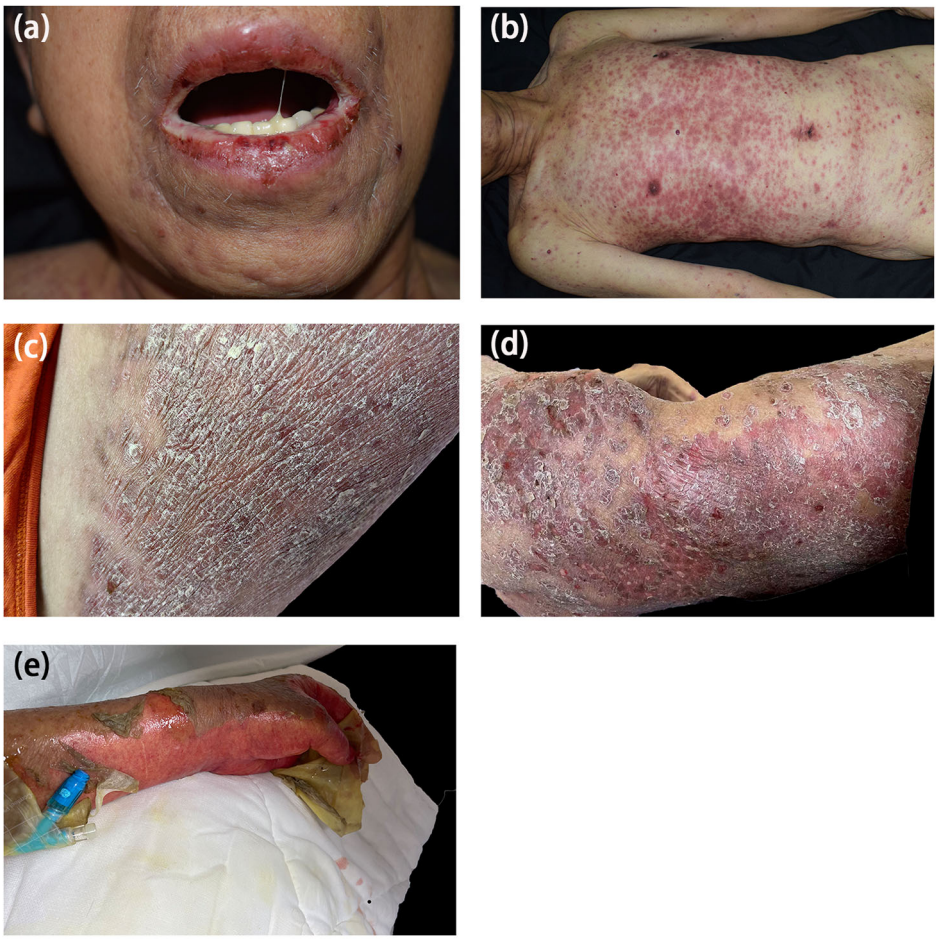


FIGURE 1
Clinical features. Case 1 **(A, B)** Buccal mucosa ulcers **(A)** and skin eruption on the trunk and limbs **(B)**. Case 2 **(C)** Skin eruptions on the limbs. Case 3 **(D)** Skin eruptions on the trunk. Case 4 **(E)** Multiple areas of denuded skin on the limbs were noted.

the lesions, the urologist advised him to recommence the apalutamide treatment for his prostate cancer. Thereafter his cutaneous lesions reoccurred and quickly developed to TEN with over 60% BSA involved. Moreover, necrosis of buccal and urethral mucosa was significant with exudation (Figure 1E). The Naranjo scale score for apalutamide was 9, indicating that apalutamide was the culprit. After admission, a diagnosis of TEN was made and the patient's severity-of-illness score for TEN (SCORTEN) was 5, which indicated a quite poor prognosis. Though in-time and powerful medical care including large dose methylprednisolone (80mg/day) and 80mg adalimumab once was given, he passed away due to multi-organ failure within 3 days (Figure 3D).

Discussion

According to global SPARTAN and TITAN studies, the incidence of skin rashes in the apalutamide group was as high as 23.8% and 27.1%, respectively (1). Although cutaneous lesions being considered a common adverse event in clinical trial studies, only a few reports describe the real-world features of apalutamide-induced drug eruptions. Herein, we reported a series of severe dAEs from China to emphasize the awareness of severe or even lethal prognosis when initiating apalutamide in clinical practices. Serious dAEs comprise of SJS, TEN, and drug rash with eosinophilia and systemic symptoms (DRESS). Although apalutamide has been reported to contribute to DRESS (21), the documented four patients did not have elevated eosinophils, fever or visceral damage such as abarrent liver enzymes.

Apalutamide is a second-generation, selective inhibitor of the androgen receptor (AR) developed by Aragon Pharmaceuticals, Inc. It employs a tri-modal mechanism of action: binds directly to the AR ligand-binding domain (AR-LBD) to prevent AR activation, inhibiting the translocation of AR into the nucleus, and obstructing the transcription of target genes by preventing AR and DNA incorporation (Figure 4). This, in turn, induces tumor cell death (22). In contrast to apalutamide, other nonsteroidal androgen receptor inhibitors, such as enzalutamide, are not commonly associated with a high incidence of skin rash. Apalutamide's chemical structure, when compared to enzalutamide, features a more reactive 2-cyanopyridine component that could more readily

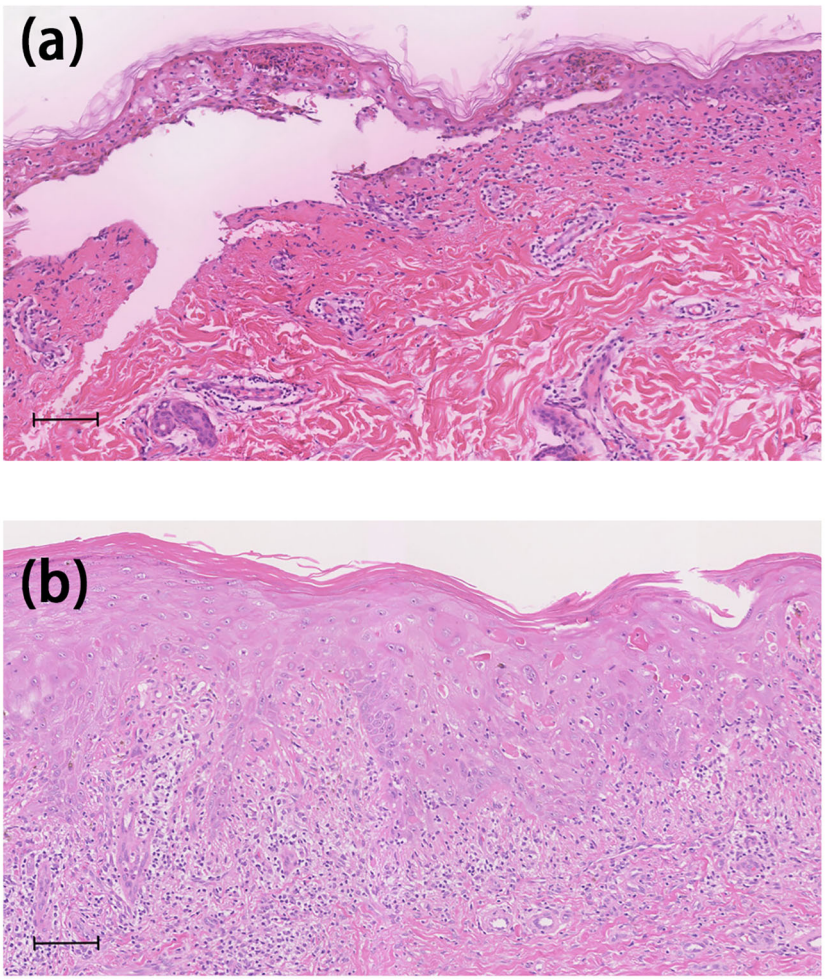


FIGURE 2
Histological features. Case 1 **(A)** Histological examination of the biopsy revealed interface dermatitis with whole-layer epidermal necrosis and dermal–epidermal separation and perivascular infiltration of lymphocytes in the upper dermis. Case 2 **(B)** Histopathological examination showed severe interface dermatitis with confluent apoptotic keratinocytes and perivascular lymphocyte and eosinophil infiltration was observed in the upper dermis. The scale bar indicates 100mm.

activate the immune system, leading to increased lymph node cellularity, T-cell, and B-cell counts. Data from Changhua Ji's team supports the hypothesis that the 2-cyanopyridine moiety in apalutamide may react with cysteine in proteins, forming haptens that could trigger an immune response. This immune response, as indicated by apalutamide's activity in the MDAM assay, may contribute to the increased potential for skin rash in patients compared to those on a placebo, as observed in the SPARTAN and TITAN clinical trials (23). Their hypothesis is consistent with Yoichiro Tohi et al., who suggested that the apalutamide-associated skin rash might not be attributed to allergic reactions but rather to a structure-specific, off-target pharmacological reaction (12). Additionally, Michie Katsut et al. found that low body weight is a risk factor for apalutamide-related cutaneous adverse events (24).

Compared to many other drugs, the incubation period of apalutamide is relatively longer with a reported median time of 82 days according to the SPARTAN trial and 80.5 days according to the TITAN trial (1). In this case series, the median time interval was around 40 days while the longest incubation period around 150 days. Long life-span and atypical cutaneous features may contribute to such phenomena. It is postulated that apalutamide has a propensity to bind to serum proteins, allowing it to circulate in the body. Clinical trial data have indicated detectable drug molecules in plasma even after a single dose of 240mg for up to 71 days (8). Therefore, with the expanded approval of apalutamide in China, dermatologists need to vigilantly assess cutaneous symptoms in patients undergoing apalutamide treatment, especially within the first 6 months of initial administration. Furthermore, the immediate discontinuation of apalutamide is crucial in managing drug-related adverse events (dAEs). Rechallenge, even at a lower dose, may be unsafe and potentially life-threatening. Similar to the patient mentioned in 'Case 4,' individuals who may be allergic to apalutamide should promptly consult with their urologist to establish a further medication plan based on a mutual understanding of such conditions.

10.3389/fimmu.2023.1291564

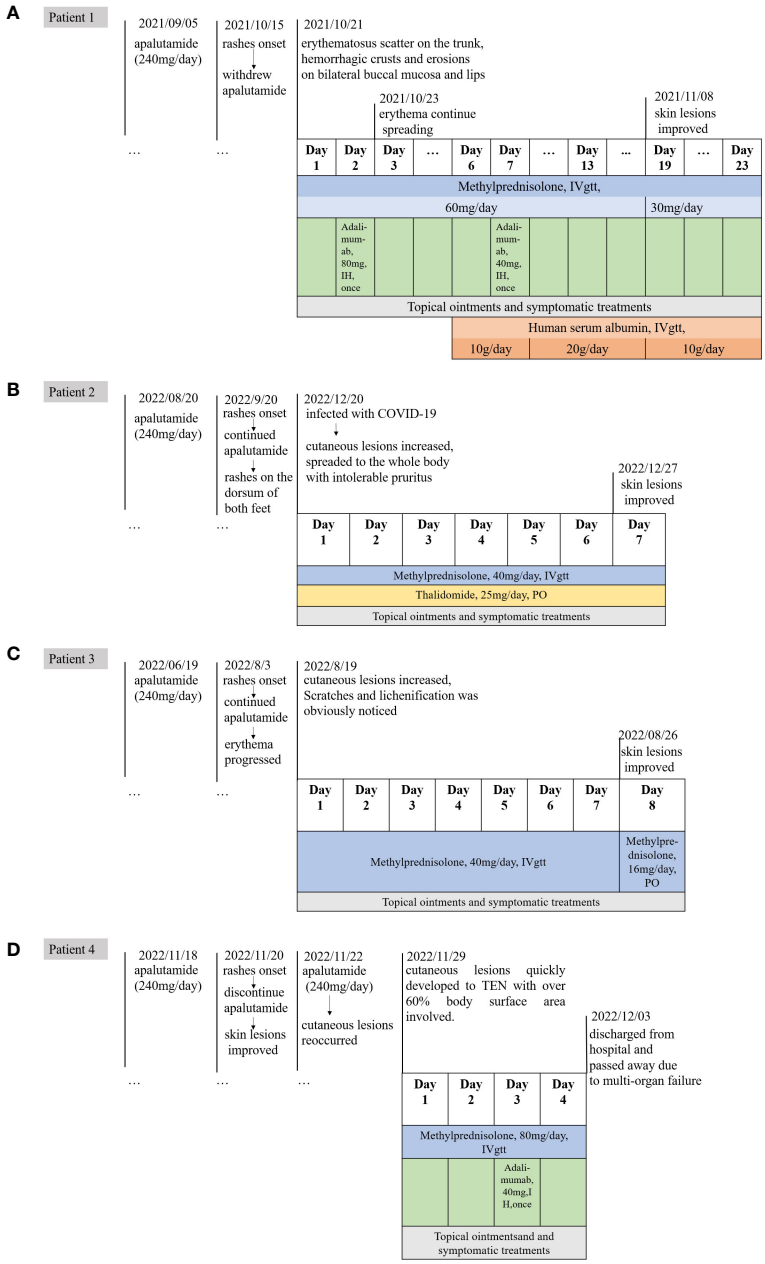


FIGURE 3
The timeline of medication history and treatments of Case1-4. **(A)** The timeline of case 1. **(B)** The timeline of case 2. **(C)** The timeline of case 3. **(D)** The timeline of case 4.

Systemic corticosteroids, immunodepressant, intravenous immunoglobulin and plasmapheresis are of great benefit to dAEs. In the past few decades, plasmapheresis also performed in patients of dAEs, however, studies have pointed out that the use of plasma exchange to treat TEN does not improve the mortality, duration of the disease, or skin healing time (25). In patients with TEN, there is a notably high expression of TNF-α in both plasma and cutaneous blister fluids. Additionally, TNF-α is overexpressed in keratinocytes, potentially inducing keratinocyte apoptosis through the caspase cascade and Fas/Fas ligand interaction (25). These findings demonstrate the initiation of TNF-α inhibitors could shorten the re-epithelization time and thus promote skin healing significantly (14). For instance, studies by Hunger et al. and Wang et al. have demonstrated that TEN patients treated with TNF-α inhibitors experienced faster recovery compared to those treated with immunoglobulins or corticosteroids (25). Thus TNF-α inhibitor may be a promising treatment option in the management of apalutamide associated TEN.

Conclusion

While the overall prognosis of severe drug-related adverse events (dAEs) may be discouraging, prompt withdrawal of the

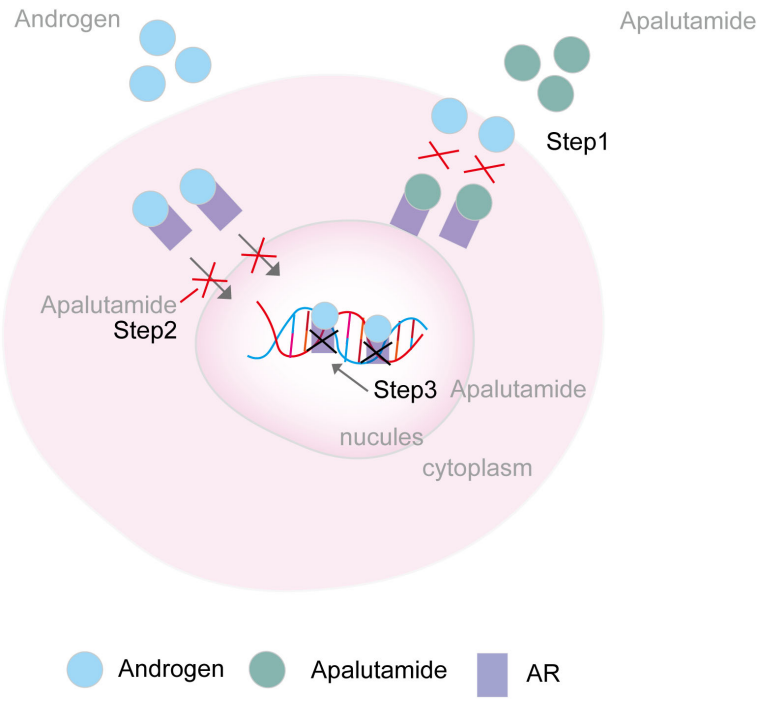


FIGURE 4
Mechanism of AR inhibitors. Step 1. Apalutamide binds directly to the AR ligand-binding domain and prevents AR activation; Step 2. Apalutamide inhibits the translocation of AR in the nucleus. Step 3. Apalutamide inhibits the transcription of target genes via preventing the AR and DNA incorporation AR, androgen receptor.

medication without rechallenge can make the difference in saving a life.

Special and adequate attention should be paid to apalutamide-attributed severe cutaneous adverse effects. The early and accurate diagnosis of apalutamide-related drug eruption is vital for the ultimate prognosis of the patient, and maintaining close contact with dermatologists is indispensable. Though overall prognosis of severe dAEs may be disappointing, prompt withdrawal of the medication and without rechallege may be life-saving.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Human Ethics Review Committee of the Second Affiliated Hospital to Zhejiang University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

QW: Writing – original draft, Writing – review & editing. HC: Writing – original draft. XZ: Writing – original draft. HW: Writing – original draft. ZT: Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This research was supported by Zhejiang Provincial Natural Science Foundation of China under Grant No.LY19H110001 and the Medical Health Science and Technology Project of Zhejiang Provincial Health Commission under NO.2021RC005.

Acknowledgments

We thank the patients for giving us permission to publish this case series.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Uemura H, Koroki Y, Iwaki Y, Imanaka K, Kambara T, Lopez-Gitlitz A, et al. Skin rash following Administration of Apalutamide in Japanese patients with Advanced Prostate Cancer: an integrated analysis of the phase 3 SPARTAN and TITAN studies and a phase 1 open-label study. *BMC Urol* (2020) 20(1):139. doi: 10.1186/s12894-020-00689-0

2. Miyagawa F, Akioka N, Yoshida N, Ogawa K, Asada H. Psoriatic skin lesions after apalutamide treatment. *Acta dermato-venereologica* (2022) 102:adv00659. doi: 10.2340/actadv.v102.858

3. Oda H, Tanaka F, Hayakawa A, Tanaka H, Takagi M, Yamagiwa A. A case of apalutamide–induced toxic epidermal necrolysis that was treated with plasma exchange. *Nihon Toseki Igakkai Zasshi* (2022) 55(1):29–33. doi: 10.4009/jsdt.55.29

4. Ducharme O, Sanchez-Pena P, Pham-Ledard A, Beylot-Barry M, Milpied B. The first case of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome caused by apalutamide, a novel oral androgen receptor antagonist. *Contact Dermatitis* (2022) 86(4):313–5. doi: 10.1111/cod.14024

5. Honda T, Tohi Y, Kaku Y, Kimura N, Kato T, Haba R, et al. Acute generalized exanthematous pustulosis during apalutamide treatment in a patient with prostate cancer. *IJU Case Rep* (2022) 5(6):497–500. doi: 10.1002/iju5.12525

6. Baah N, Skandamis G. Novel case of eruptive keratoacanthomas associated with apalutamide treatment for prostate cancer. *SKIN J Cutaneous Med* (2022) 6:324–7. doi: 10.25251/skin.6.4.10

7. Huang Y, Luo J, Luo J, Leng Y, Han Q, Wen J, et al. *Toxic epidermal necrolysis associated with apalutamide: a case report and brief review of the literatures*. Authorea Preprints (2022). doi: 10.22541/au.165392104.40579095/v1

8. Endo Y, Oka A, Uehara A, Toki S, Motegi S-i, Ishikawa O, et al. Fatal case of toxic epidermal necrolysis due to apalutamide used as a novel prostate cancer drug. *J Dermatol* (2020) 47(10):359–60. doi: 10.1111/1346-8138.15510

9. Katayama H, Saeki H, Osada SI. Maculopapular drug eruption caused by apalutamide: case report and review of the literature. *J Nippon Med School = Nippon Ika Daigaku zasshi* (2022) 89(5):550–4. doi: 10.1272/jnms.JNMS.2022_89-503

10. Shima K, Nomura T, Yamada Y, Usui S, Kobayashi T, Kabashima K. Maculopapular-type drug eruptions caused by apalutamide: case series and a review of the literature. *J Eur Acad Dermatol Venereology: JEADV* (2022) 36(2):113–5. doi: 10.1111/jdv.17657

11. Hsu Y-SO, Hsieh T-S, Huang P-W, Chu C-Y. Drug reaction with eosinophilia and systemic symptoms with features resembling Stevens–Johnson syndrome/toxic epidermal necrolysis related to apalutamide. *J Eur Acad Dermatol Venereol* (2023) 37 (2):246–8. doi: 10.1111/jdv.18660

12. Tohi Y, Kataoka K, Miyai Y, Kaku Y, Dainichi T, Haba R, et al. Apalutamide-associated skin rash in patients with prostate cancer: Histological evaluation by skin biopsy. *IJU Case Rep* (2021) 4(5):299–302. doi: 10.1002/iju5.12331

13. Kawakami Y, Mitsui M, Takamoto H, Yamamoto Y. Apalutamide-induced exanthematous drug eruption displaying spongiotic dermatitis successfully treated with dose reduction. *Int J Dermatol* (2021) 60(8):315–7. doi: 10.1111/ijd.15420

14. Miyagawa A, Adachi T, Kobayashi Y, Takamiyagi S, Arakawa H, Futatsugi K, et al. Plasmapheresis as a promising treatment option in apalutamide-associated toxic epidermal necrolysis. *J Dermatol* (2022) 49(3):102–3. doi: 10.1111/1346-8138.16248

15. Osawa K, Kiniwa Y, Shimosato Y, Midorikawa H, Shirai T, Sano T, et al. Toxic epidermal necrolysis caused by apalutamide: A case report of treatment using etanercept with conventional steroid therapy. *Acta dermato-venereologica* (2022) 102: adv00723. doi: 10.2340/actadv.v102.2243

16. Tohi Y, Kato T, Fukuhara H, Kobayashi K, Ohira S, Ikeda K, et al. Real-world analysis of apalutamide-associated skin adverse events in Japanese patients with advanced prostate cancer: a multi-institutional study in the Chu-shikoku Japan Urological Consortium. *Int J Clin Oncol* (2022) 27(8):1348–55. doi: 10.1007/s10147-022-02183-z

17. Pan A, Reingold RE, Zhao JL, Moy A, Kraehenbuehl L, Dranitsaris G, et al. Dermatological adverse events in prostate cancer patients treated with the androgen receptor inhibitor apalutamide. *J Urol* (2022) 207(5):1010–9. doi: 10.1097/JU.0000000000002425

18. Frey N, Jossi J, Bodmer M, Bircher A, Jick SS, Meier CR, et al. The epidemiology of stevens-johnson syndrome and toxic epidermal necrolysis in the UK. *J Invest Dermatol* (2017) 137(6):1240–7. doi: 10.1016/j.jid.2017.01.031

19. Yang MS, Lee JY, Kim J, Kim GW, Kim BK, Kim JY, et al. Incidence of Stevens-Johnson syndrome and toxic epidermal necrolysis: A nationwide population-based study using national health insurance database in Korea. *PloS One* (2016) 11(11): e0165933. doi: 10.1371/journal.pone.0165933

20. Frantz R, Huang S, Are A, Motaparthi K. Stevens-Johnson syndrome and toxic epidermal necrolysis: A review of diagnosis and management. *Medicina (Kaunas)* (2021) 57(9):895. doi: 10.3390/medicina57090895

21. Hsu YO, Hsieh TS, Huang PW, Chu CY. Drug reaction with eosinophilia and systemic symptoms with features resembling Stevens-Johnson syndrome/toxic epidermal necrolysis related to apalutamide. *J Eur Acad Dermatol Venereology: JEADV* (2023) 37(2):e246-e248. doi: 10.1111/jdv.18660

22. Alkhudair NA. Apalutamide: emerging therapy for non-metastatic castration-resistant prostate cancer. *Saudi Pharm J* (2019) 27(3):368–72. doi: 10.1016/j.jsps.2018.12.005

23. Ji C, Guha M, Zhu X, Whritenour J, Hemkens M, Tse S, et al. Enzalutamide and apalutamide: *in vitro* chemical reactivity studies and activity in a mouse drug allergy model. *Chem Res Toxicol* (2020) 33(1):211–22. doi: 10.1021/acs.chemrestox.9b00247

24. Katsuta M, Kimura T, Tashiro K, Murakami M, Hata K, Yanagisawa T, et al. Low body weight as a risk factor for apalutamide-related cutaneous adverse events. *Anticancer Res* (2022) 42(4):2023–8. doi: 10.21873/anticanres.15682

25. Zhang J, Lei Z, Xu C, Zhao J, Kang X. Current perspectives on severe drug eruption. *Clin Rev Allergy Immunol* (2021) 61(3):282–98. doi: 10.1007/s12016-021-08859-0

frontiers | Frontiers in Immunology

TYPE Systematic Review
PUBLISHED 22 January 2024
DOI 10.3389/fimmu.2024.1255825

OPEN ACCESS

EDITED BY
Yannick Degboé,
Centre Hospitalier Universitaire de Toulouse, France

REVIEWED BY
Brigida Anna Maiorano,
IRCCS Casa Sollievo della Sofferenza Hospital, Italy
Stuart D Rosen,
Imperial College, United Kingdom

*CORRESPONDENCE
Jingbo Zhang
zjb4226189@163.com

RECEIVED 09 July 2023
ACCEPTED 03 January 2024
PUBLISHED 22 January 2024

CITATION
Zhang C, Wei F, Ma W and Zhang J (2024) Immune-related cardiovascular toxicities of PD-1/PD-L1 inhibitors in solid tumors: an updated systematic review and meta-analysis. *Front. Immunol.* 15:1255825. doi: 10.3389/fimmu.2024.1255825

Immune-related cardiovascular toxicities of PD-1/PD-L1 inhibitors in solid tumors: an updated systematic review and meta-analysis

Chi Zhang, Fengtao Wei, Wenhan Ma and Jingbo Zhang*

Department of Cardiology, The Second Hospital of Shandong University, Jinan, Shandong, China

Purpose: The objective of this study was to investigate the risk of cardiovascular toxicities related to PD-1/PD-L1 inhibitors in solid tumors.

Methods: A literature search was performed following the participants, interventions, comparisons, outcomes, and study design (PICOS) principles, and the study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Data analysis was conducted using Review Manager version 5.4.

Results: This meta-analysis included 69 randomized controlled trials (RCTs) divided into five groups based on the treatment regimens: PD-1/PD-L1 + chemotherapy versus chemotherapy, PD-1/PD-L1 versus chemotherapy, PD-1/PD-L1 versus placebo, PD-1/PD-L1 + CTLA-4 versus PD-1/PD-L1 and PD-1/PD-L1 + CTLA-4 versus chemotherapy. Compared to chemotherapy treatment alone, PD-1/PD-L1 +chemotherapy significantly increased the risk of hypertension [all-grade (OR = 1.27, 95% CI [1.05, 1.53], p = 0.01); grade 3–5 (OR = 1.36, 95% CI [1.04, 1.79], p = 0.03)], hypotension [all-grade (OR = 2.03, 95% CI [1.19, 3.45], p = 0.009); grade 3–5 (OR = 3.60, 95% CI [1.22, 10.60], p = 0.02)], arrhythmia [all-grade (OR = 1.53, 95% CI [1.02, 2.30], p = 0.04); grade 3–5 (OR = 2.91, 95% CI [1.33, 6.39], p = 0.008)] and myocarditis [all-grade (OR = 2.42, 95% CI [1.06, 5.54], p = 0.04)]. The risk of all-grade hypotension (OR = 2.87, 95% CI [1.26, 6.55], p = 0.01) and all-grade arrhythmia (OR = 2.03, 95% CI [1.13, 3.64], p = 0.02) significantly increased when treated with PD-1/PD-L1 inhibitors compared to the placebo. The risks of cardiovascular toxicities are significantly higher with PD-1+CTLA-4 compared to PD-1 alone (OR = 2.02, 95% CI [1.12, 3.66], p = 0.02).

Conclusion: PD-1/PD-L1 inhibitor leads to an increased risk of cardiovascular toxicities, especially hypertension, hypotension, arrhythmia, and myocarditis.

KEYWORDS

PD-1/PD-L1 inhibitors, solid tumors, cardiotoxicity, vascular toxicity, meta-analysis

Introduction

In recent years, the programmed cell death 1/programmed cell death 1 ligand 1 (PD-1/PD-L1) inhibitor has been used as an immunotherapy and has led to substantial advancements in the prognosis of diverse cancer types (1). It can enhance the immune response by blocking the inhibitory signal of the T cell response and exerting anti-tumor effects (2). However, the enhanced destructive effect of T cells can also damage normal cells and tissues. Clinicians are becoming aware of its adverse effects on almost all organ types (3). Adverse effects often include immune-related pneumonitis, liver damage, endocrine organ abnormalities, and adverse skin reactions (4). Although cardiovascular toxicities, such as myocarditis, arrhythmia, blood pressure abnormalities, and heart failure, are uncommon, their prognoses are poor (5, 6). Therefore, additional attention should be paid to cardiovascular toxicity.

PD-1/PD-L1 inhibitors are currently recommended in various therapeutic combinations. Previous reviews and meta-analyses have summarized cardiovascular toxicities associated with different treatment regimens (7, 8). The completion of more clinical trials may have affected the original analysis results. The original topic that could not be analyzed because of insufficient data may have to be reoperated and completed. Therefore, given that cardiovascular toxicities are now considered major determinants of prognosis (9), it is necessary to conduct a new meta-analysis for this study. This will further guide the antitumor treatment of patients with solid tumors.

Materials and methods

Search strategy and selection criteria

This study was consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (10). Randomized controlled trials (RCTs) on solid tumors with cardiovascular toxicities published between July 2013 and May 2023 were searched based on the principle of PICOS (participants, interventions, comparisons, outcomes, and study design). The following medical subject heading (MeSH) terms were used: nivolumab, pembrolizumab, atezolizumab, tislelizumab, penpulimab, avelumab, durvalumab, camrelizumab, Opdivo, Bavencio, Keytruda, Imfinzi, AK105, MPDL3280A, Tecentriq, MK-3475, and BMS 963558. RCTs mentioned in the relevant reviews and references were also searched to avoid missing data. Five individuals were selected for literature search and data extraction. All conflicts were jointly discussed and resolved by the corresponding author.

The following selection criteria were used: 1) RCTs published between July 2013 and May 2023; 2) participants diagnosed with solid tumors treated with at least one PD-1 or PD-L1 inhibitor; 3) clinical trials reporting all-grade or grade 3–5 adverse effects; 4) research published in English. The exclusion criteria were as follows: 1) no treatment with PD-1/PD-L1; 2) non-RCT studies; 3) RCTs not involving cardiovascular toxicities; 4) single-arm studies without a control group.

Data extraction

Five individuals independently obtained the following baseline information from the included studies: year of publication, name of the first author, name of the study, national clinical trial (NCT) number, treatment lines, names of tumors, names of drugs, treatment arms, and the total number of people included in each study.

Publication bias and quality assessments

The Cochrane Collaboration tool was used to evaluate the risk of bias in the RCTs and funnel plots were used to evaluate publication bias (11). Seven sources of bias were evaluated in each RCT: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). Each domain was independently assigned a 'high', 'low', or 'unclear' risk of bias by all authors, with disagreements adjudicated by the corresponding author.

Heterogeneity assessment and statistical analysis

Review Manager (RevMan) version 5.4. was used to analyze the relevant data using the Mantel–Haenszel method (12). I^2 values were applied to estimate heterogeneity among the included clinical trials, which were classified into three grades: low, moderate, and high (I2 values <25%, 25%–50%, and >50%, respectively) (13). When I^2 was greater than 50%, significant heterogeneity was considered, and the source of heterogeneity was determined by subgroup analysis. Owing to the inherent heterogeneity among the included trials, the random effect (RE) was applied to analyze the odds ratio (OR) and corresponding 95% confidence interval (CI) (14). Funnel plots derived from the fixed effect (FE) model were used to evaluate publication bias. All reported P values were two-sided, and $P < 0.05$ was deemed to be statistically significant.

Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, Randomized Controlled Trial; ICI, Immune Checkpoint Inhibitor; PD-1, Programmed cell death 1; PD-L1, Programmed cell death 1 ligand 1; CTLA-4, anti-cytotoxic T-lymphocyte antigen-4; HR, Hazard Ratios; OR, Odds Ratio; CI, Confidence Interval; RE, Random Effect; FE, Fixed Effect; NSCLC, Non-Small-Cell Lung Cancer; SCLC, Small-Cell Lung Cancer; BRCA, Breast Cancer; UC, Urothelial Carcinoma; HNSCC, Head and Neck Squamous Cell Carcinoma; CCA, Cervical Cancer; TNBC, Triple-Negative Breast Cancer; GC, Gastric Cancer; GC/GJC, Gastric or gastro-oesophageal junction cancer; ESCC, Oesophagea/Esophagea Squamous Cell Carcinoma; NPC, Nasopharyngeal Cancer; CRC, Colorectal Cancer; EOC, Epithelial Ovarian Cancer; OC, Ovarian Cancer; GEC, Gastroesophageal adenocarcinoma; RCC, Renal Cell Carcinoma; PCA, Prostate Cancer; HCC, Hepatocellular Carcinoma; EC, Esophageal Cancer; MPM, Malignant Pleural Mesothelioma; N/A, not available.

Results

Literature search results

We retrieved 638 relevant records from the PubMed database. The RCTs screening process was shown in Figure 1, and the baseline characteristics are presented in Table 1. Bias assessments of the included trials were completed and were presented in Figure 2. After thoroughly reviewing the complete texts of all trials included in this meta-analysis, a total of 10 prevalent cardiovascular toxicities were incorporated, comprising hypertension (n = 36) (22, 24, 25, 29–32, 34–37, 39, 40, 42–48, 51, 52, 54, 56, 62, 63, 65, 68, 69, 71, 72, 75, 77, 78, 81, 83, 84), hypotension (n = 14) (25, 29–32, 36, 40, 42, 52, 62, 68, 71, 75, 76, 78, 83, 84), arrhythmia (n = 32) (21–24, 29, 30, 32, 36, 37, 41, 42, 45–47, 57, 58, 61, 62, 65–69, 71, 72, 75, 76, 78, 83, 84), myocarditis (n = 31) (17, 21–25, 28, 30, 31, 33, 37, 38, 49, 50, 52, 53, 56, 59, 62, 63, 67, 68, 70, 72–74, 78–81, 84, 91), heart failure (n = 17) (20, 22, 25, 30–32, 34, 37, 45–47, 49, 62, 65, 67, 68, 78), myocardial infarction (n = 22) (15, 16, 23, 27, 30, 34, 36, 37, 39, 40, 46, 47, 52, 55, 62, 63, 65, 68, 70, 72, 78, 83, 84), pericardial diseases (n = 4) (32, 68, 76, 78), thrombosis (n = 18) (15, 25–27, 30, 34, 36, 40, 47, 52, 55, 62, 67, 68, 71, 76, 78, 83), embolism (n = 21) (15, 20, 22, 27, 30, 36, 38, 40–42, 45–48, 55, 62, 66–68, 83, 84), and vasculitis (n = 13) (19, 25, 27, 32, 51, 62, 64, 67, 68, 72, 80–84).

Characteristics of identified trials

We first divided the 63 clinical trials into five groups according to treatment regimen. The specific grouping methods are as follows.

Group 1: PD-1/PD-L1 + chemotherapy versus chemotherapy; n = 34 (15, 16, 19–51, 91). Seventeen clinical trials included PD-1 (15–17, 19–32) and seventeen clinical trials included PD-L1 (33–51).

Group 2: PD-1/PD-L1 versus chemotherapy; n = 16 (30, 45, 51–67). Ten clinical trials included PD-1 (30, 52–62) and six included PD-L1 (45, 51, 63–67).

Group 3: PD-1/PD-L1 versus placebo; n = 15 (17, 27, 68–82, 84). Nine clinical trials included PD-1 (68–77) and six included PD-L1 (78–84).

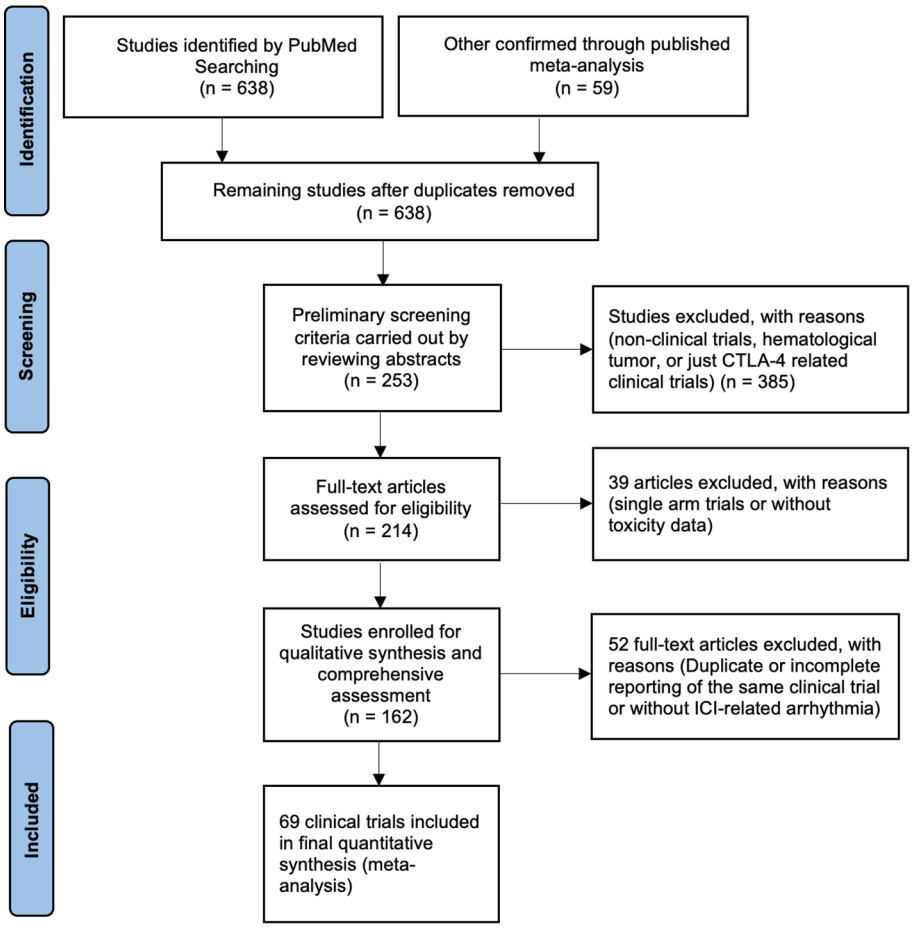


FIGURE 1
The flow diagram of the included randomized controlled trials (RCTs).

10.3389/fimmu.2024.1255825

TABLE 1 The baseline characteristics of the RCTs included in this meta-analysis (Total of 69 clinical trials).

NO	First author and year	Study	Treatment lines	Tumor type	Drug	PD-1/ PD-L1	Treatment regimen	Enrollment
PD-1/PD-L1 + chemotherapy VS chemotherapy								
1	Forde PM, 2022 (15)	CheckMate 816 (NCT 02998528)	first line	NSCLC	Nivolumab	PD-1	Nivolumab + platinum-based chemotherapy VS platinum-based chemotherapy	352
2	Langer CJ, 2016 (16)	KEYNOTE-021 (NCT 02039674)	first line	NSCLC	Pembrolizumab	PD-1	Pembrolizumab + carboplatin VS carboplatin + pemetrexed	121
3	Rodríguez-Abreu D, 2021 (17)	KEYNOTE-189 (NCT 02578680)	first line	NSCLC	Pembrolizumab	PD-1	Pembrolizumab + pemetrexed-platinum VS pemetrexed-platinum	607
	Garassino MC, 2023 (18)							
4	Novello S, 2023 (19)	KEYNOTE-407 (NCT 02775435)	first line	NSCLC	Pembrolizumab	PD-1	Pembrolizumab + carboplatin +paclitaxel/nab-paclitaxel VS carboplatin + paclitaxel/ nab-paclitaxel	558
5	Zhou C, 2021 (20)	CameL (NCT 03134872)	first line	NSCLC	Camrelizumab	PD-1	Camrelizumab + carboplatin + pemetrexed VS carboplatin + pemetrexed	412
6	Wang Z, 2023 (21)	CHOICE-01 (NCT 03856411)	first line	NSCLC	Toripalimab	PD-1	Toripalimab + nab-paclitaxel + carboplatin VS nab-paclitaxel + carboplatin	464
7	Lu Z, 2022 (22)	ORIENT-15 (NCT 03748134)	first line	ESCC	Sintilimab	PD-1	Sintilimab + cisplatin + paclitaxel VS cisplatin + paclitaxel	659
8	Luo H, 2021 (23)	ESCORT-1st (NCT 03691090)	first line	ESCC	Camrelizumab	PD-1	Camrelizumab + paclitaxel + cisplatin VS paclitaxel + cisplatin	595
9	Wang ZX, 2022 (24)	JUPITER-06 (NCT 03829969)	first line	ESCC	Toripalimab	PD-1	Toripalimab + paclitaxel + cisplatin VS paclitaxel + cisplatin	514
10	Xu J, 2023 (25)	RATIONALE-306 (NCT 03783442)	first line	ESCC	Tislelizumab	PD-1	Tislelizumab + platinum agent and fluoropyrimidine/ capecitabine/paclitaxel VS platinum agent and fluoropyrimidine/ capecitabine/paclitaxel	645
11	Janjigian YY, 2021 (26)	CheckMate 649 (NCT 02872116)	first line	GJC	Nivolumab	PD-1	Nivolumab + capecitabine +oxaliplatin / leucovorin +fluorouracil+oxaliplatin VS capecitabine+oxaliplatin / leucovorin +fluorouracil+oxaliplatin	1549
12	Kang YK, 2022 (27)	CheckMate 649 (NCT 02872116)	first line	GC/GJC	Nivolumab	PD-1	Nivolumb + oxaliplatin + capecitabine VS oxaliplatin + capecitabin	717
13	Tolaney SM, 2020 (28)	NCT 03051659	second or others	BRCA	Pembrolizumab	PD-1	Pembrolizumab + eribulin VS eribulin	88
14	Schmid P, 2022 (29)	KEYNOTE-522 (NCT 03036488)	first line	TNBC	Pembrolizumab	PD-1	Pembrolizumab + paclitaxel + carboplatin VS paclitaxel + carboplatin	1172
15	Powles T, 2021 (30)	KEYNOTE-361 (NCT 02853305)	first line	UC	Pembrolizumab	PD-1	Pembrolizumab + gemcitabine+cisplatin/ carboplatin VS gemcitabine +cisplatin/carboplatin	691

(Continued)

TABLE 1 Continued

NO	First author and year	Study	Treatment lines	Tumor type	Drug	PD-1/ PD-L1	Treatment regimen	Enrollment
16	Mai HQ, 2021 (31)	JUPITER-02 (NCT 03581786)	first line	NPC	Toripalimab	PD-1	Toripalimab +gemcitabine-cisplatin VS gemcitabine-cisplatin	289
17	Yang Y, 2021 (32)	CAPTAIN-1st (NCT 03707509)	first line	NPC	Camrelizumab	PD-1	Camrelizumab + gemcitabine + cisplatin VS gemcitabine + cisplatin	263
18	Nishio M, 2021 (33)	IMpower132 (NCT 02657434)	first line	NSCLC	Atezolizumab	PD-L1	Atezolizumab + carboplatin / cisplatin and pemetrexed VS carboplatin / cisplatin and pemetrexed	565
19	Socinski MA, 2018 (34)	IMpower150 (NCT 02366143)	first line	NSCLC	Atezolizumab	PD-L1	Atezolizumab + bevacizumab + carboplatin + paclitaxel VS bevacizumab + carboplatin + paclitaxel	787
	Reck M, 2020 (35)							
20	West H, 2019 (36)	IMpower130 (NCT 02367781)	first line	NSCLC	Atezolizumab	PD-L1	Atezolizumab + carboplatin + nab-paclitaxel VS carboplatin + nab-paclitaxel	705
21	Zhou C, 2022 (37)	GEMSTONE-302 (NCT 03789604)	first line	NSCLC	Sugemalimab	PD-L1	Sugemalimab + platinum-based chemotherapy VS platinum-based chemotherapy	479
22	Johnson ML, 2023 (38)	POSEIDON (NCT 03164616)	first line	NSCLC	Durvalumab	PD-L1	Durvalumab + platinum-based chemotherapy VS platinum-based chemotherapy	667
23	Paz-Ares L, 2019 (39)	CASPIAN (NCT 03043872)	first line	SCLC	Durvalumab	PD-L1	Durvalumab + platinum–etoposide VS platinum–etoposide	531
	Goldman JW, 2021 (40)							
24	Wang J, 2022 (41)	CAPSTONE-1 (NCT 03711305)	first line	SCLC	Adebrelimab	PD-L1	Adebrelimab + carboplatin + etoposide VS carboplatin + etoposide	462
25	Pusztai L, 2021 (42)	I-SPY2 (NCT 01042379)	first line	BRCA	Durvalumab	PD-L1	Durvalumab + olaparib + paclitaxel VS paclitaxel	372
26	Emens LA, 2021 (43)	IMpassion130 (NCT 02425891)	first line	TNBC	Atezolizumab	PD-L1	Atezolizumab + nab-paclitaxel VS nab-paclitaxel	890
27	Mittendorf EA, 2020 (44)	IMpassion031 (NCT 03197935)	first line	TNBC	Atezolizumab	PD-L1	Atezolizumab + nab-paclitaxel + doxorubicin + cyclophosphamide VS nab-paclitaxel + doxorubicin + cyclophosphamide	331
28	Pujade-Lauraine E, 2021 (45)	JAVELIN Ovarian 200 (NCT 02580058)	first line	Multiple cancers	Avelumab	PD-L1	Avelumab + pegylated liposomal doxorubicin VS pegylated liposomal doxorubicin	359
29	Lee NY, 2021 (46)	JAVELIN Head and Neck 100 (NCT 02952586)	first line	HNSCC	Avelumab	PD-L1	Avelumab +chemoradiotherapy VS chemoradiotherapy	692
30	Monk BJ, 2021 (47)	JAVELIN Ovarian 100 (NCT 02718417)	first line	EOC	Avelumab	PD-L1	Avelumab + carboplatin + paclitaxel VS carboplatin + paclitaxel + observation	662

(Continued)

TABLE 1 Continued

NO	First author and year	Study	Treatment lines	Tumor type	Drug	PD-1/ PD-L1	Treatment regimen	Enrollment
31	Moore KN, 2021 (48)	IMagyn050/GOG 3015/ENGOT-OV39 (NCT 03038100)	first line	OC	Atezolizumab	PD-L1	Atezolizumab + bevacizumab + carboplatin + paclitaxel VS bevacizumab + carboplatin + paclitaxel	1286
32	Powles T, 2022 (49)	IMbassador 250 (NCT 03016312)	second or others	PCA	Atezolizumab	PD-L1	Atezolizumab + enzalutamide VS enzalutamide	750
33	Mettu NB, 2022 (50)	BACCI (NCT 02873195)	second or others	CRC	Atezolizumab	PD-L1	Atezolizumab + capecitabine + bevacizumab VS capecitabine + bevacizumab	132
34	Galsky MD, 2020 (51)	IMvigor130 (NCT 02807636)	first line	UC	Atezolizumab	PD-L1	Atezolizumab+platinum-based chemotherapy VS platinum-based chemotherapy	843
PD-1/PD-L1 VS chemotherapy								
1	Huang J, 2020 (52)	ESCORT (NCT 03099382)	second or others	ESCC	Camrelizumab	PD-1	Camrelizumab VS docetaxel/irinotecan	448
2	Kojima T, 2020 (53)	KEYNOTE-181 (NCT 02564263)	second or others	ESCC	Pembrolizumab	PD-1	Pembrolizumab VS paclitaxel/ docetaxel/irinotecan	610
3	Chan ATC, 2023 (54)	KEYNOTE-122 (NCT 02611960)	second or others	NPC	Pembrolizumab	PD-1	Pembrolizumab VS capecitabine/ gemcitabine/docetaxel	228
4	Diaz LA Jr, 2022 (55)	KEYNOTE-177 (NCT 02563002)	first line	CRC	Pembrolizumab	PD-1	Pembrolizumab VS 5-fluorouracil–based therapy	296
	André T, 2020 (56)							
5	Powles T, 2021 (30)	KEYNOTE-361 (NCT 02853305)	first line	UC	Pembrolizumab	PD-1	Pembrolizumab VS gemcitabine +cisplatin/carboplatin	644
6	Winer EP, 2021 (57)	KEYNOTE-119 (NCT 02555657)	second or others	TNBC	Pembrolizumab	PD-1	Pembrolizumab VS capecitabine/eribulin/ gemcitabine/vinorelbine	601
7	Herbst RS, 2016 (58)	KEYNOTE-010 (NCT 01905657)	second or others	NSCLC	Pembrolizumab	PD-1	Pembrolizumab VS docetaxel	652
8	Mok TSK, 2019 (59)	KEYNOTE-042 (NCT 02220894)	first line	NSCLC	Pembrolizumab	PD-1	Pembrolizumab VS platinum-based chemotherapy	1251
	de Castro G Jr, 2023 (60)							
9	Borghaei H, 2015 (61)	CheckMate 057 (NCT 01673867)	second or others	NSCLC	Nivolumab	PD-1	Nivolumab VS docetaxel	555
10	Sezer A, 2021 (62)	EMPOWER-Lung 1 (NCT 03088540)	first line	NSCLC	Cemiplimab	PD-1	Cemiplimab VS platinum-doublet chemotherapy	697
11	Barlesi F, 2018 (63)	JAVELIN Lung 200 (NCT 02395172)	second or others	NSCLC	Avelumab	PD-L1	Avelumab VS docetaxel	758
12	Jassem J, 2021 (64)	IMpower110 (NCT 02409342)	first line	NSCLC	Atezolizumab	PD-L1	Atezolizumab VS platinum-based chemotherapy	549
	Herbst RS, 2020 (65)							
13	Galsky MD, 2020 (51)	IMvigor130 (NCT 02807636)	first line	UC	Atezolizumab	PD-L1	Atezolizumab VS platinum-based chemotherapy	744

(Continued)

TABLE 1 Continued

NO	First author and year	Study	Treatment lines	Tumor type	Drug	PD-1/ PD-L1	Treatment regimen	Enrollment
14	van der Heijden MS, 2021 (66)	IMvigor211 (NCT 02302807)	second or others	UC	Atezolizumab	PD-L1	Atezolizumab VS vinflunine/ paclitaxel/docetaxel	902
15	Powles T, 2020 (67)	DANUBE (NCT 02516241)	first line	UC	Durvalumab	PD-L1	Durvalumab VS gemcitabine +cisplatin/carboplatin	658
16	Pujade-Lauraine E, 2021 (45)	JAVELIN Ovarian 200 (NCT 02580058)	first line	Multiple cancers	Avelumab	PD-L1	Avelumab VS pegylated liposomal doxorubicin	364
PD-1/PD-L1 VS placebo								
1	Choueiri TK, 2021 (68)	KEYNOTE-564 (NCT 03142334)	second or others	RCC	Pembrolizumab	PD-1	Pembrolizumab VS placebo	984
	Powles T, 2022 (69)							
2	Janjigian YY, 2021 (70)	KEYNOTE-811 (NCT 03615326)	second or others	GC	Pembrolizumab	PD-1	Pembrolizumab VS Placebo	433
3	Cohen EEW, 2019 (71)	KEYNOTE-040 (NCT 02252042)	second or others	HNSCC	Pembrolizumab	PD-1	Pembrolizumab VS Standard-of-Care	480
4	Colombo N, 2021 (72)	KEYNOTE-826 (NCT 03635567)	first line	CCA	Pembrolizumab	PD-1	Pembrolizumab VS Placebo	616
5	Eggermont AMM, 2020 (73)	KEYNOTE-054 (NCT 02362594)	second or others	melanoma	Pembrolizumab	PD-1	Pembrolizumab VS Placebo	1011
6	Long GV, 2022 (74)	KEYNOTE-716 (NCT 03553836)	second or others	melanoma	Pembrolizumab	PD-1	Pembrolizumab VS Placebo	969
7	Zimmer L, 2020 (75)	IMMUNED (NCT 02523313)	second or others	melanoma	Nivolumab	PD-1	Nivolumab VS Placebo	107
8	Fennell DA, 2021 (76)	CONFIRM (NCT 03063450)	second or others	mesothelioma	Nivolumab	PD-1	Nivolumab VS placebo	332
9	Sugawara S, 2021 (77)	TASUKI-52 (NCT 03117049)	first line	NSCLC	Nivolumab	PD-1	Nivolumab VS Placebo	548
10	Antonia SJ, 2017 (78)	PACIFIC (NCT 02125461)	second or others	NSCLC	Durvalumab	PD-L1	Durvalumab VS Placebo	709
11	Zhou Q, 2022 (79)	GEMSTONE-301 (NCT 03728556)	second or others	NSCLC	Sugemalimab	PD-L1	Sugemalimab VS placebo	381
12	Felip E, 2021 (80)	IMpower010 (NCT 02486718)	second or others	NSCLC	Atezolizumab	PD-L1	Atezolizumab VS placebo	990
	Kenmotsu H, 2022 (81)							
13	Horn L, 2018 (82)	IMpower133 (NCT 02763579)	first line	SCLC	Atezolizumab	PD-L1	Atezolizumab VS Placebo	394
14	Bellmunt J, 2021 (83)	IMvigor010 (NCT 02450331)	first line	UC	Atezolizumab	PD-L1	Atezolizumab VS Observation	787

(Continued)

TABLE 1 Continued

NO	First author and year	Study	Treatment lines	Tumor type	Drug	PD-1/ PD-L1	Treatment regimen	Enrollment
15	Pal SK, 2022 (84)	IMmotion010 (NCT 03024996)	second or others	RCC	Atezolizumab	PD-L1	Atezolizumab VS placebo	773
PD-1/PD-L1 + CTLA-4 VS PD-1/PD-L1								
1	Antonia SJ, 2016 (85)	CheckMate 032 (NCT 01928394)	second or others	SCLC	Nivolumab	PD-1	Nivolumab + ipilimumab VS nivolumab	159
2	Boyer M, 2021 (86)	KEYNOTE-598 (NCT 03302234)	first line	NSCLC	Pembrolizumab	PD-1	Pembrolizumab+ipilimumab VS pembrolizumab	563
3	Gettinger SN, 2021 (87)	Lung-MAP S1400I (NCT 02785952)	second or others	SCLC	Nivolumab	PD-1	Nivolumab + ipilimumab VS nivolumab	247
4	Hodi FS, 2018 (88)	CheckMate 067 (NCT 01844505)	first line	melanoma	Nivolumab	PD-1	Nivolumab + ipilimumab VS Nivolumab	626
5	Powles T, 2020 (67)	DANUBE (NCT 02516241)	first line	UC	Durvalumab	PD-L1	Durvalumab + tremelimumab VS Durvalumab	685
PD-1/PD-L1 + CTLA-4 VS chemotherapy								
1	Baas P, 2021 (89)	CheckMate 743 (NCT 02899299)	first line	pleural mesothelioma	Nivolumab	PD-1	Nivolumab + ipilimumab VS chemotherapy	584
2	Paz-Ares L, 2021 (90)	CheckMate 9LA (NCT 03215706)	first line	NSCLC	Nivolumab	PD-1	Nivolumab + ipilimumab VS chemotherapy	707
3	Powles T, 2020 (67)	DANUBE (NCT 02516241)	first line	UC	Durvalumab	PD-L1	Durvalumab + tremelimumab VS Chemotherapy	653

PD-1, Programmed cell death 1; PD-L1, Programmed cell death 1 ligand 1; CTLA-4, anti-cytotoxic T-lymphocyte antigen-4; HR, Hazard Ratios; OR, Odds Ratio; CI, Confidence Interval; RE, Random Effect; FE, Fixed Effect; NSCLC, Non-Small-Cell Lung Cancer; SCLC, Small-Cell Lung Cancer; BRCA, Breast Cancer; UC, Urothelial Carcinoma; HNSCC, Head and Neck Squamous Cell Carcinoma; CCA, Cervical Cancer; TNBC, Triple-Negative Breast Cancer; GC, Gastric Cancer; GC/GJC, Gastric or gastro-oesophageal junction cancer; ESCC, Oesophagea/Esophagea Squamous Cell Carcinoma; NPC, Nasopharyngeal Cancer; CRC, Colorectal Cancer; EOC, Epithelial Ovarian Cancer; OC, Ovarian Cancer; GEC, Gastroesophageal adenocarcinoma; RCC, Renal Cell Carcinoma; PCA, Prostate Cancer; HCC, Hepatocellular Carcinoma; EC, Esophageal Cancer; MPM, Malignant Pleural Mesothelioma.

Group 4: PD-1/PD-L1 + CTLA-4 versus PD-1/PD-L1; n = 5 (67, 85–88). Four clinical trials included PD-1 (85–88) and one included PD-L1 (67).

Group 5: PD-1/PD-L1 + CTLA-4 versus chemotherapy; n = 3 (67, 89, 90). Two clinical trials included PD-1 (89, 90) and one included PD-L1 (67).

Risk of hypertension

Thirty-six clinical trials reported hypertension (22, 24, 25, 29–32, 34–37, 39, 40, 42–48, 51, 52, 54, 56, 62, 63, 65, 68, 69, 71, 72, 75, 77, 78, 81, 83, 84). In comparison to chemotherapy, PD-1/PD-L1 + chemotherapy resulted in a significantly increased risk of all-grade hypertension (OR = 1.27, 95% CI [1.05, 1.53], p = 0.01, I^2 = 0%; Figure 2A1), especially for the subgroup of first-line treatment (OR = 1.27, 95% CI [1.05, 1.53], p = 0.01, I^2 = 0%; Figure 2A1) (22, 24, 25, 29, 31, 32, 35–37, 40, 42–47, 51). Similar trend were also be found in grade 3–5 hypertension (OR = 1.36, 95% CI [1.04, 1.79], p = 0.03, I^2 = 0%; Figure 2A2). Among them, the PD-1 subgroup (OR = 1.64, 95% CI [1.03, 2.62], p = 0.04, I^2 = 0%; Figure 2A2), first-line treatment (OR = 1.36, 95% CI [1.04. 1.79], p = 0.03, I^2 = 0%; Figure 2A2), or urothelial carcinoma (UC) (OR = 2.48, 95% CI [1.26, 4.85], p = 0.008, I^2 = 0%; Figure 2A3) were more likely to cause grade 3–5 hypertension (22, 24, 25, 29–32, 34, 36, 37, 40, 42–47, 51). No heterogeneity was observed among the studies.

Compared with chemotherapy alone (Figure 2B) (45, 51, 52, 54, 56, 62, 63, 65) or the placebo (Figure 2C) (68, 71, 72, 75, 77), the effects of PD-1/PD-L1 inhibitors on hypertension, indicated by non-significant statistical analysis results, were weaker than those of the control groups. The corresponding funnel plots are shown in the Supplementary Data (Supplementary Figure 2).

Risk of hypotension

There were fourteen clinical trials reporting hypotension (25, 29–32, 36, 40, 42, 52, 62, 68, 71, 75, 76, 78, 83, 84). The risk of all-grade hypotension (OR = 2.03, 95% CI [1.19, 3.45], p = 0.009, I^2 = 13%; Figure 3A1) and grade 3–5 hypotension (OR = 3.60, 95% CI [1.22, 10.60], p = 0.02, I^2 = 0%; Figure 3A3) associated with chemotherapy were significantly lower than those associated with PD-1/PD-L1 + chemotherapy. This difference was particularly notable in the PD-1 subgroup [(all-grade (OR = 2.43, 95% CI [1.23, 4.79], p = 0.01, I^2 = 0%; Figure 3A1); grade 3–5 (OR = 4.65,

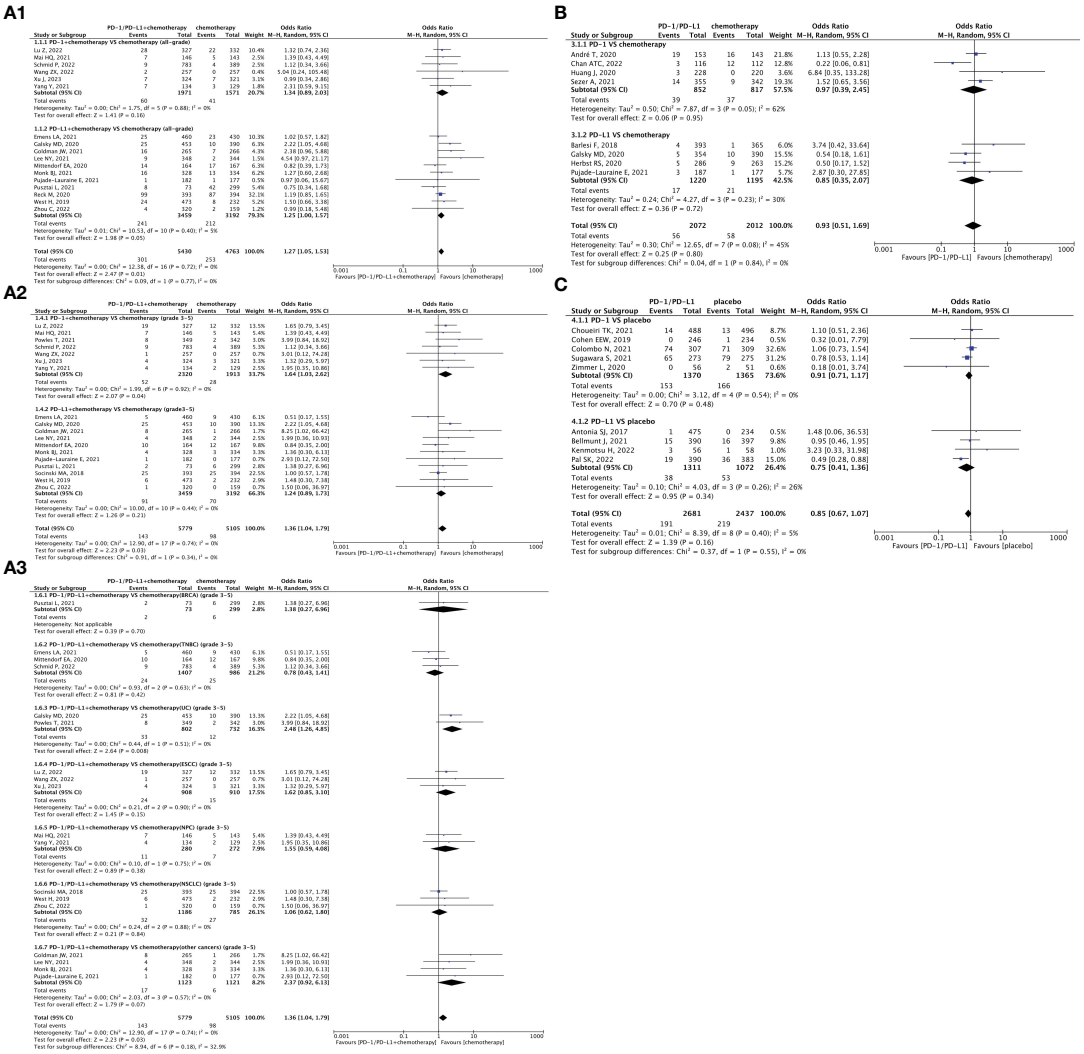


FIGURE 2
Forest plots depicting the risk of hypertension in PD-1/PD-L1 + chemotherapy versus chemotherapy. **(A1)** The risk of hypertension of all-grade: subgroup analyses were conducted according to PD-1/PD-L1. **(A2)** The risk of hypertension of grade 3-5: subgroup analyses were performed based on PD-1/PD-L1. **(A3)** The risk of hypertension of grade 3-5: subgroup analyses were performed based on types of tumors. Forest plot depicting the risk of hypertension in PD-1/PD-L1 versus chemotherapy. **(B)** The risk of hypertension of all-grade: subgroup analysis was conducted according to PD-1/PD-L1. Forest plot depicting the risk of hypertension in PD-1/PD-L1 versus placebo. **(C)** The risk of hypertension of all-grade: subgroup analysis was conducted according to PD-1/PD-L1.

95% CI [1.21, 17.87], p = 0.03, I^2 = 0%; Figure 3A3], and first-line treatment subgroup [all-grade (OR = 2.03, 95% CI [1.19. 3.45], p = 0.009, I^2 = 13%; Figure 3A1); grade 3–5 (OR = 3.60, 95% CI [1.22, 10.60], p = 0.02, I^2 = 0%; Figure 3A3)] (25, 29, 31, 36, 40, 42). Furthermore, in the subgroup of breast cancer (BRCA), PD-1/PD-L1 + chemotherapy exhibited a tendency toward a higher risk of all-grade hypotension (OR = 3.50, 95% CI [1.03, 11.96], p = 0.05, I^2 = 49%; Figure 3A2).

Compared to placebo, PD-1/PD-L1 substantially increased the risk of all-grade hypotension (OR = 2.87, 95% CI [1.26, 6.55], p = 0.01, I^2 = 0%; Figure 3B), especially PD-L1 (OR = 3.03, 95% CI [1.16, 7.94], p = 0.02, I^2 = 0%; Figure 3B) (68, 71, 75, 76, 78, 83, 84). No significant heterogeneity was observed in the aforementioned results. PD-1/PD-L1 did not demonstrate a higher risk of grade 3–5 hypotension when compared to chemotherapy alone (Figure 3C) (30, 52, 62). The corresponding funnel plots are shown in Supplementary Data (Supplementary Figure 3).

Risk of arrhythmia

Thirty-two clinical trials reported arrhythmia (21–24, 29, 30, 32, 36, 37, 41, 42, 45–47, 57, 58, 61, 62, 65–69, 71, 72, 75, 76, 78, 83, 84). Compared with chemotherapy, the combination of PD-1/PD-L1

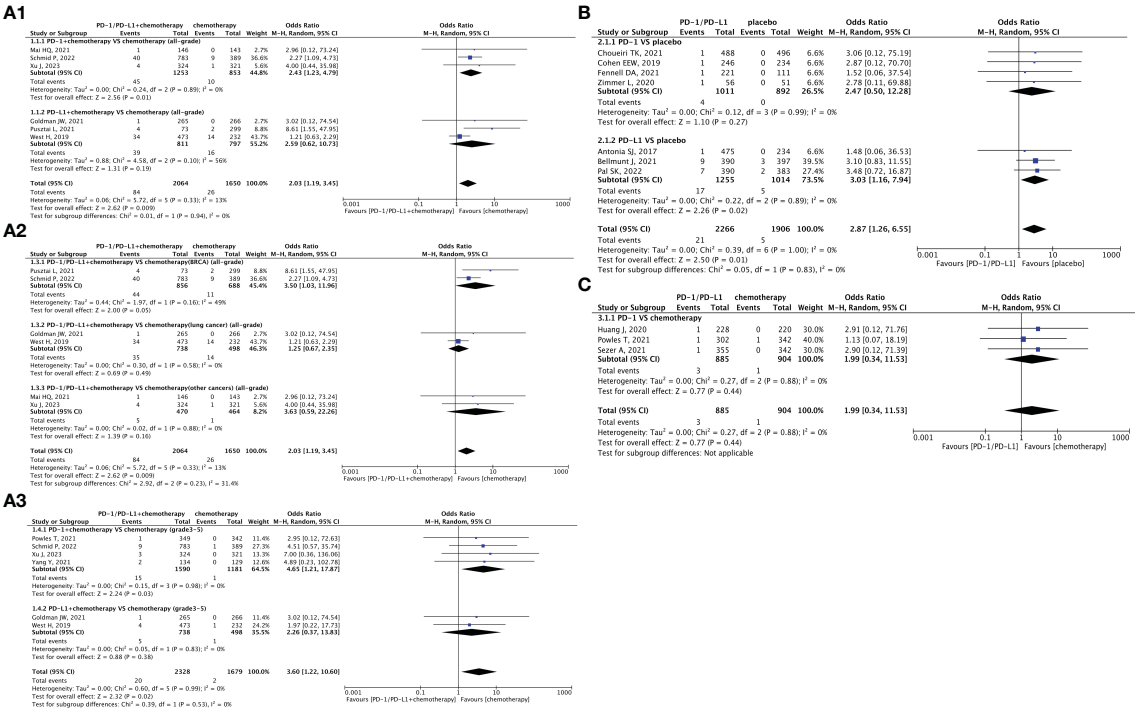


FIGURE 3
Forest plots depicting the risk of hypotension in PD-1/PD-L1 + chemotherapy versus chemotherapy. **(A1)** The risk of hypotension of all-grade: subgroup analyses were conducted according to PD-1/PD-L1. **(A2)** The risk of hypotension of all-grade: subgroup analyses were conducted according to types of tumors. **(A3)** The risk of hypotension of grade 3-5: subgroup analysis was conducted according to PD-1/PD-L1. Forest plot depicting the risk of hypotension in PD-1/PD-L1 versus placebo. **(B)** The risk of hypotension of all-grade: subgroup analysis was conducted according to PD-1/PD-L1. Forest plot depicting the risk of hypotension in PD-1/PD-L1 versus chemotherapy. **(C)** The risk of hypotension of grade 3-5: subgroup analysis was conducted according to PD-1.

inhibitors with chemotherapy exhibited a significantly higher risk of all-grade arrhythmia (OR = 1.53, 95% CI [1.02, 2.30], p = 0.04, I^2 = 21%; Figure 4A1) and grade 3–5 arrhythmia (OR = 2.91, 95% CI [1.33, 6.39], p = 0.008, I^2 = 0%; Figure 4A3). This effect was particularly prominent in the subgroups of first-line treatment [all-grade (OR = 1.53, 95% CI [1.02, 2.30], p = 0.04, I^2 = 21%; Figure 4A1); grade 3–5 (OR = 2.91, 95% CI [1.33, 6.39], p = 0.008, I^2 = 0%; Figure 4A3)], and non-small cell lung cancer (NSCLC) [all-grade (OR = 2.69, 95% CI [1.30, 5.57], p = 0.007, I^2 = 0%; Figure 4A2); grade 3–5 (OR = 8.09, 95% CI [1.07, 61.36], p = 0.04; Figure 4A4)] (21–24, 29, 30, 32, 36, 40–42, 46, 47). Specifically, the combination of PD-L1 and chemotherapy demonstrated a higher risk of causing all-grade arrhythmias (OR = 1.80, 95% CI [1.03, 3.14], p = 0.04, I^2 = 16%; Figure 4A1), whereas PD-1 combined with chemotherapy was more prone to inducing grade 3–5 arrhythmia (OR = 3.54, 95% CI [1.07, 11.68], p = 0.04, I^2 = 0%; Figure 4A3). Additionally, among BRCA patients, there was an increased risk of developing all-grade arrhythmia with PD-1/PD-L1 + chemotherapy (OR = 2.23, 95% CI [1.03, 4.85], p = 0.04; Figure 4A2). Notably, no significant heterogeneity was observed among the findings.

When comparing PD-1/PD-L1 inhibitors (nivolumab and pembrolizumab) with chemotherapy (specifically docetaxel), it was observed that nivolumab and pembrolizumab carried a lower risk of inducing hypotension; however, the difference was not statistically significant (Figure 4B) (30, 45, 57, 58, 61, 62, 65–67). Compared to placebo, PD-1/PD-L1 inhibitors showed a tendency toward a higher risk of all-grade arrhythmia (OR = 2.03, 95% CI [1.13, 3.64], p = 0.02, I^2 = 0%; Figure 5A), particularly within the PD-L1 subgroup (OR = 2.20, 95% CI [1.11, 4.34], p = 0.02, I^2 = 0%; Figure 5A1) and second-line treatment subgroup (OR = 2.00, 95% CI [1.10, 3.63], p = 0.02, I^2 = 0%; Figure 5A2) (68, 71, 72, 75, 76, 78, 83, 84). No heterogeneity was observed in the aforementioned results. The corresponding funnel plots are presented in Supplementary Data (Supplementary Figures 4, 5).

Risk of myocarditis

The adverse effects of myocarditis were reported in thirty-one clinical trials (17, 21–25, 28, 30, 31, 33, 37, 38, 49, 50, 52, 53, 56, 59, 62, 63, 67, 68, 70, 72–74, 78–81, 84, 91). No significant difference was observed in the risk of myocarditis between PD-1/PD-L1 monotherapy and chemotherapy (Figure 6A) (52, 53, 56, 59, 62, 63, 67, 80) or between PD-1/PD-L1 monotherapy and placebo (Figure 6B) (22, 68, 70, 72–74). However, the risk of all-grade myocarditis associated with chemotherapy was significantly lower than that associated with PD-1/PD-L1 + chemotherapy (OR = 2.42,

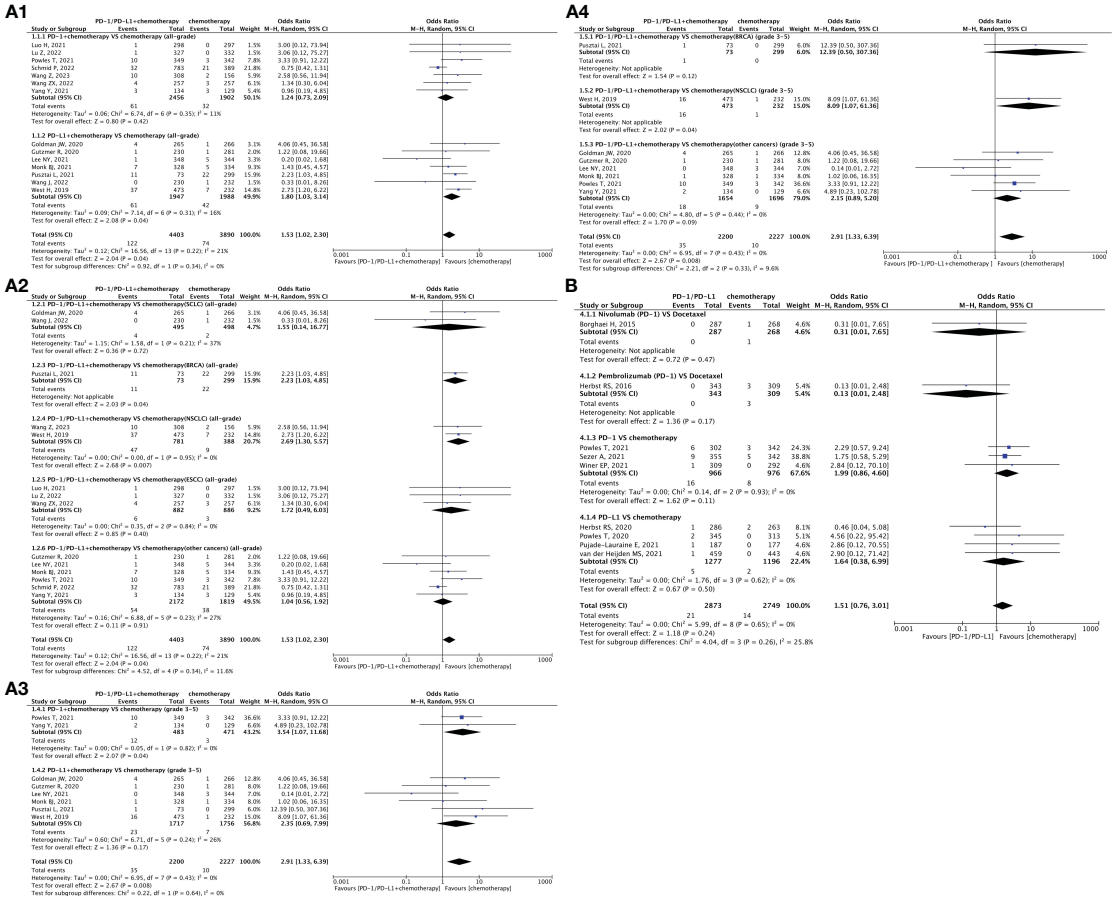


FIGURE 4
Forest plots depicting the risk of arrhythmia in PD-1/PD-L1 + chemotherapy versus chemotherapy. **(A1)** The risk of arrhythmia of all-grade: subgroup analyses were conducted according to PD-1/PD-L1. **(A2)** The risk of arrhythmia of all-grade: subgroup analyses were conducted according to types of tumors. **(A3)** The risk of arrhythmia of grade 3-5: subgroup analyses were conducted according to PD-1/PD-L1. **(A4)** The risk of arrhythmia of grade 3-5: subgroup analyses were conducted according to types of tumors. Forest plot depicting the risk of arrhythmia in PD-1/PD-L1 versus chemotherapy. **(B)** The risk of arrhythmia of all-grade: subgroup analysis was conducted according to PD-1/PD-L1.

95% CI [1.06, 5.54], p = 0.04, I^2 = 0%; Figure 6C) (17, 21–25, 28, 30, 31, 33, 37, 38, 50, 69, 91). No heterogeneity was found in the above result. The corresponding funnel plots are provided in the Supplementary Data (Supplementary Figures 6A–C).

Risk of cardiovascular toxicity associated with CTLA-4

Five clinical trials compared PD-1/PD-L1 + CTLA-4 with PD-1/PD-L1 (67, 85–88). Among them, four RCTs included PD-1, and the results suggested a significantly higher risk following combination therapy than following PD-1 monotherapy (OR = 2.02, 95% CI [1.12, 3.66], p = 0.02, I^2 = 0%; Figure 6D). Three clinical trials compared PD-1/PD-L1 + CTLA-4 versus chemotherapy (67, 89, 90). Only one of these studies involved PD-L1 combined with CTLA-4, and the results indicated a lower risk of cardiovascular toxicity for this treatment than chemotherapy (OR = 0.10, 95% CI [0.01, 0.79], p = 0.03; Figure 6E). The corresponding funnel plots are provided in the Supplementary Data (Supplementary Figure 6D, E).

Risk of myocardial infarction, heart failure, and pericardial diseases

There were twenty-two clinical trials reporting on myocardial infarction (15, 16, 23, 27, 30, 34, 36, 37, 39, 40, 46, 47, 52, 55, 62, 63, 65, 68, 70, 72, 78, 83, 84). Heart failure was reported in seventeen clinical trials (20, 22, 25, 30–32, 34, 37, 45–47, 49, 62, 65, 67, 68, 78). Only four clinical trials reported pericardial diseases (32, 68, 76, 78). No statistically significant differences were observed in the risk of all-grade heart failure between the PD-1/PD-L1 versus chemotherapy or PD-1/PD-L1 + chemotherapy versus chemotherapy groups (20, 22, 25, 31, 32, 34, 37, 45–47, 49, 62, 63, 65, 67), myocardial infarction (15, 16, 23, 27, 30, 34, 36, 37, 39, 40, 46, 47, 52, 55, 62, 63, 65), or pericardial diseases (32, 68, 76, 78). Additionally, no statistically significant difference was observed in

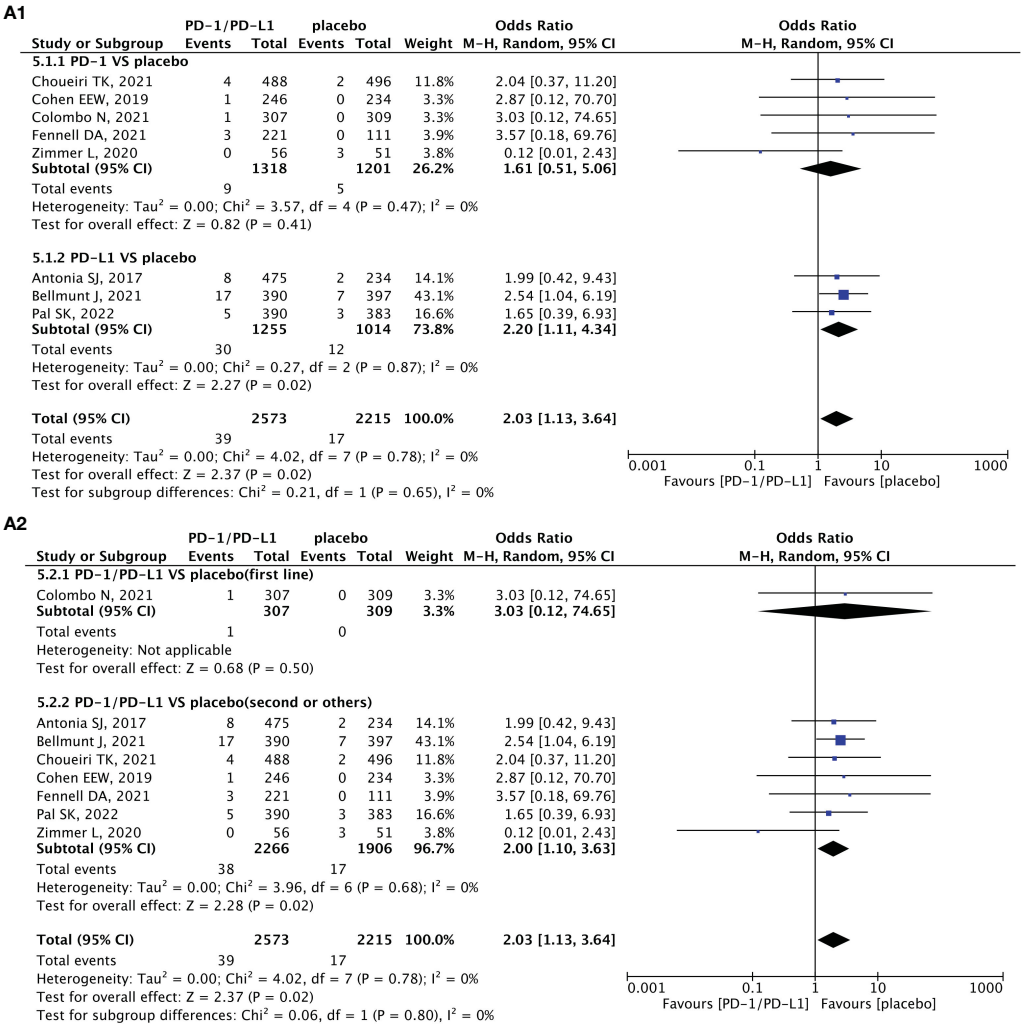


FIGURE 5
Forest plots depicting the risk of arrhythmia in PD-1/PD-L1 versus placebo. **(A1)** The risk of arrhythmia of all-grade: subgroup analyses were conducted according to PD-1/PD-L1. **(A2)** The risk of arrhythmia of all-grade: subgroup analyses were conducted according to treatment lines.

the risk of all-grade heart failure (78, 84) or myocardial infarction (68, 70, 72, 78, 83, 84) with PD-1/PD-L1 or placebo. The specific statistical data is presented in Tables 2, 3.

Risk of embolism, thrombosis, and vasculitis

Twenty-one clinical trials reported embolism (15, 20, 22, 27, 30, 36, 38, 40–42, 45–48, 55, 62, 66–68, 83, 84), eighteen reported thrombosis (15, 25–27, 30, 34, 36, 40, 47, 52, 55, 62, 67, 68, 71, 76, 78, 83) and thirteen reported vasculitis (19, 25, 27, 32, 51, 62, 64, 67, 68, 72, 80–84). No significant differences were observed in the risk of all-grade embolism between the PD-1/PD-L1 versus chemotherapy/placebo group and the PD-1/PD-L1 + chemotherapy versus chemotherapy group (15, 20, 22, 27, 30, 36, 38, 40–42, 45–48, 55, 62, 66–68, 83, 84), thrombosis (15, 25–27, 30, 34, 36, 40, 47, 52, 55, 62, 67, 68, 71, 76, 78, 83), or vasculitis (19, 25, 27, 32, 51, 62, 64, 67, 68, 72, 80–84). The specific statistical data is presented in Tables 2, 3.

Discussion

This meta-analysis included recently completed RCTs and provided updated information on the cardiotoxicity of PD-1/PD-L1 inhibitors. With a larger sample size and more detailed subgroups, this study provided several novel findings, indicating that the combination of PD-1/PD-L1 inhibitors with chemotherapy carries a considerably higher risk of myocarditis and hypotension than conventional chemotherapy alone. An increasing number of people are now paying attention to the cardiovascular toxicities of PD-1/PD-L1, and this study provides strong supporting evidence for these concerns. Additionally, it assists doctors in making preliminary assessments of the potential causes of these side effects when they detect cardiovascular issues in patients. This, in turn, allows for a more significant

10.3389/fimmu.2024.1255825

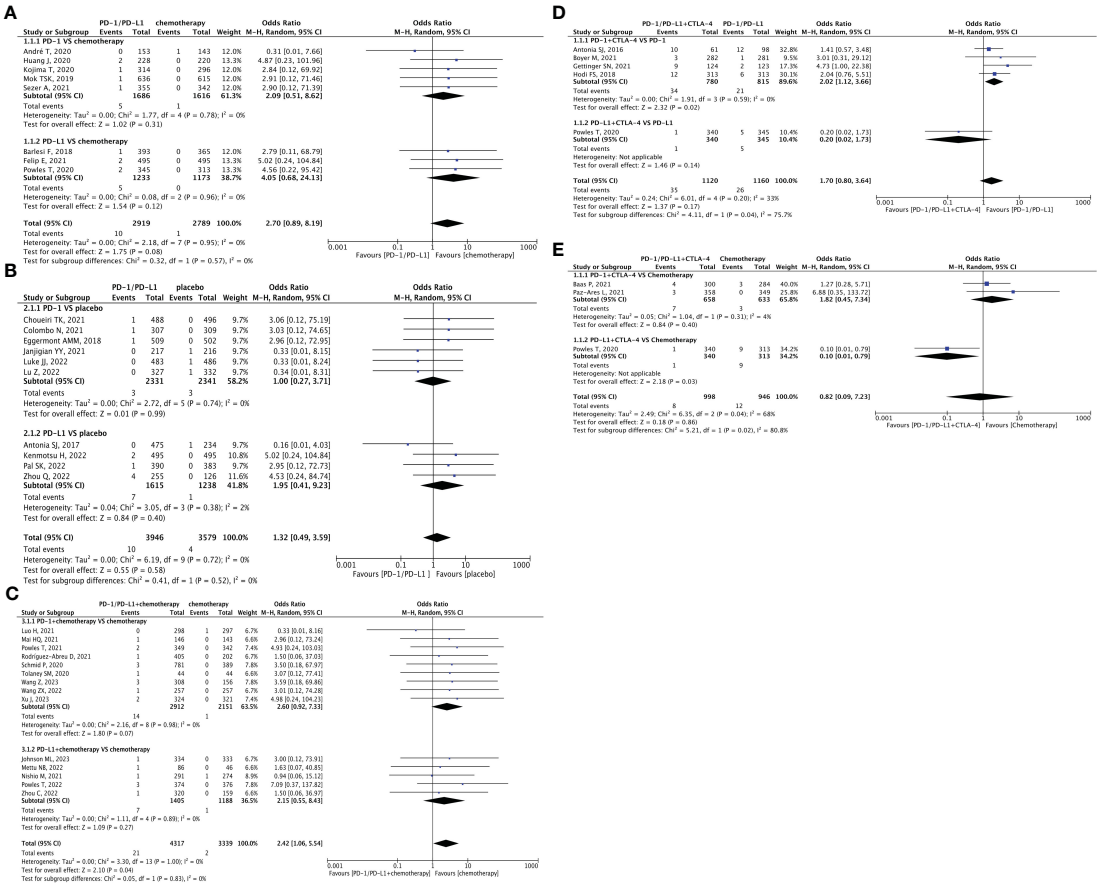


FIGURE 6
Forest plot depicting the risk of myocarditis in PD-1/PD-L1 versus chemotherapy. **(A)** The risk of myocarditis of all-grade: subgroup analysis was conducted according to PD-1/PD-L1. Forest plot depicting the risk of myocarditis in PD-1/PD-L1 versus placebo. **(B)** The risk of myocarditis of all-grade: subgroup analysis was conducted according to PD-1/PD-L1. Forest plot depicting the risk of myocarditis in PD-1/PD-L1 + chemotherapy versus chemotherapy. **(C)** The risk of myocarditis of all-grade: subgroup analysis was conducted according to PD-1/PD-L1. Forest plot depicting the risk of cardiovascular toxicities in PD-1/PD-L1 + CTLA-4 versus PD-1/PD-L1. **(D)** The risk of cardiovascular toxicities of all-grade: subgroup analysis was conducted according to PD-1/PD-L1. Forest plot depicting the risk of cardiovascular toxicities in PD-1/PD-L1 + CTLA-4 versus chemotherapy. **(E)** The risk of cardiovascular toxicities of all-grade: subgroup analysis was conducted according to PD-1/PD-L1.

TABLE 2 The risk of all-grade myocardial infarction, heart failure, pericardial diseases, embolism, thrombosis and vasculis: subgroup analyses were carried out based on PD-1/PD-L1.

Treatment regimen		PD-1/PD-L1+chemotherapy VS chemotherapy	PD-1/PD-L1 VS chemotherapy	PD-1/PD-L1 VS placebo
myocardial infraction	PD-1	OR=0.69, 95% CI [0.11, 4.40], p=0.70	OR=0.80, 95% CI [0.20, 3.29], p=0.76	OR=2.16, 95% CI [0.46, 10.09], p=0.33
	PD-L1	OR=0.86, 95% CI [0.32, 2.32], p=0.77	OR=0.92, 95% CI [0.10, 8.91], p=0.95	OR=1.91, 95% CI [0.32, 11.36], p=0.48
heart failure	PD-1	OR=1.43, 95% CI [0.33, 6.26], p=0.64	OR=0.72, 95% CI [0.16, 3.24], p=0.67	OR=2.04, 95% CI [0.18, 22.54], p=0.56
	PD-L1	OR=1.17, 95% CI [0.52, 2.63], p=0.70	OR=0.56, 95% CI [0.13, 2.30], p=0.42	OR=3.22, 95% CI [0.37, 28.43], p=0.29
pericardial diseases	PD-1	OR=0.96, 95% CI [0.06, 15.55], p=0.98	N/A	OR=3.82, 95% CI [0.44, 33.23], p=0.22
	PD-L1	OR=2.42, 95% CI [0.46, 12.82], p=0.03	N/A	OR=2.48, 95% CI [0.12, 51.79], p=0.56

(Continued)

TABLE 2 Continued

Treatment regimen		PD-1/PD-L1+chemotherapy VS chemotherapy	PD-1/PD-L1 VS chemotherapy	PD-1/PD-L1 VS placebo
emobolism	PD-1	OR=1.17, 95% CI [0.33, 4.13], p=0.81	OR=1.28, 95% CI [0.15, 10.61], p=0.82	OR=1.37, 95% CI [0.09, 19.88], p=0.82
	PD-L1	OR=1.05, 95% CI [0.66, 1.66], p=0.85	OR=1.49, 95% CI [0.18, 12.17], p=0.71	OR=1.03, 95% CI [0.26, 4.01], p=0.97
thrombosis	PD-1	OR=0.67, 95% CI [0.15, 2.98], p=0.60	OR=0.96, 95% CI [0.29, 3.15], p=0.95	OR=0.54, 95% CI [0.09, 3.47], p=0.52
	PD-L1	OR=1.74, 95% CI [0.79, 3.84], p=0.17	OR=0.18, 95% CI [0.01, 3.77], p=0.27	OR=0.58, 95% CI [0.12, 2.73], p=0.49
vasculitis	PD-1	OR=0.80, 95% CI [0.20, 3.29], p=0.76	OR=0.32, 95% CI [0.01, 7.89], p=0.49	OR=5.07, 95% CI [0.24, 105.95], p=0.30
	PD-L1	OR=0.80, 95% CI [0.20, 3.29], p=0.76	OR=0.83, 95% CI [0.17, 4.01], p=0.81	OR=1.02, 95% CI [0.24, 4.43], p=0.98

PD-1, Programmed cell death 1; PD-L1, Programmed cell death 1 ligand 1; OR, Odds Ratio; CI, Confidence Interval; N/A, not available.

TABLE 3 The risk of all-grade myocardial infarction, heart failure, pericardial diseases, embolism, thrombosis and vasculis: subgroup analyses were carried out based on treatment lines.

Treatment regimen		PD-1/PD-L1+chemotherapy VS chemotherapy	PD-1/PD-L1 VS chemotherapy	PD-1/PD-L1 VS placebo
myocardial infraction	first line	OR=0.82, 95% CI [0.34, 1.96], p=0.65	OR=1.22, 95% CI [0.30, 4.98], p=0.78	OR=1.62, 95% CI [0.20, 13.22], p=0.65
	second or others	N/A	OR=0.31, 95% CI [0.03, 3.03], p=0.32	OR=2.28, 95% CI [0.56, 9.25], p=0.25
heart failure	first line	OR=1.08, 95% CI [0.52, 2.25], p=0.84	OR=0.48, 95% CI [0.16, 1.45], p=0.19	N/A
	second or others	OR=4.05, 95% CI [0.45, 36.44], p=0.21	OR=4.67, 95% CI [0.22, 97.56], p=0.32	OR=2.62, 95% CI [0.52, 13.16], p=0.24
pericardial diseases	first line	OR=1.90, 95% CI [0.45, 7.93], p=0.38	N/A	N/A
	second or others	N/A	N/A	OR=3.30, 95% CI [0.57, 19.25], p=0.18
emobolism	first line	OR=1.06, 95% CI [0.69, 1.64], p=0.79	OR=1.21, 95% CI [0.26, 5.65], p=0.81	OR=0.33, 95% CI [0.01, 8.24], p=0.50
	second or others	N/A	OR=2.90, 95% CI [0.12, 71.42], p=0.51	OR=1.34, 95% CI [0.39, 4.65], p=0.64
thrombosis	first line	OR=1.41, 95% CI [0.70, 2.83], p=0.34	OR=0.64, 95% CI [0.20, 2.09], p=0.46	OR=0.54, 95% CI [0.09, 3.47], p=0.52
	second or others	N/A	OR=2.91, 95% CI [0.12, 71.76], p=0.51	OR=0.58, 95% CI [0.12, 2.73], p=0.49
vasculitis	first line	OR=1.51, 95% CI [0.86, 2.65], p=0.15	OR=0.82, 95% CI [0.17, 3.97], p=0.80	OR=1.35, 95% CI [0.09, 19.84], p=0.82
	second or others	N/A	OR=0.33, 95% CI [0.01, 8.19], p=0.50	OR=1.38, 95% CI [0.27, 7.19], p=0.70

PD-1: Programmed cell death 1; PD-L1: Programmed cell death 1 ligand 1; OR: Odds Ratio; CI: Confidence Interval; N/A, not available.

improvement in patient prognosis without compromising their anti-tumor treatment. Additionally, this study supports previous meta-analyses (7, 8) and preclinical evidence (9) (92, 93), highlighting the substantial increase in cardiovascular toxicities associated with PD-1/PD-L1 inhibitors. Flow cytometry and metabolomic assays revealed that PD-1/PD-L1 treatment in mice resulted in an increase in the overall lymphocyte count and changes in lipid metabolism within the cardiac tissue. These findings provide evidence that PD-1/PD-L1 disrupts immune homeostasis and energy production in the heart (9). Furthermore, single-cell sequencing revealed that endothelial cells constituted the majority of cells in the cardiac interstitium. Notably, these endothelial cells, along with cardiomyocytes and vascular endothelial cells, exhibit high levels of PD-L1 expression on their surfaces (92, 93). The use of PD-1/PD-L1 inhibitors can enable T cells to nonselectively target normal cells in the heart. Consequently, these factors increase the risk of cardiovascular toxicity.

This study demonstrated a notable increase in the risk of hypertension with the use of PD-1/PD-L1 inhibitors in combination with chemotherapy (22, 24, 25, 29, 31, 32, 35–37, 40, 42–47, 51). This trend was specifically observed in the subgroups of PD-1 inhibitors, first-line treatment, and urothelial carcinoma (UC), which has not been reported in previous meta-analyses. This phenomenon may be attributed to the immune-enhancing effects of PD-1/PD-L1 inhibitors. Owing to the high expression of PD-L1 on vascular endothelial cells (94), medications that enhance non-specific attack by T cells can also cause damage to vascular endothelial cells. This weakens the ability of cells to regulate blood pressure, leading to blood pressure fluctuations (95). However, the exact mechanism requires further investigation. In addition, while PD-1/PD-L1 did not exhibit statistically significant outcomes compared with chemotherapy or placebo, it can be inferred that PD-1/PD-L1 carries a reduced risk of inducing hypertension compared with the placebo group. This novel fact should be applied in clinical settings; when hypertension occurs after using PD-1/PD-L1, initial focus should be on identifying factors unrelated to this medication, such as potential drug interactions, unhealthy lifestyle choices, underlying health conditions, age, or gender.

Despite the lack of significant differences in the risk of heart failure among the treatment regimens in this study (20, 22, 25, 31, 32, 34, 37, 45–47, 49, 62, 63, 65, 67, 78, 84), the potential detrimental effects of PD-1/PD-L1 on cardiac function should not be overlooked. Michel et al. (9) observed that six of seven patients with stage IV progressive melanoma treated with PD-1 had decreased left ventricular ejection fraction (LVEF) and exhibited no significant signs of myocarditis four weeks after the first treatment. In addition, this study also concluded that PD-1/PD-L1 alone (68, 71, 75, 76, 78, 83, 84) or in combination with chemotherapy (25, 29, 31, 36, 40, 42) leads to an appreciably higher risk of hypotension, which was first reported in a meta-analysis, and could not be ruled out as a manifestation of reduced ejection following a decrease in cardiac function due to PD-1/PD-L1. This trend was particularly evident in the PD-1 + chemotherapy, PD-L1 alone, first-line treatment, or breast cancer subgroups. In addition to diminished cardiac pumping, hypotension cannot exclude the less common drug-induced hypersensitivity syndrome (DIHS), which results from excessive activation of T-cell function by immune checkpoint inhibitors (ICIs) (96). Vasodilation and increased permeability of the vessel wall lead to plasma extravasation, which reduces the intravascular blood volume and vasogenic hypotension. However, the exact mechanisms remain to be further elucidated.

In a comparison of PD-1/PD-L1 + chemotherapy versus chemotherapy (21–24, 29, 30, 32, 36, 40–42, 46, 47) and PD-1/PD-L1 versus placebo (68, 71, 72, 75, 76, 78, 83, 84), the use of PD-1/PD-L1-related therapy was associated with a considerably increased risk of arrhythmias. Particularly in the NSCLC subgroup, the combination of PD-1/PD-L1 inhibitors with chemotherapy led to a notably higher occurrence of all-grade or grade 3–5 arrhythmia (21, 36). This is broadly consistent with the results of previous meta-analyses or reviews by Herrmann and Liu et al. (7, 97). In addition, although there was no statistically significant difference in the risk of arrhythmia between PD-1/PD-L1 inhibitors and chemotherapy, the two PD-1 inhibitors, nivolumab and pembrolizumab, exhibited a lower risk of arrhythmia than docetaxel. Thus, more important with docetaxel is the prevention of several serious complications, such as myocardial ischemia due to abnormal heart rhythms. Additionally, positive results may be obtained concerning the apparent subjective discomfort experienced by the patients. Currently, physicians can easily ascertain abnormal heart rhythms and collect these data using Holter (24h dynamic electrocardiogram) or other devices. However, additional fundamental research is required to investigate the mechanisms by which PD-1/PD-L1 affects the cardiac conduction system.

Clinical evidence has indicated that immunotherapy can cause myocarditis, which should be taken seriously. The severity of immune-associated myocarditis varies from mild cases without apparent inflammation to severe cases that may be associated with heart failure, cardiogenic shock, and a high mortality rate in the case of rapidly progressing fulminant myocarditis (98, 99). Hu et al. concluded that immunotherapy drastically increased the risk of myocardial disease compared with conventional antitumor therapy (100). This is the first study to provide evidence that the combination of PD-1/PD-L1 inhibitors and chemotherapy is associated with an elevated risk of myocarditis (17, 21–25, 28, 30, 31, 33, 37, 38, 50, 69, 91). However, no positive results were obtained in the subgroup analysis, which should be conducted in additional RCTs. The exact mechanism of immune-associated myocarditis remains unclear, but some preclinical studies have made some conjectures, such as inflammation due to T-cell activation (101). Given the poor prognosis of this disease, more clinical data and basic research are required.

The combination of PD-1/PD-L1 and CTLA-4 blockade substantially enhances the immune responses and survival rates in certain cancers (102). However, it also increases the risk of adverse effects. This study found that the risk of cardiovascular toxicity following PD-1 combined with CTLA-4 treatment was noticeably higher than following PD-1 treatment alone, and these results were consistent with prior findings. Preclinical trials have revealed that when PD-1 on the surface of myocardial cells binds to PD-L1 on the surface of T lymphocytes, it prevents T lymphocytes from attacking the myocardium. CTLA-4, on the other hand, prevents lymphocyte

proliferation and spread. Therefore, the simultaneous inhibition of both pathways inevitably leads to indiscriminate T lymphocyte attacks on myocardial tissue, resulting in an increased risk of cardiovascular toxicity with the combined use of ICIs (103). Further research is required to decrease the occurrence of adverse event while maintaining the efficacy of the combination.

Cardiovascular toxicities associated with ICIs can be indicated by several biomarkers, including inflammatory markers such as C-reactive protein, erythrocyte sedimentation rate, and white blood cell count, as well as cardiac injury markers like troponin I, creatine kinase-MB, and brain natriuretic peptide. The development of ICI adverse effects is attributed to excessive enhancement of immune function, leading to inadvertent harm to normal cells. In response, we initially administered symptomatic treatments involving a variety of immunosuppressive agents, including corticosteroids, cytotoxic drugs, calcineurin inhibitors, and biologics. Secondly, the severity of the adverse effects needs to be assessed to determine whether temporary or permanent discontinuation of the medication is warranted. In addition, screening specific patients before initiating treatment can help prevent adverse effects. For instance, it is not recommended for individuals with autoimmune diseases, organ transplant recipients, patients with active hepatitis, or elderly patients to use ICIs. Furthermore, patients with pre-existing cardiovascular disorders should be monitored (104).

This meta-analysis further refined the cardiovascular toxicity of PD-1/PD-L1 through a comprehensive analysis of 69 RCTs. Moreover, there was no heterogeneity or insignificant heterogeneity among the RCTs included in this meta-analysis; thus, the results were reliable. However, this study had some limitations. Only 11% of the original studies searched reported the above cardiovascular toxicity events. In an initial comparison of morbidity data, PD-1/PD-L1 treatment resulted in a higher number of cardiovascular adverse events than conventional treatment. However, the final meta-analysis did not yield positive results. First, it can be inferred that PD-1/PD-L1 therapy is safe. However, it should also be noted that cardiovascular adverse events may not have received sufficient attention from doctors and patients, resulting in patients not seeking medical treatment promptly or first consulting physicians not collecting data on time. Therefore, due to the lack of sufficient sample size, this study was unable to collect baseline information for subgroup analyses of additional possible risk factors or to shed light on the specifics of chemotherapy. Furthermore, this meta-analysis exclusively included RCTs; most of these only reported a greater than certain percentage of cardiovascular toxicities, which may lead to the underreporting of some rare diseases with low incidence.

Conclusion

The combination of PD-1/PD-L1 with chemotherapy increases the risk of hypertension, hypotension, arrhythmia, and myocarditis. The incidence of hypotension or arrhythmia associated with PD-1/PD-L1 inhibitors was substantially higher than that associated with placebo. When hypertension is observed in patients receiving PD-1/PD-L1 inhibitors, factors other than ICIs should be considered as potential contributors in the first instance.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

CZ: Conceptualization, Data curation, Investigation, Methodology, Software, Writing – original draft. FW: Writing – original draft. WM: Writing – original draft. JZ: Investigation, Supervision, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Natural Science Foundation of Shandong Province (ZR2021MH245).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2024.1255825/full#supplementary-material

SUPPLEMENTARY FIGURE 1
The assessment of bias risk in the studies included in this meta-analysis.

SUPPLEMENTARY FIGURE 2
Funnel plots depicting the risk of hypertension in PD-1/PD-L1 + chemotherapy versus chemotherapy. **(A1)** The risk of hypertension of all-grade: subgroup analysis was conducted according to PD-1/PD-L1. **(A2)** The risk of hypertension of grade 3-5: subgroup analyses were conducted according to PD-1/PD-L1. **(A3)** The risk of hypertension of grade 3-5:

subgroup analyses were conducted according to types of tumors. Funnel plot depicting the risk of hypertension in PD-1/PD-L1 versus chemotherapy. **(B)** The risk of hypertension of all-grade: subgroup analysis was conducted according to PD-1/PD-L1. Funnel plot depicting the risk of hypertension in PD-1/PD-L1 versus placebo. **(C)** The risk of hypertension of all-grade: subgroup analysis was conducted according to PD-1/PD-L1.

SUPPLEMENTARY FIGURE 3

Funnel plots depicting the risk of hypotension in PD-1/PD-L1 + chemotherapy versus chemotherapy. **(A1)** The risk of hypotension of all-grade: subgroup analyses were conducted according to PD-1/PD-L1. **(A2)** The risk of hypotension of all-grade: subgroup analyses were conducted according to types of tumors. **(A3)** The risk of hypotension of grade 3-5: subgroup analysis was conducted according to PD-1/PD-L1. Funnel plot depicting the risk of hypotension in PD-1/PD-L1 versus placebo. **(B)** The risk of hypotension of all-grade: subgroup analysis was conducted according to PD-1/PD-L1. Funnel plot depicting the risk of hypotension in PD-1/PD-L1 versus chemotherapy. **(C)** The risk of hypotension of grade 3-5: subgroup analysis was conducted according to PD-1.

SUPPLEMENTARY FIGURE 4

Funnel plots depicting the risk of arrhythmia in PD-1/PD-L1 + chemotherapy versus chemotherapy. **(A1)** The risk of arrhythmia of all-grade: subgroup analyses were conducted according to PD-1/PD-L1. **(A2)** The risk of arrhythmia of all-grade: subgroup analyses were conducted according to types of tumors. **(A3)** The risk of arrhythmia of grade 3-5: subgroup analyses were conducted according to PD-1/PD-L1. **(A4)** The risk of arrhythmia of grade 3-5: subgroup analyses were conducted according to types of tumors. Funnel plot depicting the risk of arrhythmia in PD-1/PD-L1 versus chemotherapy. **(B)** The risk of arrhythmia of all-grade: subgroup analysis was conducted according to PD-1/PD-L1.

SUPPLEMENTARY FIGURE 5

Funnel plot depicting the risk of arrhythmia in PD-1/PD-L1 versus placebo. **(A1)** The risk of arrhythmia of all-grade: subgroup analyses were conducted according to PD-1/PD-L1. **(A2)** The risk of arrhythmia of all-grade: subgroup analyses were conducted according to treatment lines.

SUPPLEMENTARY FIGURE 6

Funnel plot depicting the risk of myocarditis in PD-1/PD-L1 versus chemotherapy. **(A)** The risk of myocarditis of all-grade: subgroup analysis was conducted according to PD-1/PD-L1. Funnel plot depicting the risk of myocarditis in PD-1/PD-L1 versus placebo. **(B)** The risk of myocarditis of all-grade: subgroup analysis was conducted according to PD-1/PD-L1. Funnel plot depicting the risk of myocarditis in PD-1/PD-L1 + chemotherapy versus chemotherapy. **(C)** The risk of myocarditis of all-grade: subgroup analysis was conducted according to PD-1/PD-L1. Funnel plot depicting the risk of cardiovascular toxicities in PD-1/PD-L1 + CTLA-4 versus PD-1/PD-L1. **(D)** The risk of cardiovascular toxicities of all-grade: subgroup analysis was conducted according to PD-1/PD-L1. Funnel plot depicting the risk of cardiovascular toxicities in PD-1/PD-L1 + CTLA-4 versus chemotherapy. **(E)** The risk of cardiovascular toxicities of all-grade: subgroup analysis was conducted according to PD-1/PD-L1.

References

1. Kraehenbuehl L, Weng C-H, Eghbali S, Wolchok JD, Merghoub T. Enhancing immunotherapy in cancer by targeting emerging immunomodulatory pathways. *Nat Rev Clin Oncol* (2022) 19(1):37–50. doi: 10.1038/s41571-021-00552-7

2. Boussiotis VA. Molecular and biochemical aspects of the PD-1 checkpoint pathway. *N Engl J Med* (2016) 375(18):1767–78. doi: 10.1056/NEJMra1514296

3. Joseph A, Simonaggio A, Stoclin A, Vieillard-Baron A, Geri G, Oudard S, et al. Immune-related adverse events: a retrospective look into the future of oncology in the intensive care unit. *Ann Intensive Care* (2020) 10(1):143. doi: 10.1186/s13613-020-00761-w

4. Brahmer JR, Abu-Sbeih H, Ascierto PA, Brufsky J, Cappelli LC, Cortazar FB, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. *J For Immunotherapy Cancer* (2021) 9(6). doi: 10.1136/jitc-2021-002435

5. Thuny F, Naidoo J, Neilan TG. Cardiovascular complications of immune checkpoint inhibitors for cancer. *Eur Heart J* (2022) 43(42):4458–68. doi: 10.1093/eurheartj/ehac456

6. Salem J-E, Manouchehri A, Moey M, Lebrun-Vignes B, Bastarache L, Pariente A, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. *Lancet Oncol* (2018) 19 (12):1579–89. doi: 10.1016/S1470-2045(18)30608-9

7. Liu S, Gao W, Ning Y, Zou X, Zhang W, Zeng L, et al. Cardiovascular toxicity with PD-1/PD-L1 inhibitors in cancer patients: A systematic review and meta-analysis. *Front Immunol* (2022) 13:908173. doi: 10.3389/fimmu.2022.908173

8. Kennedy LB, Salama AKS. A review of cancer immunotherapy toxicity. *CA Cancer J Clin* (2020) 70(2):86–104. doi: 10.3322/caac.21596

9. Michel L, Helfrich I, Hendgen-Cotta UB, Mincu R-I, Korste S, Mrotzek SM, et al. Targeting early stages of cardiotoxicity from anti-PD1 immune checkpoint inhibitor therapy. *Eur Heart J* (2022) 43(4):316–29. doi: 10.1093/eurheartj/ehab430

10. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PloS Med* (2009) 6(7): e1000097. doi: 10.1371/journal.pmed.1000097

11. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* (1997) 315(7109):629–34. doi: 10.1136/bmj.315.7109.629

12. Delgado-Rodríguez M, Sillero-Arenas M. Systematic review and meta-analysis. *Med Intensiva (Engl Ed)* (2018) 42(7):444–53. doi: 10.1016/j.medin.2017.10.003

13. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* (2003) 327(7414):557–60. doi: 10.1136/bmj.327.7414.557

14. Norton EC, Dowd BE, Maciejewski ML. Odds ratios-current best practice and use. *JAMA.* (2018) 320(1):84–5. doi: 10.1001/jama.2018.6971

15. Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med* (2022) 386(21):1973–85. doi: 10.1056/NEJMoa2202170

16. Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol* (2016) 17(11):1497–508. doi: 10.1016/S1470-2045(16)30498-3

17. Rodríguez-Abreu D, Powell SF, Hochmair MJ, Gadgeel S, Esteban E, Felip E, et al. Pemetrexed plus platinum with or without pembrolizumab in patients with previously untreated metastatic nonsquamous NSCLC: protocol-specified final analysis from KEYNOTE-189. *Ann Oncol* (2021) 32(7):881–95. doi: 10.1016/j.annonc.2021.04.008

18. Garassino MC, Gadgeel S, Speranza G, Felip E, Esteban E, Dómine M, et al. Pembrolizumab plus pemetrexed and platinum in nonsquamous non-small-cell lung cancer: 5-year outcomes from the phase 3 KEYNOTE-189 study. *J Clin Oncol* (2023) 41 (11):1992–8. doi: 10.1200/jco.22.01989

19. Novello S, Kowalski DM, Luft A, Gümüş M, Vicente D, Mazières J, et al. Pembrolizumab plus chemotherapy in squamous non-small-cell lung cancer: 5-year update of the phase III KEYNOTE-407 study. *J Clin Oncol* (2023) 41(11):1999–2006. doi: 10.1200/JCO.22.01990

20. Zhou C, Chen G, Huang Y, Zhou J, Lin L, Feng J, et al. Camrelizumab plus carboplatin and pemetrexed versus chemotherapy alone in chemotherapy-naive patients with advanced non-squamous non-small-cell lung cancer (CameL): a randomised, open-label, multicentre, phase 3 trial. *Lancet Respir Med* (2021) 9 (3):305–14. doi: 10.1016/S2213-2600(20)30365-9

21. Wang Z, Wu L, Li B, Cheng Y, Li X, Wang X, et al. Toripalimab plus chemotherapy for patients with treatment-naive advanced non-small-cell lung cancer: A multicenter randomized phase III trial (CHOICE-01). *J Clin Oncol* (2023) 41(3):651–63. doi: 10.1200/JCO.22.00727

22. Lu Z, Wang J, Shu Y, Liu L, Kong L, Yang L, et al. Sintilimab versus placebo in combination with chemotherapy as first line treatment for locally advanced or metastatic oesophageal squamous cell carcinoma (ORIENT-15): multicentre, randomised, double blind, phase 3 trial. *BMJ.* (2022) 377:e068714. doi: 10.1136/bmj-2021-068714

23. Luo H, Lu J, Bai Y, Mao T, Wang J, Fan Q, et al. Effect of camrelizumab vs placebo added to chemotherapy on survival and progression-free survival in patients with advanced or metastatic esophageal squamous cell carcinoma: the ESCORT-1st randomized clinical trial. *JAMA.* (2021) 326(10):916–25. doi: 10.1001/jama.2021.12836

24. Wang Z-X, Cui C, Yao J, Zhang Y, Li M, Feng J, et al. Toripalimab plus chemotherapy in treatment-naïve, advanced esophageal squamous cell carcinoma (JUPITER-06): A multi-center phase 3 trial. *Cancer Cell* (2022) 40(3):277–88.e3. doi: 10.1016/j.ccell.2022.02.007

25. Xu J, Kato K, Raymond E, Hubner RA, Shu Y, Pan Y, et al. Tislelizumab plus chemotherapy versus placebo plus chemotherapy as first-line treatment for advanced or metastatic oesophageal squamous cell carcinoma (RATIONALE-306): a global, randomised, placebo-controlled, phase 3 study. *Lancet Oncol* (2023) 24(5):483–95. doi: 10.1016/S1470-2045(23)00108-0

26. Janjigian YY, Shitara K, Moehler M, Garrido M, Salman P, Shen L, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet* (2021) 398(10294):27–40. doi: 10.1016/S0140-6736(21)00797-2

27. Kang Y-K, Chen L-T, Ryu M-H, Oh D-Y, Oh SC, Chung HC, et al. Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer (ATTRACTION-4): a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* (2022) 23(2):234–47. doi: 10.1016/S1470-2045(21)00692-6

28. Tolaney SM, Barroso-Sousa R, Keenan T, Li T, Trippa L, Vaz-Luis I, et al. Effect of eribulin with or without pembrolizumab on progression-free survival for patients with hormone receptor-positive, ERBB2-negative metastatic breast cancer: A randomized clinical trial. *JAMA Oncol* (2020) 6(10):1598–605. doi: 10.1001/jamaoncol.2020.3524

29. Schmid P, Cortes J, Dent R, Pusztai L, McArthur H, Kümmel S, et al. Event-free survival with pembrolizumab in early triple-negative breast cancer. *N Engl J Med* (2022) 386(6):556–67. doi: 10.1056/NEJMoa2112651

30. Powles T, Csőszi T, Özgüroğlu M, Matsubara N, Géczi L, Cheng SYS, et al. Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): a randomised, open-label, phase 3 trial. *Lancet Oncol* (2021) 22(7):931–45. doi: 10.1016/S1470-2045(21)00152-2

31. Mai H-Q, Chen Q-Y, Chen D, Hu C, Yang K, Wen J, et al. Toripalimab or placebo plus chemotherapy as first-line treatment in advanced nasopharyngeal carcinoma: a multicenter randomized phase 3 trial. *Nat Med* (2021) 27(9):1536–43. doi: 10.1038/s41591-021-01444-0

32. Yang Y, Qu S, Li J, Hu C, Xu M, Li W, et al. Camrelizumab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (CAPTAIN-1st): a multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol* (2021) 22(8):1162–74. doi: 10.1016/S1470-2045(21)00302-8

33. Nishio M, Saito H, Goto K, Watanabe S, Sueoka-Aragane N, Okuma Y, et al. IMpower132: Atezolizumab plus platinum-based chemotherapy vs chemotherapy for advanced NSCLC in Japanese patients. *Cancer Sci* (2021) 112(4):1534–44. doi: 10.1111/cas.14817

34. Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med* (2018) 378(24):2288–301. doi: 10.1056/NEJMoa1716948

35. Reck M, Wehler T, Orlandi F, Nogami N, Barone C, Moro-Sibilot D, et al. Safety and patient-reported outcomes of atezolizumab plus chemotherapy with or without bevacizumab versus bevacizumab plus chemotherapy in non-small-cell lung cancer. *J Clin Oncol* (2020) 38(22):2530–42. doi: 10.1200/JCO.19.03158

36. West H, McCleod M, Hussein M, Morabito A, Rittmeyer A, Conter HJ, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* (2019) 20(7):924–37. doi: 10.1016/S1470-2045(19)30167-6

37. Zhou C, Wang Z, Sun Y, Cao L, Ma Z, Wu R, et al. Sugemalimab versus placebo, in combination with platinum-based chemotherapy, as first-line treatment of metastatic non-small-cell lung cancer (GEMSTONE-302): interim and final analyses of a double-blind, randomised, phase 3 clinical trial. *Lancet Oncol* (2022) 23(2):220–33. doi: 10.1016/S1470-2045(21)00650-1

38. Johnson ML, Cho BC, Luft A, Alatorre-Alexander J, Geater SL, Laktionov K, et al. Durvalumab with or without tremelimumab in combination with chemotherapy as first-line therapy for metastatic non-small-cell lung cancer: the phase III POSEIDON study. *J Clin Oncol* (2023) 41(6):1213–27. doi: 10.1200/JCO.22.00975

39. Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet.* (2019) 394(10212):1929–39. doi: 10.1016/S0140-6736(19)32222-6

40. Goldman JW, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol* (2021) 22(1):51–65. doi: 10.1016/S1470-2045(20)30539-8

41. Wang J, Zhou C, Yao W, Wang Q, Min X, Chen G, et al. Adebrelimab or placebo plus carboplatin and etoposide as first-line treatment for extensive-stage small-cell lung cancer (CAPSTONE-1): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* (2022) 23(6):739–47. doi: 10.1016/S1470-2045(22)00224-8

42. Pusztai L, Yau C, Wolf DM, Han HS, Du L, Wallace AM, et al. Durvalumab with olaparib and paclitaxel for high-risk HER2-negative stage II/III breast cancer: Results from the adaptively randomized I-SPY2 trial. *Cancer Cell* (2021) 39(7):989–98.e5. doi: 10.1016/j.ccell.2021.05.009

43. Emens LA, Adams S, Barrios CH, Diéras V, Iwata H, Loi S, et al. First-line atezolizumab plus nab-paclitaxel for unresectable, locally advanced, or metastatic triple-negative breast cancer: IMpassion130 final overall survival analysis. *Ann Oncol* (2021) 32(8):983–93. doi: 10.1016/j.annonc.2021.05.355

44. Mittendorf EA, Zhang H, Barrios CH, Saji S, Jung KH, Hegg R, et al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. *Lancet.* (2020) 396(10257):1090–100. doi: 10.1016/S0140-6736(20)31953-X

45. Pujade-Lauraine E, Fujiwara K, Ledermann JA, Oza AM, Kristeleit R, Ray-Coquard I-L, et al. Avelumab alone or in combination with chemotherapy versus chemotherapy alone in platinum-resistant or platinum-refractory ovarian cancer (JAVELIN Ovarian 200): an open-label, three-arm, randomised, phase 3 study. *Lancet Oncol* (2021) 22(7):1034–46. doi: 10.1016/S1470-2045(21)00216-3

46. Lee NY, Ferris RL, Psyrri A, Haddad RI, Tahara M, Bourhis J, et al. Avelumab plus standard-of-care chemoradiotherapy versus chemoradiotherapy alone in patients with locally advanced squamous cell carcinoma of the head and neck: a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. *Lancet Oncol* (2021) 22(4):450–62. doi: 10.1016/S1470-2045(20)30737-3

47. Monk BJ, Colombo N, Oza AM, Fujiwara K, Birrer MJ, Randall L, et al. Chemotherapy with or without avelumab followed by avelumab maintenance versus chemotherapy alone in patients with previously untreated epithelial ovarian cancer (JAVELIN Ovarian 100): an open-label, randomised, phase 3 trial. *Lancet Oncol* (2021) 22(9):1275–89. doi: 10.1016/S1470-2045(21)00342-9

48. Moore KN, Bookman M, Sehouli J, Miller A, Anderson C, Scambia G, et al. Atezolizumab, bevacizumab, and chemotherapy for newly diagnosed stage III or IV ovarian cancer: placebo-controlled randomized phase III trial (IMagyn050/GOG 3015/ENGOT-OV39). *J Clin Oncol* (2021) 39(17):1842–55. doi: 10.1200/JCO.21.00306

49. Powles T, Yuen KC, Gillessen S, Kadel EE, Rathkopf D, Matsubara N, et al. Atezolizumab with enzalutamide versus enzalutamide alone in metastatic castration-resistant prostate cancer: a randomized phase 3 trial. *Nat Med* (2022) 28(1):144–53. doi: 10.1038/s41591-021-01600-6

50. Mettu NB, Ou F-S, Zemla TJ, Halfdanarson TR, Lenz H-J, Breakstone RA, et al. Assessment of capecitabine and bevacizumab with or without atezolizumab for the treatment of refractory metastatic colorectal cancer: A randomized clinical trial. *JAMA Netw Open* (2022) 5(2):e2149040. doi: 10.1001/jamanetworkopen.2021.49040

51. Galsky MD, Arija JÁA, Bamias A, Davis ID, De Santis M, Kikuchi E, et al. Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet.* (2020) 395(10236):1547–57. doi: 10.1016/S0140-6736(20)30230-0

52. Huang J, Xu J, Chen Y, Zhuang W, Zhang Y, Chen Z, et al. Camrelizumab versus investigator's choice of chemotherapy as second-line therapy for advanced or metastatic oesophageal squamous cell carcinoma (ESCORT): a multicentre, randomised, open-label, phase 3 study. *Lancet Oncol* (2020) 21(6):832–42. doi: 10.1016/S1470-2045(20)30110-8

53. Kojima T, Shah MA, Muro K, Francois E, Adenis A, Hsu C-H, et al. Randomized phase III KEYNOTE-181 study of pembrolizumab versus chemotherapy in advanced esophageal cancer. *J Clin Oncol* (2020) 38(35):4138–48. doi: 10.1200/JCO.20.01888

54. Chan ATC, Lee VHF, Hong RL, Ahn MJ, Chong WQ, Kim SB, et al. Pembrolizumab monotherapy versus chemotherapy in platinum-pretreated, recurrent or metastatic nasopharyngeal cancer (KEYNOTE-122): an open-label, randomized, phase III trial. *Ann Oncol* (2023) 34(3):251–61. doi: 10.1016/j.annonc.2022.12.007

55. Diaz LA, Shiu K-K, Kim T-W, Jensen BV, Jensen LH, Punt C, et al. Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study. *Lancet Oncol* (2022) 23(5):659–70. doi: 10.1016/S1470-2045(22)00197-8

56. André T, Shiu K-K, Kim TW, Jensen BV, Jensen LH, Punt C, et al. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. *N Engl J Med* (2020) 383(23):2207–18. doi: 10.1056/NEJMoa2017699

57. Winer EP, Lipatov O, Im S-A, Goncalves A, Muñoz-Couselo E, Lee KS, et al. Pembrolizumab versus investigator-choice chemotherapy for metastatic triple-negative breast cancer (KEYNOTE-119): a randomised, open-label, phase 3 trial. *Lancet Oncol* (2021) 22(4):499–511. doi: 10.1016/S1470-2045(20)30754-3

58. Herbst RS, Baas P, Kim D-W, Felip E, Pérez-Gracia JL, Han J-Y, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet.* (2016) 387(10027):1540–50. doi: 10.1016/S0140-6736(15)01281-7

59. Mok TSK, Wu Y-L, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet.* (2019) 393(10183):1819–30. doi: 10.1016/S0140-6736(18)32409-7

60. de Castro G, Kudaba I, Wu Y-L, Lopes G, Kowalski DM, Turna HZ, et al. Five-year outcomes with pembrolizumab versus chemotherapy as first-line therapy in

patients with non-small-cell lung cancer and programmed death ligand-1 tumor proportion score ≥ 1% in the KEYNOTE-042 study. *J Clin Oncol* (2023) 41 (11):1986–91. doi: 10.1200/JCO.21.02885

61. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* (2015) 373(17):1627–39. doi: 10.1056/NEJMoa1507643

62. Sezer A, Kilickap S, Gümüş M, Bondarenko I, Özgüroğlu M, Gogishvili M, et al. Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial. *Lancet.* (2021) 397(10274):592–604. doi: 10.1016/S0140-6736(21)00228-2

63. Barlesi F, Vansteenkiste J, Spigel D, Ishii H, Garassino M, de Marinis F, et al. Avelumab versus docetaxel in patients with platinum-treated advanced non-small-cell lung cancer (JAVELIN Lung 200): an open-label, randomised, phase 3 study. *Lancet Oncol* (2018) 19(11):1468–79. doi: 10.1016/S1470-2045(18)30673-9

64. Jassem J, de Marinis F, Giaccone G, Vergnenegre A, Barrios CH, Morise M, et al. Updated overall survival analysis from IMpower110: atezolizumab versus platinum-based chemotherapy in treatment-naive programmed death-ligand 1-selected NSCLC. *J Thorac Oncol Off Publ Int Assoc For Study Lung Canc* (2021) 16(11):1872–82. doi: 10.1016/j.jtho.2021.06.019

65. Herbst RS, Giaccone G, de Marinis F, Reinmuth N, Vergnenegre A, Barrios CH, et al. Atezolizumab for first-line treatment of PD-L1-selected patients with NSCLC. *N Engl J Med* (2020) 383(14):1328–39. doi: 10.1056/NEJMoa1917346

66. van der Heijden MS, Loriot Y, Durán I, Ravaud A, Retz M, Vogelzang NJ, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma: A long-term overall survival and safety update from the phase 3 IMvigor211 clinical trial. *Eur Urol* (2021) 80(1):7–11. doi: 10.1016/j.eururo.2021.03.024

67. Powles T, van der Heijden MS, Castellano D, Galsky MD, Loriot Y, Petrylak DP, et al. Durvalumab alone and durvalumab plus tremelimumab versus chemotherapy in previously untreated patients with unresectable, locally advanced or metastatic urothelial carcinoma (DANUBE): a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol* (2020) 21(12):1574–88. doi: 10.1016/S1470-2045(20)30541-6

68. Choueiri TK, Tomczak P, Park SH, Venugopal B, Ferguson T, Chang Y-H, et al. Adjuvant pembrolizumab after nephrectomy in renal-cell carcinoma. *N Engl J Med* (2021) 385(8):683–94. doi: 10.1056/NEJMoa2106391

69. Powles T, Tomczak P, Park SH, Venugopal B, Ferguson T, Symeonides SN, et al. Pembrolizumab versus placebo as post-nephrectomy adjuvant therapy for clear cell renal cell carcinoma (KEYNOTE-564): 30-month follow-up analysis of a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* (2022) 23 (9):1133–44. doi: 10.1016/S1470-2045(22)00487-9

70. Janjigian YY, Kawazoe A, Yañez P, Li N, Lonardi S, Kolesnik O, et al. The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer. *Nature* (2021) 600(7890):727–30. doi: 10.1038/s41586-021-04161-3

71. Cohen EEW, Soulières D, Le Tourneau C, Dinis J, Licitra L, Ahn M-J, et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. *Lancet.* (2019) 393(10167):156–67. doi: 10.1016/S0140-6736(18)31999-8

72. Colombo N, Dubot C, Lorusso D, Caceres MV, Hasegawa K, Shapira-Frommer R, et al. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. *N Engl J Med* (2021) 385(20):1856–67. doi: 10.1056/NEJMoa2112435

73. Eggermont AMM, Blank CU, Mandala M, Long GV, Atkinson VG, Dalle S, et al. Longer follow-up confirms recurrence-free survival benefit of adjuvant pembrolizumab in high-risk stage III melanoma: updated results from the EORTC 1325-MG/KEYNOTE-054 trial. *J Clin Oncol* (2020) 38(33):3925–36. doi: 10.1200/JCO.20.02110

74. Long GV, Luke JJ, Khattak MA, de la Cruz Merino L, Del Vecchio M, Rutkowski P, et al. Pembrolizumab versus placebo as adjuvant therapy in resected stage IIB or IIC melanoma (KEYNOTE-716): distant metastasis-free survival results of a multicentre, double-blind, randomised, phase 3 trial. *Lancet Oncol* (2022) 23(11):1378–88. doi: 10.1016/S1470-2045(22)00559-9

75. Zimmer L, Livingstone E, Hassel JC, Fluck M, Eigentler T, Loquai C, et al. Adjuvant nivolumab plus ipilimumab or nivolumab monotherapy versus placebo in patients with resected stage IV melanoma with no evidence of disease (IMMUNED): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet.* (2020) 395 (10236):1558–68. doi: 10.1016/S0140-6736(20)30417-7

76. Fennell DA, Ewings S, Ottensmeier C, Califano R, Hanna GG, Hill K, et al. Nivolumab versus placebo in patients with relapsed Malignant mesothelioma (CONFIRM): a multicentre, double-blind, randomised, phase 3 trial. *Lancet Oncol* (2021) 22(11):1530–40. doi: 10.1016/S1470-2045(21)00471-X

77. Sugawara S, Lee JS, Kang JH, Kim HR, Inui N, Hida T, et al. Nivolumab with carboplatin, paclitaxel, and bevacizumab for first-line treatment of advanced nonsquamous non-small-cell lung cancer. *Ann Oncol* (2021) 32(9):1137–47. doi: 10.1016/j.annonc.2021.06.004

78. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med* (2017) 377(20):1919–29. doi: 10.1056/NEJMoa1709937

79. Zhou Q, Chen M, Jiang O, Pan Y, Hu D, Lin Q, et al. Sugemalimab versus placebo after concurrent or sequential chemoradiotherapy in patients with locally advanced, unresectable, stage III non-small-cell lung cancer in China (GEMSTONE-301): interim results of a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol* (2022) 23(2):209–19. doi: 10.1016/S1470-2045(21)00630-6

80. Felip E, Altorki N, Zhou C, Csőszi T, Vynnychenko I, Goloborodko O, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. *Lancet.* (2021) 398(10308):1344–57. doi: 10.1016/S0140-6736(21)02098-5

81. Kenmotsu H, Sugawara S, Watanabe Y, Saito H, Okada M, Chen-Yoshikawa TF, et al. Adjuvant atezolizumab in Japanese patients with resected stage IB-IIIA non-small cell lung cancer (IMpower010). *Cancer Sci* (2022) 113(12):4327–38. doi: 10.1111/cas.15564

82. Horn L, Mansfield AS, Szczęsna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med* (2018) 379(23):2220–9. doi: 10.1056/NEJMoa1809064

83. Bellmunt J, Hussain M, Gschwend JE, Albers P, Oudard S, Castellano D, et al. Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* (2021) 22(4):525–37. doi: 10.1016/S1470-2045(21)00004-8

84. Pal SK, Uzzo R, Karam JA, Master VA, Donskov F, Suarez C, et al. Adjuvant atezolizumab versus placebo for patients with renal cell carcinoma at increased risk of recurrence following resection (IMmotion010): a multicentre, randomised, double-blind, phase 3 trial. *Lancet.* (2022) 400(10358):1103–16. doi: 10.1016/S0140-6736(22)01658-0

85. Antonia SJ, López-Martin JA, Bendell J, Ott PA, Taylor M, Eder JP, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol* (2016) 17 (7):883–95. doi: 10.1016/S1470-2045(16)30098-5

86. Boyer M, Şendur MAN, Rodríguez-Abreu D, Park K, Lee DH, Çiçin I, et al. Pembrolizumab plus ipilimumab or placebo for metastatic non-small-cell lung cancer with PD-L1 tumor proportion score ≥ 50%: randomized, double-blind phase III KEYNOTE-598 study. *J Clin Oncol* (2021) 39(21):2327–38. doi: 10.1200/JCO.20.03579

87. Gettinger SN, Redman MW, Bazhenova L, Hirsch FR, Mack PC, Schwartz LH, et al. Nivolumab plus ipilimumab vs nivolumab for previously treated patients with stage IV squamous cell lung cancer: the lung-MAP S1400I phase 3 randomized clinical trial. *JAMA Oncol* (2021) 7(9):1368–77. doi: 10.1001/jamaoncol.2021.2209

88. Hodi FS, Chiarion-Sileni V, Gonzalez R, Grob J-J, Rutkowski P, Cowey CL, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. *Lancet Oncol* (2018) 19(11):1480–92. doi: 10.1016/S1470-2045(18)30700-9

89. Baas P, Scherpereel A, Nowak AK, Fujimoto N, Peters S, Tsao AS, et al. First-line nivolumab plus ipilimumab in unresectable Malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. *Lancet.* (2021) 397(10272):375–86. doi: 10.1016/S0140-6736(20)32714-8

90. Paz-Ares L, Ciuleanu T-E, Cobo M, Schenker M, Zurawski B, Menezes J, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. *Lancet Oncol* (2021) 22(2):198–211. doi: 10.1016/S1470-2045(20)30641-0

91. Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, et al. Pembrolizumab for early triple-negative breast cancer. *N Engl J Med* (2020) 382 (9):810–21. doi: 10.1056/NEJMoa1910549

92. Ren Z, Yu P, Li D, Li Z, Liao Y, Wang Y, et al. Single-cell reconstruction of progression trajectory reveals intervention principles in pathological cardiac hypertrophy. *Circulation.* (2020) 141(21):1704–19. doi: 10.1161/CIRCULATIONAHA.119.043053

93. Wang L, Yu P, Zhou B, Song J, Li Z, Zhang M, et al. Single-cell reconstruction of the adult human heart during heart failure and recovery reveals the cellular landscape underlying cardiac function. *Nat Cell Biol* (2020) 22(1):108–19. doi: 10.1038/s41556-019-0446-7

94. Liu S, Qin T, Liu Z, Wang J, Jia Y, Feng Y, et al. anlotinib alters tumor immune microenvironment by downregulating PD-L1 expression on vascular endothelial cells. *Cell Death Dis* (2020) 11(5):309. doi: 10.1038/s41419-020-2511-3

95. Magder S. The meaning of blood pressure. *Crit Care* (2018) 22(1):257. doi: 10.1186/s13054-018-2171-1

96. Mirza S, Hill E, Ludlow SP, Nanjappa S. Checkpoint inhibitor-associated drug reaction with eosinophilia and systemic symptom syndrome. *Melanoma Res* (2017) 27 (3):271–3. doi: 10.1097/CMR.0000000000000326

97. Herrmann J. Adverse cardiac effects of cancer therapies: cardiotoxicity and arrhythmia. *Nat Rev Cardiol* (2020) 17(8):474–502. doi: 10.1038/s41569-020-0348-1

98. Andres MS, Ramalingam S, Rosen SD, Baksi J, Khattar R, Kirichenko Y, et al. The spectrum of cardiovascular complications related to immune-checkpoint inhibitor treatment : Including myocarditis and the new entity of non inflammatory left ventricular dysfunction. *Cardiooncology.* (2022) 8(1):21. doi: 10.1186/s40959-022-00147-w

99. Dong H, Qi Y, Kong X, Wang Z, Fang Y, Wang J. PD-1/PD-L1 inhibitor-associated myocarditis: epidemiology, characteristics, diagnosis, treatment, and potential mechanism. *Front Pharmacol* (2022) 13:835510. doi: 10.3389/fphar.2022.835510

100. Hu J, Tian R, Ma Y, Zhen H, Ma X, Su Q, et al. Risk of cardiac adverse events in patients treated with immune checkpoint inhibitor regimens: A systematic review and meta-analysis. *Front Oncol* (2021) 11:645245. doi: 10.3389/fonc.2021.645245

101. Lichtman AH. The heart of the matter: protection of the myocardium from T cells. *J Autoimmun* (2013) 45:90–6. doi: 10.1016/j.jaut.2013.05.004

102. Rotte A. Combination of CTLA-4 and PD-1 blockers for treatment of cancer. *J Exp Clin Cancer Res* (2019) 38(1):255. doi: 10.1186/s13046-019-1259-z

103. Love VA, Grabie N, Duramad P, Stavrakis G, Sharpe A, Lichtman A. CTLA-4 ablation and interleukin-12 driven differentiation synergistically augment cardiac pathogenicity of cytotoxic T lymphocytes. *Circ Res* (2007) 101(3):248–57. doi: 10.1161/CIRCRESAHA.106.147124

104. Heinzerling L, Ott PA, Hodi FS, Husain AN, Tajmir-Riahi A, Tawbi H, et al. Cardiotoxicity associated with CTLA4 and PD1 blocking immunotherapy. *J For Immunotherapy Canc* (2016) 4:50. doi: 10.1186/s40425-016-0152-y

frontiers | Frontiers in Immunology

TYPE Review
PUBLISHED 15 February 2024
DOI 10.3389/fimmu.2024.1266850

OPEN ACCESS

EDITED BY
Giacomo Cafaro,
University of Perugia, Italy

REVIEWED BY
Andrea Alberti,
University of Brescia, Italy
Davide Smussi,
University of Brescia, Italy

*CORRESPONDENCE
Jun Chen
chenjundl@vip.sina.com

†These authors have contribute equally to this work

RECEIVED 25 July 2023
ACCEPTED 02 February 2024
PUBLISHED 15 February 2024

CITATION
Lin M-X, Zang D, Liu C-G, Han X and Chen J (2024) Immune checkpoint inhibitor-related pneumonitis: research advances in prediction and management. *Front. Immunol.* 15:1266850. doi: 10.3389/fimmu.2024.1266850

Immune checkpoint inhibitor-related pneumonitis: research advances in prediction and management

Mei-Xi Lin†, Dan Zang†, Chen-Guang Liu†, Xu Han† and Jun Chen*

Department of Oncology, The Second Hospital of Dalian Medical University, Dalian, China

The advent of immune-checkpoint inhibitors (ICIs) has revolutionized the treatment of malignant solid tumors in the last decade, producing lasting benefits in a subset of patients. However, unattended excessive immune responses may lead to immune-related adverse events (irAEs). IrAEs can manifest in different organs within the body, with pulmonary toxicity commonly referred to as immune checkpoint inhibitor-related pneumonitis (CIP). The CIP incidence remains high and is anticipated to rise further as the therapeutic indications for ICIs expand to encompass a wider range of malignancies. The diagnosis and treatment of CIP is difficult due to the large individual differences in its pathogenesis and severity, and severe CIP often leads to a poor prognosis for patients. This review summarizes the current state of clinical research on the incidence, risk factors, predictive biomarkers, diagnosis, and treatment for CIP, and we address future directions for the prevention and accurate prediction of CIP.

KEYWORDS

malignancy, immune checkpoint inhibitor-related pneumonitis, diagnosis, treatment, prediction

1 Introduction

Immune checkpoint inhibitors (ICIs) target tumor cells through the immune system and have innovated the treatment of many advanced malignancies. These inhibitors have received approval for diverse indications, such as programmed cell death receptor 1 (PD-1) inhibitors (e.g., Pembrolizumab), cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors (e.g., Ipilimumab), and programmed cell death ligand 1 (PD-L1) inhibitors (e.g., Atezolizumab). However, inhibition of the immune checkpoint/receptor axis can disturb the normal mechanisms involved in immune tolerance and lead to immune-related adverse events (irAEs) (1). Despite the significant clinical benefits of ICIs, irAEs often carry the risk of discontinuation, drug switching, and patient deterioration. In comparison with

chemotherapy-related adverse events, irAEs generally depict a delayed onset and longer duration, and effective management relies on early recognition and timely intervention, including discontinuation, immunosuppression, and/or immunomodulatory strategies (2). However, severe irAEs are sometimes fatal, and among them, immune checkpoint inhibitor-related pneumonitis (CIP) can lead to widespread respiratory symptoms and parenchymal abnormalities, and consequently result in respiratory failure, even death. CIP is termed a highly common cause of fatality associated with anti-PD-1/PD-L1 immunotherapy and accounts for approximately 35% of causes of fatalities (3, 4). Although clinical trials have shown a rare incidence of CIP (usually <5%) (5), real-world studies have shown that its incidence ranges from 5% to 19% in lung cancer cohorts (6, 7). Prior research has indicated that individuals with irAEs have significantly longer overall survival (OS) and progression-free survival (PFS) than individuals without irAEs. However, there was no significant correlation between CIP and the efficacy of immunotherapy in subgroup analysis (8, 9). In contrast, one study observed improved ICI efficacy of grade 1-2 CIP, whereas no correlation was observed between grade 3-4 CIP and the efficacy of ICIs (10). A meta-analysis suggested that adverse effects in other organs, such as endocrine and skin, were associated with benefits in OS analysis, while CIP was significantly heterogeneous (11). Diagnosing and treating CIP can be challenging due to its wide range of symptoms, ranging from asymptomatic cases to severe acute respiratory distress syndrome. Furthermore, our understanding of the pathogenesis underlying CIP remains limited. For the occurrence of CIP, immunotherapeutic drugs need to be suspended, and corticosteroid therapy, as well as empirical anti-infective therapy, is given. However, this also leads to delays in anti-tumor therapy. Therefore, it is necessary to identify risk factors and explore more effective biomarkers to prevent the occurrence of CIP and to better manage the adverse effects that have already occurred. Herein, we combed through ideas for CIP management based on clinical experience, and the mechanism, incidence, risk factors, diagnosis, treatment, and predictive biomarkers of CIP are narratively summarized, aiming to analyze the clinical features of CIP and guide the management of CIP patients.

2 Mechanism of CIP

Normally, when non-self cells such as tumor cells are detected, antigen-presenting cells (APCs) such as dendritic cells and macrophages internalize and deliver tumor antigens via the major histocompatibility complex (MHC). The MHC then binds to T-cell receptors. When additional synergistic interactions occur, such as those involving the CD28 receptor, T cells are fully activated, initiating a cascade of cytotoxic responses aimed at eliminating the tumor (12, 13). During T cell activation, there is also an upregulation of various inhibitory receptors that serve as immune checkpoints. Immune checkpoint proteins including CTLA-4 and PD-1 play a key role by initiating various pathways to inhibit T cell function. PD-1 expression has been observed on a variety of immune cells, including B cells, T cells, and natural killer (NK) cells. In addition, PD-1 binding to the ligands PD-L1 and PD-L2 has been observed to inhibit previously activated T cells in peripheral tissues. CTLA-4 functions by competing with the T cell fibrinolytic receptor CD28 for binding to T cell fibrinolytic factors. As a result, it reduces interleukin-2 (IL-2) production and T-cell proliferation. The tightly regulated signaling of CTLA-4 and PD-1 plays a critical role in maintaining self-tolerance within the immune system. However, tumor cells can use these pathways to evade the immune response and create a growth-promoting microenvironment (14). ICIs primarily target two key immune checkpoint pathways, CTLA-4 and PD-1, which are commonly involved in down-regulating T cell activation and effector functions. By inhibiting these pathways, ICIs can enhance T cell-mediated anti-tumor immune responses without the typical limitations of these checkpoints (15).

Interference with the immune checkpoint pathway is the primary mechanism for enhancing the immune response against tumor cells, but this pathway has also been implicated in the emergence of various irAEs. IrAEs are coordinated predominantly by T-cells, and significant infiltration of CD4+ and CD8+ cells can be observed in conjunction with the onset of irAEs (16). Additionally, an ensemble of immune cells and mediators, including B cells, granulocytes, and cytokines, are also implicated in this process (17). This heightened immune activity culminates in reactions that resemble autoimmune responses, which are characteristic of irAEs. A variety of mechanisms have been suggested to be involved in the development of irAEs. Postow et al. (18) proposed four potential mechanisms for irAEs. (1) Enhanced targeted T-cell activity can attack cross-antigens shared between tumors and normal lung tissue, leading to off-target toxicity. Multiple experiments examined significant CD4+ T lymphocyte and CD8+ T lymphocyte increases in lung tissues and BAL of CIP patients, reflecting a lymphocyte-mediated hyperimmune response (19–21). (2) Increased levels of preexisting autoantibodies. Osorio JC et al. demonstrated that patients treated with anti-PD-1 therapy may develop thyroid dysfunction if antithyroid antibodies are present in the body, and a possible mechanism for this is that anti-PD-1 therapy, in addition to mediating T-cell immunity, modulates humoral immunity and enhances preexisting antithyroid antibodies (22). (3) Increased levels of inflammatory cytokines. (4) Direct binding of ICIs to normal tissues. For example, anti-CTLA-4 antibodies can directly bind to CTLA-4 expressed on the pituitary gland, thus triggering pituitary inflammation (23). According to Zhai et al., the mechanism of CIP may be more relevant to the first three theories since PD-1/PD-L1 is expressed predominantly in immune cells and virtually none in normal lung tissue (24) (Figure 1). Currently, the key biological mechanisms underlying CIP are poorly understood, and it is difficult to determine whether they are caused by disturbances in the local immune response, hypersensitivity, direct drug effects, or a combination of factors. The episodic, unpredictable, and relatively rare nature of CIP makes it difficult to study systematically, and the mechanisms may be different in patients with steroid-refractory. The combination of mechanistic biochemical *in vitro* studies, construction of animal models, and the use of human specimens in translational research

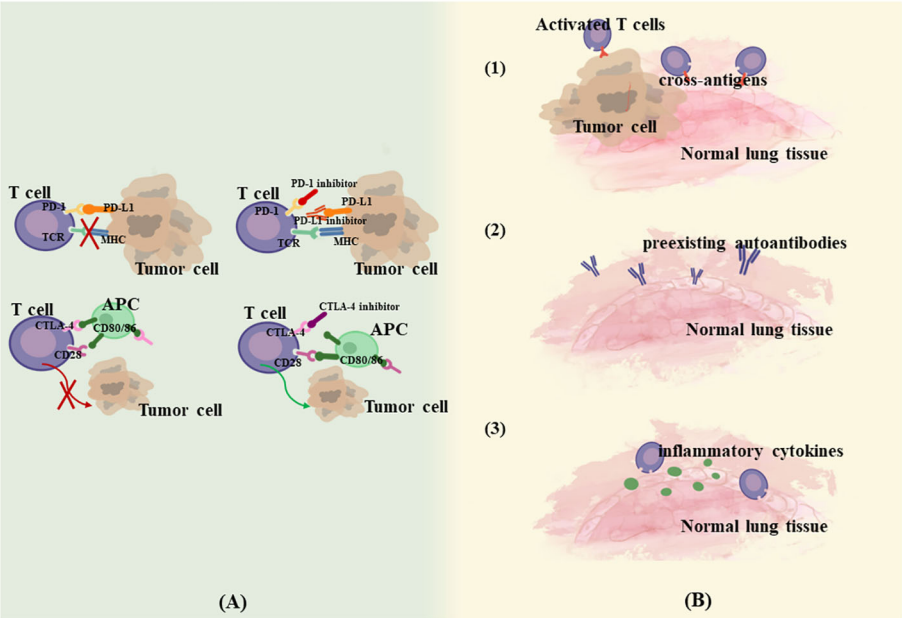


FIGURE 1
Mechanism of CIP. **(A)**. Anti-tumor mechanism of ICIs. **(B)**. Possible mechanism of CIP. (1) Enhanced targeted T-cell activity attack cross-antigens shared between tumors and normal lung tissue. (2) Increased levels of preexisting autoantibodies. (3) Increased levels of inflammatory cytokines.

may contribute to a better understanding of the biological mechanism. Reference can also be made to existing knowledge of the biology of lung diseases such as interstitial lung disease (ILD) and drug-associated pneumonitis.

3 Real-world incidence of CIP

The incidence of CIP in daily clinical practice and the identification of patients at risk of these potentially life-threatening irAEs are critical to addressing the more at-risk patients with lung cancer. Real-world data (RWD) has become increasingly important in this field considering the accelerated approval of cancer immunotherapies. Initially observed at an incidence of 3-5% in clinical trials, CIP was observed to be more common in the real world (25). A study involving 315 patients with lung cancer treated primarily with nivolumab or pembrolizumab depicted a 9.5% incidence of CIP. The median time to diagnosis was 52.5 days, with most patients with CIP depicting a high severity of the disease. Additionally, during the ongoing CIP treatment, eight patients (27%) unfortunately succumbed to the condition. Chao et al. (26) reviewed a study in which CIP occurred in 20 of 164 patients with non-small cell lung cancer (NSCLC) treated with ICIs, accounting for 12.2%. Naidoo J et al. (7) counted 915 patients with various types of advanced solid tumors treated with anti-PD-1/PD-L1 antibodies, 43 of whom suffered from varying degrees of pneumonitis, with a higher prevalence of pneumonitis with combination immunotherapy compared with monotherapy (10% vs. 3%). Suzuki Y et al. reported a prospective study that specifically assessed the incidence and risk factors for CIP in clinical practice in 138 patients with advanced NSCLC who were mainly treated with nivolumab as second or later line. The incidence of CIP was found to be 14.5% (with approximately 6% of ≥ grade 3 events occurring earlier than low-grade events), which is much higher than commonly described in clinical trials or meta-analyses (27). It has been reported (28–30) that although mild CIP can occur more than six months after the start of ICIs, most of the severe CIP have an earlier onset. Moreover, 10-20% of CIP end up being incurable or even leading to death. Thus, CIP occurs far more often than is commonly recognized and is prone to serious adverse outcomes, requiring strict monitoring during drug administration (Table 1).

4 Risk factors of CIP

The uncontrolled activation and proliferation of T cells can result in an excessive release of cytokines, triggering an excessive immune response and contributing to the development of CIP. With combination chemotherapy and ICIs now being first-line treatments for many malignant solid tumors, the need to understand potential increased risk of CIP is even more critical. Any delay in the prompt treatment of CIP patients may result in exacerbation of the disease. Because symptoms are not specific, many early CIP patients are overlooked and lead to poor outcomes. Therefore, it is critical to screen people at high risk of CIP and identify predictive biomarkers to enable its early identification. There is no standardized predictive model for CIP, and the identification of various risk factors comes mainly from summarizing clinical practice. The characteristics of the patient's primary disease, physical status, and treatment modality may influence the development of CIP. Potential severity of CIP emphasizes the need to detect baseline predictive factors

TABLE 1 The incidence of CIP in real world.

Total number	CIP patients	Incidence rate	Median onset time	Cancer type	ICIs treatment	Refs
101	22	21.78%	4.5 months	lung cancer	anti-PD-1	(1)
315	30	9.50%	1.8 months	lung cancer	anti-PD-1	(3)
270	6	2.22%	not mentioned	lung cancer	anti-PD-1 (89.3%) anti-PD-L1 (10.7%)	(8)
559	23	4.11%	not mentioned	lung cancer	anti-PD-1	(9)
71	22	30.90%	not mentioned	lung cancer	anti-PD-1 (85.9%) anti-PD-L1 (14.1%)	(10)
164	20	12.20%	2.9 months	lung cancer	anti-PD-1,anti-PD-L1	(26)
170	27	15.88%	1.2 months	lung cancer	anti-PD-1	(30)
204	38	18.63%	6.3 months	lung cancer	anti-PD-1 (91.2%) other(10.8%) Combination ICIs(30.9%)	(28)
1826	64	3.50%	2.3 months	lung cancer (75%) melanoma (20.3%) other types (4.7%)	anti-CTLA-4 (6.9%) anti-PD-1 (79.3%) anti-PD-L1 (13.8%)	(29)
406	16	3.94%	Not mentioned	renal cell carcinoma	anti-PD-1	(31)
138	20	14.50%	1.7 months	lung cancer	anti-PD-1	(27)
71	1	1.41%	1.4 months	melanoma	anti-CTLA-4	(32)

contributing to the assessment of the individual risk-benefit ratio of a treatment. It is essential to determine biomarkers that possess key advantages, such as being easy to collect, minimally invasive, and reproducible for application in actual clinical settings (33) (Figure 2).

4.1 Underlying health status

4.1.1 Underlying lung disease and smoking history

The development of CIP results in damage to the lung parenchyma, and disease of the underlying "soil" of the lungs may result in a weakened ability to resist damage. Heavy smoking affects the lungs prior to treatment with ICIs, leading to chronic respiratory diseases such as atelectasis and chronic obstructive pulmonary disease. Treatment of ICIs in patients with poor lung conditions can easily lead to CIP. Atchley et al. (3) assessed the records of lung cancer patients exposed to ICIs monotherapy or combination therapy at six centers in North Carolina (January 2004-July 2017). The research found that the development of CIP was linked independently with baseline fibrosis on chest CT scan, and a composite of obstructive lung disease was independently associated. Chao et al. (26) performed a regression analysis of NSCLC patients using PD-1/PD-L1 and found that the presence of chronic obstructive pulmonary disease (COPD) and PD-L1 expression ≥ 50% were linked to an increased CIP prevalence independently. This may be due to the fact that the inflammatory microenvironment in COPD patients differs from other patients in the presence of chronic inflammation in tissues accompanied by the recruitment and activation of neutrophils, CD4+ and CD8+ T cells, B cells, dendritic cells, and macrophages (34). The activated T cells increase in tumor and healthy lung tissues and result in modulating the inflammatory response to CIP (18, 35). Research by Zhang et al. also observed a higher grade and incidence of CIP in individuals with pre-existing ILD (36). In the research of Pérol et al. (37), the risk of CIP was also elevated in real-world individuals with a previous history of noninfectious pneumonia. The presence of ILD also has an impact on the time to onset of CIP, with studies noting that the median time to onset of pneumonia from initiation of anti-PD-1 antibody therapy was 1.3 months (range 0.3 to 2.1 months) for patients with NSCLC with preexisting ILD and 2.3 months (range 0.2 to 14.6 months) for those without preexisting ILD (38). However, there are also experimental results that contradict the above conclusions. Horiuchi et al. retrospectively evaluated 209 patients with NSClC, malignant melanoma, renal cell carcinoma (RCC), and gastric cancer (GC) treated with anti-PD-1/PD-L1. Multifactorial logistic analyses of baseline characteristics showed that a history of cigarette smoking was the only significant predictor of CIP, whereas no statistically significant associations were detected between a history or radiologic features of preexisting ILD and CIP. Smoking history is an independent influence on CIP, and the column-line graph shows that smoking history is the most influential prognostic factor (39). Multiple retrospective clinical studies reveal the correlation between smoking and the development of CIP. Smoking history is an independent influence

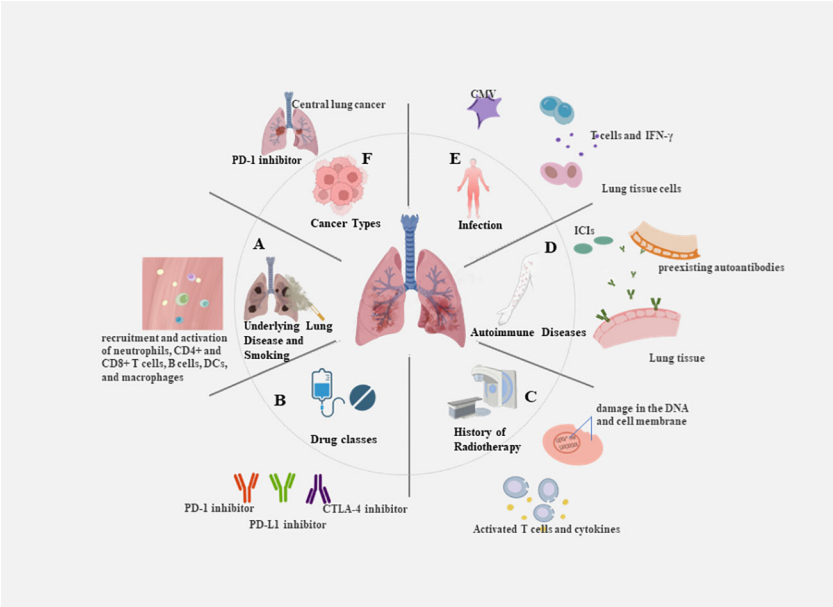


FIGURE 2
Risk factors for the occurrence of CIP. **(A)** Underlying lung disease and smoking: e.g. The inflammatory microenvironment in COPD patients is accompanied by the recruitment and activation of neutrophils, CD4+ and CD8+ T cells, B cells, dendritic cells, and macrophages. **(B)** Drug classes: e.g. PD-1 inhibitors revealed an increase in the incidence of pneumonia of any grade in comparison with PD-L1 inhibitors. **(C)** History of radiotherapy: e.g. The combination of DNA damage caused by radiotherapy and the reactivation of T cells by immunotherapy results in the release of large amounts of cytokines. **(D)** Autoimmune diseases:e.g. Patients treated with ICIs modulates humoral immunity and enhances preexisting autoantibodies. **(E)** Infection: e.g. CMV infection or reactivation can lead to severe disease in the absence of an effective immune response, with increased CD8+ T cell sensitivity and elevated levels of circulating IFN-γ. **(F)** Cancer types: e.g. Squamous cell carcinomas are predominantly central lung cancers that are more prone to causing obstructive pneumonia.

and the most influential prognostic factor in CIP (40, 41). Studies also showed that clinical outcomes of CIP worsen more frequently in patients with a history of smoking (7). The retrospective study by Okada et al. showed that ≥ 50 pack-years was an independent risk factor associated with all levels of CIP (42). However, a history of smoking has also been suggested as a prognostic marker for ICIs treatment. Studies have shown that smoking-induced DNA damage may benefit ICIs treatment, and lung cancer patients who smoked for more than 20 pack-years exhibited genetic mutations associated with a favorable response to ICIs therapy (43). In summary, smoking is beneficial to the efficacy of ICIs and is also a risk factor for CIP, depending on the frequency of smoking. This result suggests that a history of smoking and a quantitative assessment of smoking should be considered when treating lung cancer with ICIs. It is evident that a detailed understanding of the patient's lung disease history should be obtained before treatment with ICIs and more rigorous monitoring should be provided for this population; however, most previous studies have been limited to small samples, and the extent to which different underlying lung diseases contribute to CIP needs to be classified in further prospective studies.

4.1.2 Cancer types and drug classes

The incidence of CIP varies with cancer types and treatment modalities. A meta-analysis of trials involving 20 anti-PD-1 treatments for melanoma, NSCLC, and RCC indicated the heightened occurrence of all-grade and grade ≥ 3 pneumonia in individuals with NSCLC than in individuals with melanoma. Compared with melanoma, patients with RCC had a higher incidence of all-grade pneumonia but a lower incidence of grade ≥ 3 pneumonia (31). It is unclear why NSCLC may be associated with more pneumonia and treatment-related deaths, but several hypotheses seem plausible, including preexisting adverse lung conditions and prior exposures to medications associated with ILD, including paclitaxel, epidermal growth factor receptor tyrosine kinase inhibitors, and gemcitabine. Several studies have shown (44–47) PD-1 inhibitors to have lower rates of irAEs than CTLA-4 inhibitors, while combination therapy depicted higher rates of irAEs than monotherapy. A concurrent analysis of 19 trials of PD-1 and PD-L1 for NSCLC found that PD-1 inhibitors revealed an increase in the incidence of pneumonia of any grade and grade ≥ 3 in comparison with PD-L1 inhibitors. Untreated patients also had an increased incidence of pneumonia in comparison with patients who had been treated previously (48). Chen X et al. (49) found an increased risk of CIP with ICIs in combination with chemotherapy compared to chemotherapy. However, the risk was still lower than with ICIs alone or double-free combination therapy. This may be attributed, in part, to the cytotoxic effects of chemotherapeutic agents, which can lead to immunosuppression. Additionally, the use of glucocorticoids as pre-treatment for chemotherapy may contribute to immune system suppression. Glucocorticoids are also used to treat underlying lung diseases including asthma and COPD. In addition, anti-angiogenic drugs (e.g., bevacizumab) decrease pulmonary exudation and

vascular permeability, potentially aiding in the recovery of early-stage pneumonia (50). This research exhibited that squamous cell carcinoma of the lung may be a risk factor for pneumonia, and similarly, during the assessment of 87 patients with CIP, Lin X et al. found that squamous cell carcinoma subtype and ICIs monotherapy were independently and notably associated with the development of CIP (51). This correlation can be attributed to the fact that obstructive pneumonia can elevate the risk of CIP, and squamous cell carcinomas are predominantly central lung cancers that are more prone to causing obstructive pneumonia. In contrast, Pérol et al. mentioned that the only disease characteristic linked to the risk of pneumonitis is adenocarcinoma histologic subtype (37). The use of treatment combinations in a later study, ethnicity, and different smoking habits might explain these opposite findings.

4.1.3 History of radiotherapy

Radiotherapy provides excellent local control of tumor growth. However, it is important to note that radiotherapy can also exert various immunomodulatory effects. Radiotherapy can be linked to inducing damage in the DNA and cell membrane and is also involved in increasing reactive oxygen species (ROS). It further activates transcription factors and signaling pathways, modulates the immune phenotype and immunogenicity of tumor cells, restores anti-tumor T-cell responses in the tumor microenvironment, and increases tumor antigen release while improving antigen presentation and T-cell infiltration (52, 53). Many pro-inflammatory cytokines and chemokines are systemically increased in immune cells and tumor tissues after radiotherapy, which may account for the nonspecific eradication of distant tumors and metastases (54). Although ICIs can overcome T cell suppression, T cell activation depends on the engagement of antigen receptors and activating co-stimulatory molecules expressed by mature APCs. Thus, radiotherapy increases the production and expression of tumor antigens in poorly immunogenic tumors, thereby enhancing the antitumor immune response elicited by ICIs (55). Fractionated radiotherapy combined with anti-PD-1/PD-L1 antibodies produces an effective CD8+ T-cell response and improves local tumor control and long-term survival (56). Researchs have shown that prior exposure to radiotherapy elevates the risk of developing pneumonia (38, 57). Therefore, in the real world, the advent of combined treatment modalities may increase the risks associated with treatment. Barrón F et al. (1) observed a PFS of 16.8 months versus 5.6 months and a heightened remission rate in the group treated with the combined modality of radiotherapy and anti-PD-L1 (Durvalumab) in comparison with radiotherapy and placebo in individuals with NSCLC. However, combination therapy resulted in elevating the risk of pneumonia of any grade observed in both groups, leading to treatment discontinuation. Similarly, a secondary analysis of phase I KEYNOTE-001 (58) evaluated adverse events in 97 individuals with NSCLC exposed to pembrolizumab. This analysis reported that CIP occurred in 8% (2/24) of patients who had previously undergone prior chest radiotherapy, while 1% (1/73) of patients who had not previously undergone chest radiotherapy developed CIP. In terms of the mechanism of lung injury, the combination of cellular damage caused by radiotherapy and the reactivation of T cells by immunotherapy results in the release of large amounts of cytokines. These cytokines not only directly damage lung tissues through signaling pathways such as transforming growth factor-β/drosophila mothers against decapentaplegic protein (TGF-β/Smad), tumor necrosis factor-α/nuclear factor kappa-light-chain-enhancer of activated B cells (TNF-α/NF-κB), ROS/reactive nitrogen species (RNS), and (cGMP-AMP) synthase-stimulator of interferon genes (cGAS-STING), but also induce lung injury through indirect responses such as recruitment of neutrophils, macrophages, and lymphocytes. The possible crosstalk among signaling pathways mainly involves cytokines such as IL-3, IL-6, IL-10, and IL-17; TNF-α; and TGF-β (59). The resulting data suggest that particular attention should be paid to the occurrence of CIP in individuals who received radiotherapy during treatment, and we should put strict limits on the amount of radiation to which normal lung tissue is exposed through the use of lung dose-volume histograms. Nonetheless, Atchley et al. (3) performed a large retrospective analysis, no clear correlation was found between the risk of CIP and increasing age, history of chest radiotherapy, or tumor histological type, where the association needs to be further explored.

4.1.4 Autoimmune diseases

Preexisting autoimmune diseases are mostly considered contraindications to immunotherapy in the clinic due to severe immunotoxicity and the possibility of disease outbreaks. However, safety data for ICIs in patients with preexisting autoimmune diseases have been reported in several case reports and retrospective studies, which included findings of no difference in grade 3–4 irAEs in patients with or without pre-existing autoimmune disease (60, 61). Given the efficacy of ICIs for metastatic cancers, clinicians have suggested that they should be used to treat a broader population. However, the use of ICIs remains challenging, particularly with regard to the risk of causing irAEs. It is well established that ICIs treatment may trigger acute exacerbations and deterioration of autoimmune diseases. However, the safety and efficacy of ICIs in patients with pre-existing autoimmune disorders are not well documented. As a result, there is still no definitive answer regarding the safe use of ICIs in this particular patient population. Larsen et al. documented the development of anti-aminoacyl tRNA synthetase (ARS) antibody positive polymyositis at the same time as the induction of CIP by the anti-PD-1 antibody nivolumab, resulting in repeated aggravation of the pneumonitis symptoms and prolonged cycle of the treatment (62). A case report (63) documented that a male patient with antinuclear antibody-negative NSCLC was admitted to the hospital with dyspnea after receiving ICIs administration. On admission, a diagnosis of CIP was made in conjunction with imaging. Despite the administration of high-dose steroids, the patient experienced an acute exacerbation of pneumonia, along with progressive pulmonary fibrosis. Upon re-evaluation, it was discovered that the serum collected prior to the administration of ICIs contained ARS antibodies. This finding underscores the significance of reassessing pre-existing autoimmune diseases among individuals who develop CIP with atypical radiological features.

4.1.5 Infection

ICIs exert their antitumor effects by restoring suppressed T-cell function. This restoration of immune function can sometimes result in an exaggerated immune response to previous infections, leading to the exacerbation of clinical symptoms linked to infection. This phenomenon is known as immune reconstitution syndrome (IRS). Cytomegalovirus (CMV) infection is prevalent in the general population, in healthy individuals, the virus and the immune system reach a homeostatic equilibrium and establish a lifelong asymptomatic latency mainly in myeloid cells (64), while in immunocompromised individuals, CMV infection or reactivation can lead to severe disease and even death in the absence of an effective immune response, with increased CD8+ T cell sensitivity and elevated levels of circulating interferon γ (IFN-γ) compared to uninfected individuals (65). Its reactivation was observed among individuals undergoing chemotherapy and radiotherapy (66). Lin X et al. (67) explored the association of CIP development with CMV infection status. Among 29 patients with grade 3–4 CIP, 12 were CMV-IgG positive, suggesting previous CMV infection. With one exception, all patients were positive for CMV PP65 antigen, implying early viral reactivation. Among them, improvement in the symptoms was observed following glucocorticoid combination antiviral therapy, except for one case with delayed antiviral therapy. It suggested that IRS induced by CMV reactivation may be crucially involved in CIP. Although CMV reactivation is uncommon in tumor patients, it is still a risk factor for CIP in patients treated with ICIs and deserves clinical attention due to the high prevalence of latent CMV infections in the population. Studies on the mechanism of CMV reactivation and the occurrence of CIP are still limited and need deeper research. In the past three years, novel coronavirus (COVID-19) pneumonia infection has affected almost everyone and has had a huge impact on the treatment of patients with malignancy. Pinato D J et al. (68) described factors associated with the development of sequelae in COVID-19 surviving oncology patients and their relationship with survival after infection, and found that 15.0% of patients had at least one COVID-19 sequelae at the time of first oncology reassessment, including 116 (49.6%) respiratory sequelae, such as chronic cough, residual dyspnea, and shortness of breath, which undoubtedly caused irreversible damage, and residual inflammatory and interstitial fibrotic lung changes are more likely to lead to CIP, while the symptoms of COVID-19-related pulmonary syndrome may be similar to the worsening of symptoms encountered during lung cancer progression (69). The similarity of clinical and imaging findings poses a greater challenge for confirmatory evaluation, and distinguishing whether the development of pneumonia is associated with ICIs becomes more important.

4.2 Predictive clinical indicators

4.2.1 IL-6 and IL-10

Th2 cells are a distinct subpopulation of CD4+ cells that produce cytokines (e.g., IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13), which can lead to a state of heightened inflammation (70). IL-6 is often considered one of the pleiotropic pro-inflammatory cytokines (71). It plays a key role in host defense and tumorigenesis of the immune system and has been found in a variety of cancers, including breast, gastric, colorectal, lung cancer, and melanoma (72). Excessive production of IL-6 during acute radiation induction has been reported to be possibly associated with the risk of radiation pneumonia in lung cancer patients (73, 74). Lin X et al. have reported significantly higher levels of IL-6 and IL-10 at the onset of CIP compared to baseline, elevated IL-6 level was shown to be capable of independently acting as a marker of the severity of CIP and a predictor of early fatality. Furthermore, high level of IL-10 was strongly associated with severe CIP (51).IL-6 is a member of the proinflammatory cytokine family, in contrast, IL-10 has potent anti-inflammatory properties. In a previous case report, the patients' IL-10 level gradually increased before the diagnosis of CIP, returned to a near-baseline level as the CIP subsided, and increased again at the time of CIP reoccurrence (75). In the studies of Zhou C et al., the levels of IL-6 and IL-10 increased when CIP occurred and decreased during the relief process of CIP (76). IL-10 levels may increase during irAE as a compensatory response to ICIs. The pattern of change in IL-10 as a biomarker remains unclear, but it may help detect and elucidate potential mechanisms of CIP.

4.2.2 Absolute lymphocyte count

Prior research indicated that increased baseline absolute lymphocyte count (ALC) levels (>2000 cells/mL) were a risk factor for irAEs (77), while patients with both reduced ALC at baseline and persistent ALC reduction during treatment also had a shorter period of progression on medication. Lower ALC levels were associated with severe pneumonia by means of univariate analysis. It has been reported (78) that in melanoma patients treated with nivolumab, reduced ALC values were linked to the incidence of grade 3-4 CIP. This phenomenon may be due to the transport of large number of lymphocytes from the blood and their infiltration into the pneumonia lesions, leading to a decrease in ALC in the plasma, especially in severely ill patients, which manifests as a decrease in peripheral blood ALC values. Additionally, Xu H et al. (79) evaluated the condition of 667 NSCLC patients treated with at least one dose of ICIs. The resulting data found that among all grades of irAEs, pneumonia has the highest rate in grade 3 or higher irAEs. Interestingly, peripheral blood ALC was positively associated with the risk of irAEs, a paradox that may be due to differences in cancer species and differences in lymphocyte distribution.

4.2.3 Neutrophil to lymphocyte ratio

Elevated neutrophil counts are known to stimulate tumor angiogenesis and lead to disease progression or treatment resistance, while pre-treatment neutropenia and lymphocytosis, which means reduced neutrophil to lymphocyte ratio (NLR), are associated with better treatment response (80–82). However, among older patients with lung cancer aged ≥ 65 years, a higher NLR appears to be associated with a higher risk of irAEs above Grade 2. Anti-PD-1 antibodies cause abnormal activation of immune cells that attack type II alveolar epithelial cells, airway epithelial cells and endothelium. This cytotoxicity may induce systemic inflammation and increased NLR. Fujisawa et al. also reported an increase in neutrophils and a decrease in lymphocytes in grade 3 and 4 CIP

(78). Matsukane et al. assessed NLR changes in solid tumors in a recent report. The acquired data depicted that elevated NLR was remarkably linked to the development of irAEs, particularly in pneumonia. About 4 weeks before the onset of pneumonia, the NLR was elevated, significantly earlier than the specific symptoms and imaging findings of CIP. In addition, the increase of NLR in the early stage of pneumonia is closely related to the severity of pneumonia (83). On the contrary, another study (84) depicted a link between the responsiveness to ICIs treatment and NLR, while irAEs were not associated with NLR. Nevertheless, this research overlooked specific organs and only assessed individuals treated with CTLA-4 inhibitors.

4.2.4 Absolute eosinophil granulocyte count

Shibaki R et al. made a retrospective analysis of clinical data from individuals with advanced NSCLC treated with ICIs. The resulting data revealed that peripheral blood absolute eosinophil granulocyte count (AEC) was significantly higher in patients with pneumonia than in non-CIP patients. In addition, patients with high AEC had a higher objective response rate (ORR) and longer median progression-free survival (PFS) (38). Furthermore, in patients treated with ICIs, the baseline characteristics of high AEC were associated with an increased risk of CIP and better clinical outcomes. Therefore, striking a balance between the adverse effects of ICIs and their clinical benefits is crucial in optimizing patient outcomes. Additionally, predicting the incidence of CIP in advance and implementing preventive measures can potentially prolong the use of immune drugs and lead to better outcomes.

4.2.5 T-cell subsets

T-helper 17 (Th17) cells play a key role in mucosal immunity, and produce interleukin-17 (IL-17) (85). In addition, Th17 cells may act as a vital element of tissue-resident memory T cells (Trm), and these cells may provide enhanced immunity to certain pathogens for the host. Wang Y. N. et al. (86) examined the dynamic changes of Th1, Th2, and Th17 cells and regulatory T cells (Tregs) in the peripheral blood of 13 CIP patients by flow cytometric analysis. The results showed that in CIP patients, activation of Th1 and Th17 cells and suppression of Tregs cells could imbalance the ratio of T-cell subsets, and the levels of peripheral blood Th1 and Th17 cells and the ratios of Th17/Tregs and Th1/Th2 would increase with the progression of CIP. Using single-cell transcriptomics, Franken et al. confirmed that T-cell accumulation of both CD4+ and CD8+ T cells is a hallmark of CIP. T cells constitute more than half of all immune cells in the bronchoalveolar lavage fluid (BALF) of CIP patients. CD4+ T cell population showing an increase in pathogenic Th 17.1 cells, which are Th17 cells with Th1 characteristics including expression of transcription factor T-bet (encoded by TBX21) and IFN-γ. Granulocyte-macrophage colony-stimulating factor (GM-CSF) production by pathogenic Th17.1 cells has been extensively studied in several autoimmune disorders and has been shown to induce tissue inflammation. In the CD8+ T cell population, effector memory T cells were increased predominantly (87).

CIP lacks typical clinical symptoms, and 1/3 of CIP patients are asymptomatic at presentation (88). However, if some minimally invasive or noninvasive tests can screen CIP high-risk groups in advance, it will allow patients treated with immunotherapy to have a more complete medication cycle. Many retrospective studies have reported predictive risk factors for CIP, however, due to the wide variation in patient samples by region, ethnicity, and treatment modality, there are currently no clinical or biological characteristics that are predictive of CIP. As with most clinical trials, patients enrolled in ICI clinical trials are highly selected and healthier than the target population, which can affect both their response to therapy and the development of complications. Nonetheless, the above-mentioned studies also have issues such as insufficient sample size, and more new biomarkers need to be developed. Multidisciplinary involvement in translational and clinical trials, particularly the inclusion of patient populations that are similar to clinical reality and the use of serum, BALF, and lung pathology specimens, may advance the development of predictive biomarkers and help to determine whether there are biological differences that lead to variable clinical presentations, guiding the development of individualized therapies and possibly, in turn, guiding the development of phenotypically specific targeted therapeutic agents to prevent or treat CIP (Figure 3).

5 Diagnosis of CIP

The bias in the incidence of CIP in many clinical studies may stem from the lack of reporting of mild (grade 1) pneumonia, and a detailed, multidisciplinary, prospective examination is expected to uncover more occult CIP. Clinical symptoms of CIP primarily include dyspnea (53%), decreased activity tolerance, cough (35%), fever (12%), or chest pain (7%). However, about 1/3 of patients have no symptoms and only imaging abnormalities. Before the start of immunotherapy, pulmonary function, liver and kidney function, and chest imaging should be performed in high-risk patients. When patients present with new or worsening dyspnea, cough, chest pain, fever, and hypoxia, they should be alert and promptly undergo blood biochemistry and imaging to identify the cause, and once diagnosed, they should be given prompt treatment according to the grading of their condition.

5.1 Imaging manifestations

There are various classifications regarding the imaging manifestations of CIP, the features of which may be very similar to those of pneumonia, lymphovascular spread of the disease, cancer progression, and diffuse alveolar hemorrhage. Puzanov I et al. (2) proposed that CIP imaging manifests as cryptogenic organizing pneumonia, nonspecific interstitial pneumonitis, hypersensitivity pneumonia, or common interstitial pneumonitis/pulmonary fibrosis. In contrast, in several studies (7, 29), two radiological phenotypes of pneumonia were simply classified: organizing pneumonia pattern (OP) and ground glass opacities (GGO). In a previous report on drug-induced ILD (89, 90), the scattered or diffuse

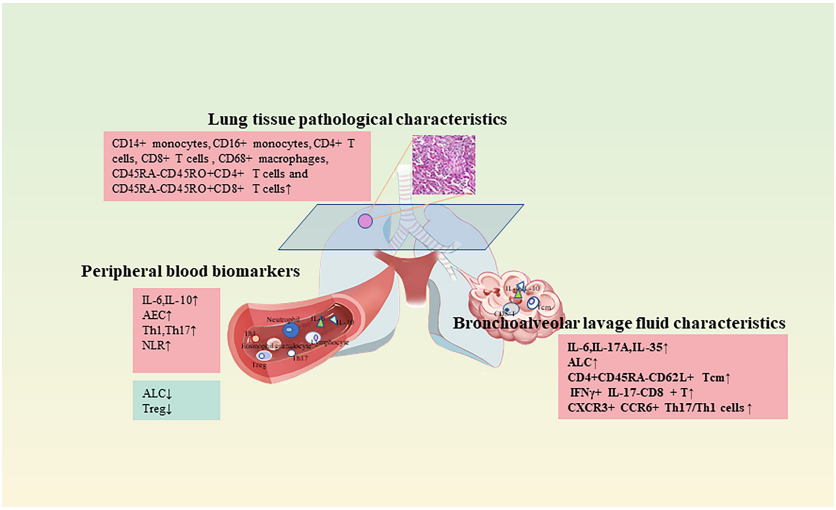


FIGURE 3
Predictive and diagnostic clinical indicators of CIP.

areas of GGO were also defined as acute interstitial pneumonia (AIP) patterns. Nobashi T. W. et al. found (50) that in patients with lung cancer, CIP occurs earlier than in other cancers, and its onset is not influenced by radiation history. Regardless of the cancer type, OP and GGO were predominant, whereas solid and asymmetric shadows were predominant in lung cancer. Additionally, no remarkable variation was observed among individuals with OP and GGO pneumonia in terms of the duration of corticosteroid therapy or treatment outcome. In a study on immune-related interstitial lung disease (ir-ILD) (27), patients with severe ir-ILD (≥ grade 3) most often showed an AIP pattern, while 50% of patients with mild ir-ILD (< grade 2) showed a COP pattern. Therefore, further studies are needed to investigate the clinical significance of the radiological phenotype in patients with CIP. In addition, the presence of pulmonary nodal disease, nodular granulomatous reaction, and sarcomatoid reaction have been reported in patients treated with anti-PD-1/anti-PD-L1 and anti-CTLA-4 inhibitors, and CIP should be considered for differentiation from such disease when chest imaging shows mediastinal or hilar lymph node enlargement or reticulonodular clouding (2).

5.2 Pulmonary function evaluation

When the patient's general status is fair, pulmonary function tests (PFTs) are recommended, which should include indexes reflecting lung ventilation, volume, and diffusion function, such as forced expiratory volume in one second (FEV1), forced vital capacity (FVC), total lung volume (TLC), and diffusing lung capacity for carbon monoxide (DLCO), etc. Decreased DLCO and restrictive ventilation dysfunction are the common abnormal changes in pulmonary function in CIP. In the prospective study of Franzen D et al., a ≥ 10% reduction in FVC from baseline or a ≥ 15% reduction in DLCO was defined as clinically significant and suggestive of pulmonary toxicity in patients with metastatic melanoma before and during treatment with ipilimumab (32). Monitoring of respiratory function prior to initiation of immunotherapy is advocated for patients with pre-existing ILD. If CIP is suspected and a high-resolution chest CT scan is negative, pulmonary function tests should be considered to identify underlying lung function abnormalities to avoid missed diagnosis of CIP (91). Suzuki et al. (27) prospectively used pre-treatment pulmonary function tests and dyspnea scales as potential predictors of CIP. Assessment of PFTs prior to ICI administration revealed that FVC and FEV1 were significantly lower in the subgroup of patients who developed pulmonary toxicity. In the lung volume measurement data, the percentage values of functional residual capacity (FRC) and TLC were also reduced in 87 of the 138 CIP patients. Because measurement of pulmonary function for diagnostic purposes is often not considered until the patient presents with dyspnea and chest pain, we recommend closer testing of pulmonary function in high-risk patients for recognition of early CIP in patients with clinically insignificant symptoms.

5.3 Bronchoalveolar lavage fluid characteristics

BALF is a lung surface lining fluid collected by repeated lavage of the broncho alveoli through electronic bronchoscopy. The biochemical components are primarily composed of phospholipids and proteins, with less nucleic acid content, and the changes in these components reflect the pathophysiological status of the body. In the early stage of CIP, the marker content in serum is low and not easily detectable, whereas BALF, taken from the bronchoalveolar area at the site of the lesion, has a higher concentration of inflammatory cytokines. Hence, it facilitates the early diagnosis of CIP and is generally less damaging to the patient. Wang Y. N. et al. (86) measured the expression levels of IL-17A and

IL-35 in the BALF of NSCLC patients receiving immunotherapy. The data indicated that the expression levels of IL-17A and IL-35 in BALF were elevated during the progression of the disease in CIP patients and were positively correlated with the levels of Th1 and Tregs cells. Hence, providing confirmation that the dynamic detection of IL-17A and IL-35 expression levels in BALF has the potential to provide valuable clinical clues and observations for the development and severity of CIP. Kowalski B et al. (92) collected BALF from 12 CIP patients, using ILD patients and healthy individuals as matched controls. The cytokines including IFN-γ, TNF-α, and interleukin were assessed. It was found that the levels of ALC, lymphocyte percentage, and IL-6 were notably higher in the BALF of CIP patients than in the control group. Suresh K et al. assessed BALF samples prospectively collected from CIP patients and non-CIP patients before starting first-line therapy (high-dose corticosteroids) for CIP. BALF immune cell populations were analyzed using flow cytometry. The resulting data revealed an increase in BAL lymphocytes in CIP patients, primarily in the number of CD4+CD45RA-CD62L+ Tcm, as well as a decrease in CTLA-4 and PD-1 expression in Tregs (19). Statistical assessment of patients with acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) treated with ICIs revealed enrichment of IFNγ+ IL-17- CD8+ T and CXCR3+ CCR6+ Th17/Th1 cells in BALF in the group developing pneumonia. The data suggested that these cells may be vitally involved in the pathophysiology of pulmonary complications related to ICIs (93).

5.4 Pathological characteristics

In clinical practice, less information is present concerning the histopathological features of CIP because the use of biopsy methods at the time of diagnosis is less common. After Larsen et al. searched an institutional file of patients treated with ICIs and conducted subsequent lung tissue sampling to exclude infectious cases, pathological sections were reviewed in 9 patients with probable CIP, of whom 7 had histological manifestations of organizing pneumonia, all subclinical or mild, and three had vague nonnecrotic gap granulomas. Pathologically, all 9 cases showed foamy macrophages and vacuolation of lung cells; 6 cases had rare eosinophils (62). These resulted in the development of acute fibrinous pneumonia or diffuse alveolar injury, which can be fatal. With the development and use of neoadjuvant therapy, a subset of patients with subclinical CIP underwent surgery after immunotherapy, and differences were noted between CT imaging and pathological evaluation of residual tumors, with pathological manifestations showing dense tumor-infiltrating lymphocytes with macrophages and tertiary lymphoid structures, tissue repair—neovascularization and proliferative fibrosis in patients with a good immune response, and the finding of dense hilar fibrosis in those who developed CIP, suggesting that examination of neoadjuvant surgical specimens can help us to understand grade 1-2 CIP (94, 95).

Imaging of lung sections can provide valuable data concerning the infiltration and distribution of immune cells during inflammation. The application of imaging mass cytometry (IMC) to paraffin-embedded lung parenchyma allowed the study of the microenvironment and cell-cell interactions in CIP. Cheng Y et al. (96) identified the immune cell types infiltrating CIP lung tissue as CD14+ monocytes, CD16+ monocytes, CD4+ T cells, CD8+ T cells, and CD68+ macrophages, and the presence of abundant T cells in the inflammatory zone, primarily CD45RA-CD45RO+CD4+ T cells and CD45RA-CD45RO+CD8+ T cells. The data suggested that memory T cells infiltrated the pneumonia tissue, which was consistent with the results in the BALF experiment described above. Furthermore, the research found an accumulation of CD4+HLR-DR+ dendritic cell (DC) and CD8+DC interactions in inflamed tissues, with CD4+DC representing the DC subpopulation that more efficiently stimulates Th1 and Th2 responses (97). These data suggest the activation of memory T cells in the CIP patient. It is worth noting that IMC preserves the complex tissue environment and provides *in situ* characterization of spatial interactions between immune cells, showing good potential for future clinical applications and basic research (98).

In summary, clinical confirmation of the diagnosis of CIP by patient symptoms, blood work, and lung CT should be combined with a comprehensive analysis. Due to the complexity of the etiology of pneumonia, patients should be diagnosed with CIP only after other causes (such as tumor progression, pulmonary infection, or pulmonary edema) have been thoroughly ruled out by microbial culture, respiratory viral polymerase chain reaction (PCR), or BALF, echocardiography, and laboratory tests. For patients at high risk of developing pulmonary toxicity, baseline PFTs may be considered. In the clinical setting, monitoring for the development of pneumonia outside of hospitalization is often neglected as patients receive cyclic immunotherapy. Home pulse oximetry measurement has made contributions in daily respiratory testing in COPD and patients with COVID-19, but its utility has not been extensively studied in CIP (99, 100). Similar to other drug reactions in the lung, the clinical and histopathological manifestations of CIP are nonspecific, and the diagnosis should be exclusionary.

6 Current status and progress in the treatment of CIP

6.1 Current status of CIP treatment

Currently, treatment for CIP varies depending on the severity of the disease, and there is little evidence of the effectiveness of retreatment after CIP. Official guidelines suggest that patients with grade 1 CIP may resume treatment with ICIs if imaging evidence of improved or subsiding pneumonia episodes is available; grade 2 CIP requires temporary discontinuation of ICIs and administration of corticosteroid therapy until symptoms are relieved; and grade 3-4 CIP requires permanent discontinuation of ICIs and hospitalization for corticosteroid therapy, empiric anti-infective therapy, and pulmonary ventilation (13, 101). The guidelines also recommend concomitant use of broad-spectrum antibiotics and immunosuppression during the examination because of the potential for overlapping manifestations of

pneumonia and infection. However, not all patients respond well to corticosteroid therapy, especially those with high-grade CIP and combined pulmonary underlying disease. Pneumonia that does not resolve within 48-72 hours with high-dose corticosteroids becomes steroid-refractory CIP. According to current guidelines, other immunosuppressive agents such as TNF-αinhibitors, intravenous immunoglobulins, cyclosporine, mycophenolate mofetil (MMF), and cyclophosphamide may be used in steroid-refractory irAEs. Balaji et al. (102) reported 12 patients with steroid-refractory CIP treated with TNF-α inhibitors (infliximab), intravenous immunoglobulin, or a combination, but the mortality rate was 75%. Beattie et al. (103) treated 26 patients with steroid-refractory pneumonia with infliximab, MMF, or a combination of both, but only 10 (38%) showed clinical remission. Thus, the optimal treatment for steroid-refractory CIP remains controversial. In-depth research is warranted to determine the effective treatment strategy for steroid-refractory CIP. In a retrospective study involving 298 patients treated with ipilimumab for melanoma, it was observed that 35% of patients necessitated steroid therapy, while 10% required systemic immunosuppression (84). These findings emphasize the importance of optimizing treatment approaches for individuals suffering from refractory irAEs.

6.2 Advances in the treatment of CIP

6.2.1 Pulsed corticosteroid therapy

Based on the original therapeutic approach, researchers have made attempts to adjust drug doses and multi-drug combinations. In recent years, some clinical examples have reported the potential application of pulse corticosteroid therapy (PCST) (104). In general, PCST refers to the continuous use of doses exceeding 250 mg of prednisone or equivalent steroids, an approach that has been shown to be useful in life-threatening autoimmune diseases. Lai K. C (105). reported two patients with grade 4 CIP who responded poorly to steroids but improved rapidly after PCST (methylprednisolone 500 mg for 3 days). Regarding the safety of this approach, a meta-analysis (106) showed that PCST did not increase the risk of adverse effects compared with oral steroid treatment or the untreated group. In conclusion, PCST is effective in CIP, but its indications for application need to be further explored due to insufficient evidence from relevant studies. Utsumi H et al. (107) documented an individual with recurrent NSCLC who developed CIP and deteriorated, and developed respiratory failure after initial pulsed treatment with methylprednisolone. The condition of the individual was successfully improved after treatment with triple therapy (high-dose corticosteroids, tacrolimus, and cyclophosphamide). This is the first report presenting the efficacy of triple therapy in steroid-refractory CIP combined with respiratory failure.

6.2.2 Tocilizumab

Biological therapy for refractory irAEs can be selected based on the pathophysiology of the particular irAEs. Expression of IL-6 promotes tumor growth and metastasis, and tocilizumab is a recombinant humanized anti-human IL-6 receptor monoclonal antibody, which has led some physicians to propose strategies to block IL-6 receptors using tocilizumab in refractory irAEs (108). For example, a retrospective analysis (109) elaborated on the use of tocilizumab in 34 of 87 patients with irAEs on nivolumab in different tumor types, including 35.3% of patients with pneumonia. Tocilizumab treatment was primarily used in serum sickness, systemic inflammatory response syndrome, and pneumonia. Clinical improvement was evident in 27 of these 34 patients. Therefore, blockade of IL-6 may be a direction for individualized treatment of patients with steroid-refractory CIP.

6.2.3 Nintedanib

In recent years, several case reports have demonstrated the efficacy of nintedanib in steroid-refractory CIP as an anti-pulmonary fibrosis agent that blocks fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGF), and vascular endothelial growth factor (VEGF). Xie X H et al. (110) described the successful treatment of nintedanib with pembrolizumab-associated pneumonia in a patient with advanced NSCLC who also had significantly elevated serum KL-6, which is considered to be an important biomarker for ILD (111). Additionally, Yamakawa H et al. (112) also reported that nintedanib replaces prednisolone for the prevention of atezolizumab-induced pneumonia in patients with idiopathic interstitial pulmonary fibrosis (IPF) combined with NSCLC. The exertion of the inhibitory influence of nintedanib on pulmonary fibrosis by targeting VEGFR is one such possible mechanism. Another alternative process is the promotion of lung recovery and reduction of lung exudation by inhibiting VEGF through nintedanib (50). Nonetheless, only a partial explanation is given by the anti-VEGF impact of nintedanib in elucidating its preventive effect on refractory CIP, as no such effect has been reported for bevacizumab in CIP. This has led to some insights on whether the combination therapy has both anticancer efficacy and CIP prevention if NSCLC patients receive nintedanib and PD-1 immunotherapy. Such research avenues require further exploration and experimental validation.

6.3 Rechallenge of ICIs

After the remission of CIP, decision of the appropriate follow-up treatment for the underlying tumor poses various challenges and risks. Research (113–115) has depicted that the recurrence rate of irAEs after rechallenge with ICIs ranges from 39% to 55% for different types of cancer. However, a recently conducted study documented that patients in the ICIs rechallenge group had a longer OS than the non-rechallenge group, however, the cohort that rechallenged ICIs after interruption is not significantly associated with a lower risk of death (116). A retrospective analysis (117) found that 20.0% of patients with advanced lung cancer CIP experienced CIP recurrence after undergoing ICIs rechallenge. Several elements were linked to CIP recurrence, such as CIP grade at initial onset (≥3), Eastern Cooperative Oncology Group performance status (ECOG PS) (≥2) and IL-6, C-reactive

protein (CRP), white blood cells (WBC), and absolute neutrophil count (ANC) levels at recurrence. Due to an analysis of the safety and efficacy of ICIs rechallenge, compared with initial ICI treatment, rechallenge showed a higher incidence for all-grade irAEs but a similar incidence for high-grade irAEs, in which initial pneumonitis was associated with a higher all-grade recurrence. No significant difference was noted between initial ICIs treatment and ICIs rechallenge for ORR and disease control rate (DCR) (118). Based on the generalization of available clinical trials, we believe that deciding whether to rechallenge CIP is an important and practical dilemma that is of increasing concern and emphasizes the need to complete trials in a clinically safe manner. It is worth noting that rechallenge of ICIs after CIP may hold promise as a treatment for patients with advanced lung cancer who initially experienced low CIP grade and good ECOG PS (0-1), as well as low IL-6 and CRP. However, further validation through prospective studies is needed to validate this finding.

7 Discussion

This article summarizes the risk factors, diagnostic features, attempts at new pathways outside of traditional therapy, and exploration of predictive biomarkers for CIP in recent years. With the increasing use of ICIs, the importance of paying attention to their adverse effects has come to the fore. Patients' pre-medication primary disease status, overall health conditions, dosing patterns of medications can affect the development of CIP. Additionally, the combination of different treatments and medications can also impact the incidence and severity of CIP. It impacts the progression of malignancy, resulting in severe pulmonary complications and secondary problems associated with its treatment.

There are many overlapping manifestations of the respiratory symptoms of CIP that are not easily detected early and are differentiated from other types of pneumonia. The diagnosis and treatment of CIP typically involve a process of excluding other potential underlying causes of lung injury. This is because CIP shares certain clinical features with other pulmonary conditions, making the differential diagnosis challenging. One complicating factor in the diagnosis of CIP is the variability in the clinical onset pattern (acute onset or occult onset). The time of onset of CIP ranges from as early as 9 days to as long as 19.2 months after the initiation of treatment (7). To address these challenges, current research is intensifying its focus on understanding the underlying mechanisms of the development of the disease and the associated alterations in the immune system. Studies are also probing the feasibility of achieving extended control over tumor progression with minimal toxicity.

Regarding the prediction of the CIPs, a knowledge gap exists that needs further research. Most of the available prospective studies exclude patients with prior underlying lung disease and autoimmune disease, whereas realistically, patients are likely to be treated with ICIs without it being clear whether they are at increased risk of developing CIP. It is essential to assess their therapeutic benefit and risk of adverse effects. This also suggests that although there is no standard risk model and specific biomarkers for predicting CIP, physicians can collect immunological indicators in serology, BALF, and pathology in addition to common diagnostic modalities in the clinic, pay attention to the populations with risk factors, especially when the indicators are abnormal but the clinical symptoms are not obvious, and pay close attention to the dynamics of the patient's condition to detect early CIP in time. If the results of these studies are further validated, using biomarkers to screen for CIP before imaging may be possible. This will help to reduce the economic burden on patients, reduce sample collection, and ensure patient safety. In addition, for patients who have developed CIP, emphasis should be placed not only on adherence to standard guideline therapies but also on the use of a wide range of cause-specific pharmacological interventions to halt the progression of pneumonia. Combinations of drug therapies are also considered. Infections are relatively common in patients who develop CIP. When corticosteroids are used to treat CIP, it is also important to be aware of their adverse effects on the antitumor response to ICIs and their increased risk of infection. In addition, empirical treatment of suspected lung infections with antibiotics before the diagnosis of CIP is confirmed to have unintended consequences, including a reduction in the clinical benefit of ICIs.

The contemporary scientific landscape has seen a burgeoning interest in multi-omics-based big data analyses, such as single-cell genomics and transcriptomics, for prognostication of cancer progression and immunotherapy responsiveness (119, 120). As such, future research endeavors should harness multidimensional approaches to construct comprehensive patient profiles, both with and without CIP. It is anticipated that through these investigative endeavors, more precise biomarkers will be unearthed and refined for superior prediction of CIP incidence. Furthermore, single-cell analyses focusing on peripheral blood mononuclear cells may unveil novel therapeutic targets that mitigate CIP without compromising cancer treatment efficacy. Collectively, these exploratory advances are poised to foster a more holistic and standardized approach to CIP management, culminating in enhanced quality of life and survival outcomes for patients undergoing immunotherapy for malignancies.

Author contributions

M-XL: Writing – original draft, Writing – review & editing. DZ: Writing – review & editing. C-GL: Writing – review & editing. XH: Writing – review & editing. JC: Supervision.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the National Natural Science Foundation of

China (82203056), the Natural Science Foundation of Liaoning Province (2023-BS-167), the Science and Technology Talent Innovation Support Plan of Dalian (2022RQ091) and the "1+X "program for Clinical Competency Enhancement–Clinical Research Incubation Project of the Second Hospital of Dalian Medical University(2022LCYJYB01).

Acknowledgments

The authors are grateful to the directors (JC) and team members of the Department of Oncology, The Second Hospital of Dalian Medical University for the guidance and wonderful mentoring that led to the writing of this paper.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Barrón F, Sánchez R, Arroyo-Hernández M, Blanco C, Zatarain-Barrón ZL, Catalán R, et al. Risk of developing checkpoint immune pneumonitis and its effect on overall survival in non-small cell lung cancer patients previously treated with radiotherapy. *Front Oncol* (2020) 10:570233. doi: 10.3389/fonc.2020.570233

2. Puzanov I, Diab A, Abdallah K, Bingham CO, Brogdon C, Dadu R, et al. Managing toxicities associated with immune checkpoint inhibitors: Consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer* (2017) 5(1):95. doi: 10.1186/s40425-017-0300-z

3. Atchley WT, Alvarez C, Saxena-Beem S, Schwartz TA, Ishizawar RC, Patel KP, et al. Immune checkpoint inhibitor-related pneumonitis in lung cancer: real-world incidence, risk factors, and management practices across six health care centers in north carolina. *Chest* (2021) 160:731–42. doi: 10.1016/j.chest.2021.02.032

4. Wang DY, Salem JE, Cohen JV, Chandra S, Menzer C, Ye F, et al. Fatal toxic effects associated with immune checkpoint inhibitors: A systematic review and meta-analysis. *JAMA Oncol* (2018) 4:1721–8. doi: 10.1001/jamaoncol.2018.3923

5. Martins F, Sofiya L, Sykiotis GP, Lamine F, Maillard M, Fraga M, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. *Nat Rev Clin Oncol* (2019) 16:563–80. doi: 10.1038/s41571-019-0218-0

6. Suresh K, Naidoo J, Lin CT, Danoff S. Immune checkpoint immunotherapy for non-small cell lung cancer: benefits and pulmonary toxicities. *Chest* (2018) 154:1416–23. doi: 10.1016/j.chest.2018.08.1048

7. Naidoo J, Wang X, Woo KM, Iyriboz T, Halpenny D, Cunningham J, et al. Pneumonitis in patients treated with anti-programmed death-1/programmed death ligand 1 therapy. *J Clin Oncol* (2017) 35:709–17. doi: 10.1200/JCO.2016.68.2005

8. Grangeon M, Tomasini P, Chaleat S, Jeanson A, Souquet-Bressand M, Khobta N, et al. Association between immune-related adverse events and efficacy of immune checkpoint inhibitors in non–small-cell lung cancer. *Clin Lung Cancer* (2019) 20:201–7. doi: 10.1016/j.cllc.2018.10.002

9. Cortellini A, Chiari R, Ricciuti B, Metro G, Perrone F, Tiseo M, et al. Correlations between the immune-related adverse events spectrum and efficacy of anti-PD1 immunotherapy in NSCLC patients. *Clin Lung Cancer*. (2019) 20:237–247.e1. doi: 10.1016/j.cllc.2019.02.006

10. Tone M, Izumo T, Awano N, Kuse N, Inomata M, Jo T, et al. High mortality and poor treatment efficacy of immune checkpoint inhibitors in patients with severe grade checkpoint inhibitor pneumonitis in non-small cell lung cancer. *Thorac Cancer* (2019) 10:2006–12. doi: 10.1111/1759-7714.13187

11. Zhou X, Yao Z, Yang H, Liang N, Zhang X, Zhang F. Are immune-related adverse events associated with the efficacy of immune checkpoint inhibitors in patients with cancer? A systematic review and meta-analysis. *BMC Med*. (2020) 18(1):87. doi: 10.1186/s12916-020-01549-2

12. Martínez-Lostao L, Anel A, Pardo J. How do cytotoxic lymphocytes kill cancer cells? *Clin Cancer Res* (2015) 21:5047–56. doi: 10.1158/1078-0432.CCR-15-0685

13. Granier C, De Guillebon E, Blanc C, Roussel H, Badoual C, Colin E, et al. Mechanisms of action and rationale for the use of checkpoint inhibitors in cancer. *ESMO Open*. (2017) 2(2):e000213. doi: 10.1136/esmoopen-2017-000213

14. Li X, Shao C, Shi Y, Han W. Lessons learned from the blockade of immune checkpoints in cancer immunotherapy. *J Hematol Oncol* (2018) 11(1):31. doi: 10.1186/s13045-018-0578-4

15. Wei SC, Duffy CR, Allison JP. Fundamental mechanisms of immune checkpoint blockade therapy. *Cancer Discov* (2018) 8:1069–86. doi: 10.1158/2159-8290.CD-18-0367

16. Kaehler KC, Piel S, Livingstone E, Schilling B, Hauschild A, SChadendorf D. Update on immunologic therapy with antiCTLA-4 antibodies in melanoma: Identification of clinical and biological response patterns, immune-related adverse events, and their management. *Semin Oncol* (2010) 37:485–98. doi: 10.1053/j.seminoncol.2010.09.003

17. Naidoo J, Page DB, Li BT, Connell LC, Schindler K, Lacouture ME, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Ann Oncol* (2015) 26(12):2375–91. doi: 10.1093/annonc/mdv383

18. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med* (2018) 378:158–68. doi: 10.1056/nejmra1703481

19. Suresh K, Naidoo J, Zhong Q, Xiong Y, Mammen J, de Flores MV, et al. The alveolar immune cell landscape is dysregulated in checkpoint inhibitor pneumonitis. *J Clin Invest* (2019) 129:4305–15. doi: 10.1172/JCI128654

20. Liang J, Wang H, Ding W, Huang J, Zhou X, Wang H, et al. Nanoparticle-enhanced chemo-immunotherapy to trigger robust antitumor immunity. *Sci Adv* (2020) 6(35):eabc3646. doi: 10.1126/sciadv.abc3646

21. Strippoli S, Fucci L, Negri A, Putignano D, Cisternino ML, Napoli G, et al. Cellular analysis of bronchoalveolar lavage fluid to narrow differential diagnosis of checkpoint inhibitor-related pneumonitis in metastatic melanoma. *J Transl Med* (2020) 18(1):473. doi: 10.1186/s12967-020-02650-z

22. Osorio JC, Ni A, Chaft JE, Pollina R, Kasler MK, Stephens D, et al. Antibody-mediated thyroid dysfunction during T-cell checkpoint blockade in patients with non-small-cell lung cancer. *Ann Oncol* (2017) 28:583–9. doi: 10.1093/annonc/mdw640

23. Caturegli P, Di Dalmazi G, Lombardi M, Grosso F, Larman HB, Larman T, et al. Hypophysitis secondary to cytotoxic T-lymphocyte–associated protein 4 blockade: insights into pathogenesis from an autopsy series. *Am J Pathol* (2016) 186:3225–35. doi: 10.1016/j.ajpath.2016.08.020

24. Zhai X, Zhang J, Tian Y, Li J, Jing W, Guo H, et al. The mechanism and risk factors for immune checkpoint inhibitor pneumonitis in non-small cell lung cancer patients. *Cancer Biol Med* (2020) 17:599–611. doi: 10.20892/j.issn.2095-3941.2020.0102

25. Abdel-Rahman O, Fouad M. Risk of pneumonitis in cancer patients treated with immune checkpoint inhibitors: A meta-analysis. *Ther Adv Respir Dis* (2016) 10:183–93. doi: 10.1177/1753465816636557

26. Chao Y, Zhou J, Hsu S, Ding N, Li J, Zhang Y, et al. Risk factors for immune checkpoint inhibitor-related pneumonitis in non-small cell lung cancer. *Transl Lung Cancer Res* (2022) 11:295–306. doi: 10.21037/tlcr-22-72

27. Suzuki Y, Karayama M, Uto T, Fujii M, Matsui T, Asada K, et al. Assessment of immune-related interstitial lung disease in patients with NSCLC treated with immune checkpoint inhibitors: A multicenter prospective study. *J Thorac Oncol* (2020) 15:1317–27. doi: 10.1016/j.jtho.2020.04.002

28. Suresh K, Psoter KJ, Voong KR, Shankar B, Forde PM, Ettinger DS, et al. Impact of checkpoint inhibitor pneumonitis on survival in NSCLC patients receiving immune checkpoint immunotherapy. *J Thorac Oncol* (2019) 14:494–502. doi: 10.1016/j.jtho.2018.11.016

29. Delaunay M, Cadranel J, Lusque A, Meyer N, Gounaut V, Moro-Sibilot D, et al. Immune-checkpoint inhibitors associated with interstitial lung disease in cancer patients. *Eur Respir J* (2017) 50(2):1700050. doi: 10.1183/13993003.00050-2017

30. Fukihara J, Sakamoto K, Koyama J, Ito T, Iwano S, Morise M, et al. Prognostic impact and risk factors of immune-related pneumonitis in patients with non–small-cell lung cancer who received programmed death 1 inhibitors. *Clin Lung Cancer* (2019) 20 (6):442–50.e4. doi: 10.1016/j.cllc.2019.07.006

31. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med* (2015) 373(19):1803–13. doi: 10.1056/nejmoa1510665

32. Franzen D, SChad K, Kowalski B, Clarenbach CF, Stupp R, Dummer R, et al. Ipilimumab and early signs of pulmonary toxicity in patients with metastastic melanoma: a prospective observational study. *Cancer Immunol Immunother* (2018) 67:127–34. doi: 10.1007/s00262-017-2071-2

33. Jia XH, Geng LY, Jiang PP, Xu H, Nan KJ, Yao Y, et al. The biomarkers related to immune related adverse events caused by immune checkpoint inhibitors. *J Exp Clin Cancer Res* (2020) 39(1):284. doi: 10.1186/s13046-020-01749-x

34. Caramori G, Ruggeri P, Mumby S, Ieni A, Lo Bello F, Chaminka V, et al. Molecular links between COPD and lung cancer: new targets for drug discovery? *Expert Opin Ther Targets*. (2019) 23:539–53. doi: 10.1080/14728222.2019.1615884

35. Day D, Hansen AR. Immune-related adverse events associated with immune checkpoint inhibitors. *BioDrugs* (2016) 30:571–84. doi: 10.1007/s40259-016-0204-3

36. Zhang M, Fan Y, Nie L, Wang G, Sun K, Cheng Y. Clinical outcomes of immune checkpoint inhibitor therapy in patients with advanced non-small cell lung cancer and preexisting interstitial lung diseases: A systematic review and meta-analysis. *Chest* (2022) 161:1675–86. doi: 10.1016/j.chest.2021.12.656

37. Pérol M. Multidisciplinary approach of immune checkpoint inhibitor–related pneumonitis: A key to address knowledge and management gaps. *J Thorac Oncol* (2020) 15:1261–4. doi: 10.1016/j.jtho.2020.05.007

38. Shibaki R, Murakami S, Matsumoto Y, Yoshida T, Goto Y, Kanda S, et al. Association of immune-related pneumonitis with the presence of preexisting interstitial lung disease in patients with non-small lung cancer receiving anti-programmed cell death 1 antibody. *Cancer Immunol Immunother* (2020) 69:15–22. doi: 10.1007/s00262-019-02431-8

39. Horiuchi K, Ikemura S, Sato T, Shimozaki K, Okamori S, Yamada Y, et al. Pre-existing interstitial lung abnormalities and immune checkpoint inhibitor-related pneumonitis in solid tumors: A retrospective analysis. *Oncologist* (2024) 29(1):e108–e117. doi: 10.1093/oncolo/oyad187

40. Li X, Lv F, Wang Y, Du Z. Establishment and validation of nomogram for predicting immuno checkpoint inhibitor related pneumonia. *BMC Pulm Med* (2022) 22 (1):331. doi: 10.1186/s12890-022-02127-3

41. Zhou P, Zhao X, Wang G. Risk factors for immune checkpoint inhibitor-related pneumonitis in cancer patients: A systemic review and meta-analysis. *Respiration* (2022) 101:1035–50. doi: 10.1159/000526141

42. Okada N, Matsuoka R, Sakurada T, Goda M, Chuma M, Yagi K, et al. Risk factors of immune checkpoint inhibitor-related interstitial lung disease in patients with lung cancer: a single-institution retrospective study. *Sci Rep* (2020) 10(1):13773. doi: 10.1038/s41598-020-70743-2

43. Chiu M, Lipka MB, Bhateja P, Fu P, Dowlati A. A detailed smoking history and determination of MYC status predict response to checkpoint inhibitors in advanced non-small cell lung cancer. *Transl Lung Cancer Res* (2020) 9:55–60. doi: 10.21037/tlcr.2020.01.03

44. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WEE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer. *N Engl J Med* (2015) 373:123–35. doi: 10.1056/nejmoa1504627

45. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. *N Engl J Med*. (2015) 373:1627–39. doi: 10.1056/nejmoa1507643

46. Weber JS, Dummer R, De Pril V, Lebbé C, Hodi FS. Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab: Detailed safety analysis from a phase 3 trial in patients with advanced melanoma. *Cancer* (2013) 119:1675–82. doi: 10.1002/cncr.27969

47. Rizvi NA, Mazières J, Planchard D, Stinchcombe TE, Dy GK, Antonia SJ, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): A phase 2, single-arm trial. *Lancet Oncol* (2015) 16:257–65. doi: 10.1016/S1470-2045(15)70054-9

48. Khunger M, Rakshit S, Pasupuleti V, Hernandez AV, Mazzone P, Stevenson J, et al. Incidence of pneumonitis with use of programmed death 1 and programmed death-ligand 1 inhibitors in non-small cell lung cancer: A systematic review and meta-analysis of trials. *Chest* (2017) 152(2):271–281. doi: 10.1016/j.chest.2017.04.177

49. Chen X, Zhang Z, Hou X, Zhang Y, Zhou T, Liu J, et al. Immune-related pneumonitis associated with immune checkpoint inhibitors in lung cancer: A network meta-analysis. *J Immunother Cancer* (2020) 8(2):e001170. doi: 10.1136/jitc-2020-001170

50. Barratt SL, Flower VA, Pauling JD, Millar AB. VEGF (Vascular endothelial growth factor) and fibrotic lung disease. *Int J Mol Sci* (2018) 19(5):1269. doi: 10.3390/ijms19051269

51. Lin X, Deng H, Yang Y, Wu J, Qiu G, Li S, et al. Peripheral blood biomarkers for early diagnosis, severity, and prognosis of checkpoint inhibitor-related pneumonitis in patients with lung cancer. *Front Oncol* (2021) 11:698832. doi: 10.3389/fonc.2021.698832

52. Walle T, Monge RM, Cerwenka A, Ajona D, Melero I, Lecanda F. Radiation effects on antitumor immune responses: Current perspectives and challenges. *Ther Adv Med Oncol* (2018) 10:1758834017742575. doi: 10.1177/1758834017742575

53. Demaria S, Golden EB, Formenti SC. Role of local radiation therapy in cancer immunotherapy. *JAMA Oncol* (2015) 1:1325–32. doi: 10.1001/jamaoncol.2015.2756

54. Demaria S, Formenti SC. Radiation as an immunological adjuvant: current evidence on dose and fractionation. *Front Oncol* (2012) 2:153. doi: 10.3389/fonc.2012.00153

55. Tang C, Wang X, Soh H, Seyedin S, Cortez M, Krishnan S, et al. Combining radiation and immunotherapy: a new systemic therapy for solid tumors? *Cancer Immunol Res* (2014) 2(9):831–8. doi: 10.1158/2326-6066.CIR-14-0069

56. Patel SH, Rimner A, Cohen RB. Combining immunotherapy and radiation therapy for small cell lung cancer and thymic tumors. *Transl Lung Cancer Res* (2017) 6:186–95. doi: 10.21037/tlcr.2017.03.04

57. Kanai O, Kim YH, Demura Y, Kanai M, Ito T, Fujita K, et al. Efficacy and safety of nivolumab in non-small cell lung cancer with preexisting interstitial lung disease. *Thorac Cancer* (2018) 9:847–55. doi: 10.1111/1759-7714.12759

58. Shaverdian N, Lisberg AE, Bornazyan K, Veruttipong D, Goldman JW, Formenti SC, et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial. *Lancet Oncol* (2017) 18:895–903. doi: 10.1016/S1470-2045(17)30380-7

59. Zhang Z, Zhou J, Verma V, Liu X, Wu M, Yu J, et al. Crossed pathways for radiation-induced and immunotherapy-related lung injury. *Front Immunol* (2021) 12:774807. doi: 10.3389/fimmu.2021.774807

60. Yeung C, Kartolo A, Holstead R, Moffat GT, Hanna L, Hopman W, et al. Safety and clinical outcomes of immune checkpoint inhibitors in patients with cancer and preexisting autoimmune diseases. *J Immunother* (2021) 44(9):362–370. doi: 10.1097/CJI.0000000000000377

61. Cortellini A, Buti S, Santini D, Perrone F, Giusti R, Tiseo M, et al. Clinical outcomes of patients with advanced cancer and pre-existing autoimmune diseases treated with anti-programmed death-1 immunotherapy: A real-world transverse study. *Oncologist* (2019) 24:e327–37. doi: 10.1634/theoncologist.2018-0618

62. Larsen BT, Chae JM, Dixit AS, Hartman TE, Peikert T, Roden AC. Clinical and histopathologic features of immune checkpoint inhibitor-related pneumonitis. *Am J Surg Pathol* (2019) 43(10):1331–1340. doi: 10.1097/PAS.0000000000001298

63. Ichihara S, Ogino H, Yoneda H, Haji K, Kagawa K, Murakami K, et al. Immune checkpoint inhibitor-related pneumonitis with atypical radiologic features in a patient with anti-aminoacyl-tRNA synthetase antibody. *Respir Med Case Rep* (2023) 41:101797. doi: 10.1016/j.rmcr.2022.101797

64. Furman D, Jojic V, Sharma S, Shen-Orr SS, Angel CJL, Onengut-Gumuscu S, et al. Cytomegalovirus infection enhances the immune response to influenza. *Sci Transl Med* (2015) 7(281):281ra43. doi: 10.1126/scitranslmed.aaa2293

65. Ciáurriz M, Zabalza A, Beloki L, Mansilla C, Pérez-Valderrama E, Lachén M, et al. The immune response to cytomegalovirus in allogeneic hematopoietic stem cell transplant recipients. *Cell Mol Life Sci* (2015) 72:4049–62. doi: 10.1007/s00018-015-1986-z

66. Schnitzler MA, Woodward RS, Brennan DC, Spitznagel EL, Dunagan WC, Bailey TC. The effects of cytomegalovirus serology on graft and recipient survival in cadaveric renal transplantation: implications for organ allocation. *Am J Kidney Dis* (1997) 29(3):428–34. doi: 10.1016/s0272-6386(97)90205-5

67. Lin X, Lu T, Li S, Xie X, Chen X, Jiang J, et al. Cytomegalovirus infection as an underestimated trigger for checkpoint inhibitor-related pneumonitis in lung cancer: a retrospective study. *Clin Trans Oncol* (2021) 23:389–96. doi: 10.1007/s12094-020-02432-5

68. Pinato DJ, Tabernero J, Bower M, Scotti L, Patel M, Colomba E, et al. Prevalence and impact of COVID-19 sequelae on treatment and survival of patients with cancer who recovered from SARS-CoV-2 infection: evidence from the OnCovid retrospective, multicentre registry study. *Lancet Oncol* (2021) 22:1669–80. doi: 10.1016/S1470-2045(21)00573-8

69. Reddy R. Imaging diagnosis of bronchogenic carcinoma (the forgotten disease) during times of COVID-19 pandemic: Current and future perspectives. *World J Clin Oncol* (2021) 12:437–57. doi: 10.5306/wjco.v12.i6.437

70. Romagnani S. T-cell subsets (Th1 versus Th2). *Ann Allergy Asthma Immunol*. (2000) 85:9–18. doi: 10.1016/S1081-1206(10)62426-X

71. Lee J, Kim HJ, Yang C-S, Kyeong H-H, Choi J-M, Hwang D-E, et al. A high-affinity protein binder that blocks the IL-6/STAT3 signaling pathway effectively suppresses non–small cell lung cancer. *Mol Ther* (2014) 22:1254–65. doi: 10.1038/mt.2014.59

72. Taniguchi K, Karin M. IL-6 and related cytokines as the critical lynchpins between inflammation and cancer. *Semin Immunol* (2014) 26:54–74. doi: 10.1016/j.smim.2014.01.001

73. Mazeron R, Etienne-Mastroianni B, Pérol D, Arpin D, Vincent M, Falchero L, et al. Predictive factors of late radiation fibrosis: A prospective study in non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* (2010) 77:38–43. doi: 10.1016/j.ijrobp.2009.04.019

74. Fu ZZ, Peng Y, Cao LY, Chen YS, Li K, Fu BH. Correlations between serum IL-6 levels and radiation pneumonitis in lung cancer patients: A meta-analysis. *J Clin Lab Anal* (2016) 30:145–54. doi: 10.1002/jcla.21828

75. McCallen JD, Naqash AR, Marie MA, Atwell DC, Muzaffar M, Sharma N, et al. Peripheral blood interleukin 6, interleukin 10, and T lymphocyte levels are associated with checkpoint inhibitor induced pneumonitis: a case report. *Acta Oncol (Madr)* (2021) 60(6):813–817. doi: 10.1080/0284186X.2021.1917001

76. Zhou C, Yang Y, Lin X, Fang N, Chen L, Jiang J, et al. Proposed clinical phases for the improvement of personalized treatment of checkpoint inhibitor–related pneumonitis. *Front Immunol* (2022) 13:935779. doi: 10.3389/fimmu.2022.935779

77. Diehl A, Yarchoan M, Hopkins A, Jaffee E, Grossman SA. Relationships between lymphocyte counts and treatment-related toxicities and clinical responses in patients with solid tumors treated with PD-1 checkpoint inhibitors. *Oncotarget* (2017) 8 (69):114268–114280. doi: 10.18632/oncotarget.23217

78. Fujisawa Y, Yoshino K, Otsuka A, Funakoshi T, Fujimura T, Yamamoto Y, et al. Fluctuations in routine blood count might signal severe immune-related adverse events in melanoma patients treated with nivolumab. *J Dermatol Sci* (2017) 88:225–31. doi: 10.1016/j.jdermsci.2017.07.007

79. Xu H, Feng H, Zhang W, Wei F, Zhou L, Liu L, et al. Prediction of immune-related adverse events in non-small cell lung cancer patients treated with immune checkpoint inhibitors based on clinical and hematological markers: Real-world evidence. *Exp Cell Res* (2022) 416(1):113157. doi: 10.1016/j.yexcr.2022.113157

80. Cupp MA, Cariolou M, Tzoulaki I, Aune D, Evangelou E, Berlanga-Taylor AJ. Neutrophil to lymphocyte ratio and cancer prognosis: an umbrella review of systematic reviews and meta-analyses of observational studies. *BMC Med* (2020) 18(1):360. doi: 10.1186/s12916-020-01817-1

81. Ethier JL, Desautels D, Templeton A, Shah PS, Amir E. Prognostic role of neutrophil-to-lymphocyte ratio in breast cancer: A systematic review and meta-analysis. *Breast Cancer Res* (2017) 19(1):2. doi: 10.1186/s13058-016-0794-1

82. Gustafson MP, Bornschlegl S, Park SS, Gastineau DA, Roberts LR, Dietz AB, et al. Comprehensive assessment of circulating immune cell populations in response to stereotactic body radiation therapy in patients with liver cancer. *Adv Radiat Oncol* (2017) 2:540–7. doi: 10.1016/j.adro.2017.08.003

83. Matsukane R, Watanabe H, Minami H, Hata K, Suetsugu K, Tsuji T, et al. Continuous monitoring of neutrophils to lymphocytes ratio for estimating the onset, severity, and subsequent prognosis of immune related adverse events. *Sci Rep* (2021) 11 (1):1324. doi: 10.1038/s41598-020-79397-6

84. Khoja L, Atenafu EG, Templeton A, Qye Y, Chappell MA, Saibil S, et al. The full blood count as a biomarker of outcome and toxicity in ipilimumab-treated cutaneous metastatic melanoma. *Cancer Med* (2016) 5:2792–9. doi: 10.1002/cam4.878

85. Iwanaga N, Kolls JK. Updates on T helper type 17 immunity in respiratory disease. *Immunology* (2019) 156:3–8. doi: 10.1111/imm.13006

86. Wang YN, Lou DF, Li DY, Jiang W, Dong JY, Gao W, et al. Elevated levels of IL-17A and IL-35 in plasma and bronchoalveolar lavage fluid are associated with checkpoint inhibitor pneumonitis in patients with non-small cell lung cancer. *Oncol Lett*. (2020) 20:611–22. doi: 10.3892/ol.2020.11618

87. Franken A, Van Mol P, Vanmassenhove S, Donders E, Schepers R, Van Brussel T, et al. Single-cell transcriptomics identifies pathogenic T-helper 17.1 cells and pro-inflammatory monocytes in immune checkpoint inhibitor-related pneumonitis. *J Immunother Cancer* (2022) 10(9):e005323. doi: 10.1136/jitc-2022-005323

88. Chuzi S, Tavora F, Cruz M, Costa R, Chae YK, Carneiro BA, et al. Clinical features, diagnostic challenges, and management strategies in checkpoint inhibitor-related pneumonitis. *Cancer Manag Res* (2017) 9:207–13. doi: 10.2147/CMAR.S136818

89. Travis WD, Costabel U, Hansell DM, King TE, Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* (2013) 188:733–48. doi: 10.1164/rccm.201308-1483ST

90. Nishino M, Ramaiya NH, Awad MM, Sholl LM, Maattala JA, Taibi M, et al. PD-1 inhibitor-related pneumonitis in advanced cancer patients: Radiographic patterns and clinical course. *Clin Cancer Res* (2016) 22:6051–60. doi: 10.1158/1078-0432.CCR-16-1320

91. Haanen J, Obeid M, Spain L, Carbonnel F, Wang Y, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* (2022) 33:1217–38. doi: 10.1016/j.annonc.2022.10.001

92. Kowalski B, Valaperti A, Bezel P, Steiner UC, Scholtze D, Wieser S, et al. Analysis of cytokines in serum and bronchoalveolar lavage fluid in patients with immune-checkpoint inhibitor-associated pneumonitis: a cross-sectional case–control study. *J Cancer Res Clin Oncol* (2022) 148:1711–20. doi: 10.1007/s00432-021-03750-z

93. Kim ST, Sheshadri A, Shannon V, Kontoyiannis DP, Kantarjian H, Garcia-Manero G, et al. Distinct immunophenotypes of T cells in bronchoalveolar lavage fluid from leukemia patients with immune checkpoint inhibitors-related pulmonary complications. *Front Immunol* (2021) 11:590494. doi: 10.3389/fimmu.2020.590494

94. Cottrell TR, Thompson ED, Forde PM, Stein JE, Duffield AS, Anagnostou V, et al. Pathologic features of response to neoadjuvant anti-PD-1 in resected non-small-cell lung carcinoma: A proposal for quantitative immune-related pathologic response criteria (irPRC). *Ann Oncol* (2018) 29:1853–60. doi: 10.1093/annonc/mdy218

95. Chaft JE, Hellmann MD, Velez MJ, Travis WD, Rusch VW. Initial experience with lung cancer resection after treatment with T-cell checkpoint inhibitors. *Ann Thorac Surg* (2017) 104:e217–8. doi: 10.1016/j.athoracsur.2017.03.038

96. Cheng Y, Wang XM, Hu Q, Sun K, Zhao X, Zhang M, et al. Imaging mass cytometry analysis of immune checkpoint inhibitor-related pneumonitis: A case report. *Front Immunol* (2022) 13:899971. doi: 10.3389/fimmu.2022.899971

97. Voisine C, Hubert F-X, Trinité B, Heslan M, Josien R. Two phenotypically distinct subsets of spleen dendritic cells in rats exhibit different cytokine production and T cell stimulatory activity. *J Immunol* (2002) 169:2284–91. doi: 10.4049/jimmunol.169.5.2284

98. Elaldi R, Hemon P, Petti L, Cosson E, Desrues B, Sudaka A, et al. High dimensional imaging mass cytometry panel to visualize the tumor immune microenvironment contexture. *Front Immunol* (2021) 12:666233. doi: 10.3389/fimmu.2021.666233

99. Marin-Oto M, Seijo LM, Divo M, Bastarrika G, Ezponda A, Calvo M, et al. Nocturnal hypoxemia and CT determined pulmonary artery enlargement in smokers. *J Clin Med* (2021) 10:1–12. doi: 10.3390/jcm10030489

100. Mbbch A, Clarke JM, Alboksmaty A, Beaney T, Elkin S, Clarke JM, et al. Effectiveness and safety of pulse oximetry in remote patient monitoring of patients with COVID-19: a systematic review. *Lancet Digit Health* (2022) 4(4):e279–e289. doi: 10.1016/S2589-7500(21)00276-4

101. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American society of clinical oncology clinical practice guideline. *J Clin Oncol* (2018) 36:1714–68. doi: 10.1200/JCO.2017.77.6385

102. Balaji A, Hsu M, Lin CT, Feliciano J, Marrone K, Brahmer JR, et al. Steroid-refractory PD-(L)1 pneumonitis: Incidence, clinical features, treatment, and outcomes. *J Immunother Cancer* (2021) 9(1):e001731. doi: 10.1136/jitc-2020-001731

103. Beattie J, Rizvi H, Fuentes P, Luo J, Schoenfeld A, Lin IH, et al. Success and failure of additional immune modulators in steroid-refractory/resistant pneumonitis related to immune checkpoint blockade. *J Immunother Cancer* (2021) 9(2):e001884. doi: 10.1136/jitc-2020-001884

104. Mejía-Vilet JM, Ayoub I. The use of glucocorticoids in lupus nephritis: new pathways for an old drug. *Front Med (Lausanne)* (2021) 8:622225. doi: 10.3389/fmed.2021.622225

105. Lai KC, Hsiao YH, Chen SC. Pulse corticosteroid therapy in the treatment of steroid-refractory immune checkpoint inhibitor-related pneumonitis: Case report and review. *Front Immunol* (2022) 13:994064. doi: 10.3389/fimmu.2022.994064

106. Edel Y, Avni T, Shepshelovich D, Reich S, Rozen-Zvi B, Elbaz M, et al. The safety of pulse corticosteroid therapy- Systematic review and meta-analysis. *Semin Arthritis Rheum* (2020) 50:534–45. doi: 10.1016/j.semarthrit.2019.11.006

107. Utsumi H, Araya J, Okuda K, Watanabe J, Takekoshi D, Fujita Y, et al. Successful treatment of steroid-refractory immune checkpoint inhibitor-related pneumonitis with triple combination therapy: a case report. *Cancer Immunol Immunother* (2020) 69:2033–9. doi: 10.1007/s00262-020-02600-0

108. Médecine Paris F, Obeid M, Martins F, Sykiotis GP, Maillard M, Fraga M, et al. New therapeutic perspectives to manage refractory immune checkpoint-related toxicities. *Lancet Oncol* (2019) (1):e54–e64. doi: 10.1016/S1470-2045(18)30828-3

109. Stroud CRG, Hegde A, Cherry C, Naqash AR, Sharma N, Addepalli S, et al. Tocilizumab for the management of immune mediated adverse events secondary to PD-1 blockade. *J Oncol Pharm Pract* (2019) 25:551–7. doi: 10.1177/1078155217745144

110. Xie XH, Deng HY, Lin XQ, Wu JH, Liu M, Xie ZH, et al. Case report: nintedanib for pembrolizumab-related pneumonitis in a patient with non-small cell lung cancer. *Front Oncol* (2021) 11:673877. doi: 10.3389/fonc.2021.673877

111. Ishikawa N, Hattori N, Yokoyama A, Kohno N. Utility of KL-6/MUC1 in the clinical management of interstitial lung diseases. *Respir Investig* (2012) 50:3–13. doi: 10.1016/j.resinv.2012.02.001

112. Yamakawa H, Oba T, Ohta H, Tsukahara Y, Kida G, Tsumiyama E, et al. Nintedanib allows retreatment with atezolizumab of combined non-small cell lung cancer/idiopathic pulmonary fibrosis after atezolizumab-induced pneumonitis: A case report. *BMC Pulm Med* (2019) 19(1):156. doi: 10.1186/s12890-019-0920-9

113. Allouchery M, Lombard T, Martin M, Rouby F, Sassier M, Bertin C, et al. Safety of immune checkpoint inhibitor rechallenge after discontinuation for grade ≥2 immune-related adverse events in patients with cancer. *J Immunother Cancer* (2020) 8(2):e001622. doi: 10.1136/jitc-2020-001622

114. Simonaggio A, Michot JM, Voisin AL, Le Pavec J, Collins M, Lallart A, et al. Evaluation of readministration of immune checkpoint inhibitors after immune-related adverse events in patients with cancer. *JAMA Oncol* (2019) 5:1310–7. doi: 10.1001/jamaoncol.2019.1022

115. Santini FC, Rizvi H, Plodkowski AJ, Ni A, Lacouture ME, Gambarin-Gelwan M, et al. Safety and efficacy of re-treating with immunotherapy after immune-related adverse events in patients with NSCLC. *Cancer Immunol Res* (2018) 6:1093–9. doi: 10.1158/2326-6066.CIR-17-0755

116. Albandar HJ, Fuqua J, Albandar JM, Safi S, Merrill SA, Ma PC. Immune-related adverse events (Irae) in cancer immune checkpoint inhibitors (ici) and survival outcomes correlation: To rechallenge or not? *Cancers (Basel)* (2021) 13:1–15. doi: 10.3390/cancers13050989

117. Lin X, Deng H, Chu T, Chen L, Yang Y, Qiu G, et al. Safety and efficacy of immunotherapy rechallenge following checkpoint inhibitor-related pneumonitis in advanced lung cancer patients: a retrospective multi-center cohort study. *Transl Lung Cancer Res* (2022) 11:2289–305. doi: 10.21037/tlcr-22-732

118. Zhao Q, Zhang J, Xu L, Yang H, Liang N, Zhang L, et al. Safety and efficacy of the rechallenge of immune checkpoint inhibitors after immune-related adverse events in patients with cancer: A systemic review and meta-analysis. *Front Immunol* (2021) 12:730320. doi: 10.3389/fimmu.2021.730320

119. Song P, Li W, Guo L, Ying J, Gao S, He J. Identification and validation of a novel signature based on NK cell marker genes to predict prognosis and immunotherapy response in lung adenocarcinoma by integrated analysis of single-cell and bulk RNA-sequencing. *Front Immunol* (2022) 13:850745. doi: 10.3389/fimmu.2022.850745

120. Peng J, Sun BF, Chen CY, Zhou JY, Chen YS, Chen H, et al. Single-cell RNA-seq highlights intra-tumoral heterogeneity and Malignant progression in pancreatic ductal adenocarcinoma. *Cell Res* (2019) 29:725–38. doi: 10.1038/s41422-019-0195-y

frontiers | Frontiers in Oncology

TYPE Systematic Review
PUBLISHED 03 June 2024
DOI 10.3389/fonc.2024.1281645

OPEN ACCESS

EDITED BY
Maria-Ioanna (marianna) Christodoulou,
European University Cyprus, Cyprus

REVIEWED BY
Xiaoxiang Zhou,
Chinese Academy of Medical Sciences and Peking Union Medical College, China
Lei Pan,
The First Hospital of China Medical University, China

*CORRESPONDENCE
Na Wang
hbykdxwn@163.com
Lei Wang
yuankundu@163.com

RECEIVED 22 August 2023
ACCEPTED 14 May 2024
PUBLISHED 03 June 2024

CITATION
Liang Y, Xu H, Liu F, Li L, Lin C, Zhang Y, Wang N and Wang L (2024) Immune-related adverse events and their effects on survival outcomes in patients with non-small cell lung cancer treated with immune checkpoint inhibitors: a systematic review and meta-analysis. *Front. Oncol.* 14:1281645. doi: 10.3389/fonc.2024.1281645

Immune-related adverse events and their effects on survival outcomes in patients with non-small cell lung cancer treated with immune checkpoint inhibitors: a systematic review and meta-analysis

Yuxiang Liang[1], Haidi Xu[1], Futao Liu[1], Lei Li[1], ChenXi Lin[1], Yaozhong Zhang[2], Na Wang[3]* and Lei Wang[1]*

[1]Department of Thoracic Surgery, The Fourth Hospital of Hebei Medical University, Shijiazhuang, China, [2]Department of Infection, The Fourth Hospital of Hebei Medical University, Shijiazhuang, China, [3]Cancer Institute, The Fourth Hospital of Hebei Medical University, Shijiazhuang, China

Background: The use of immune checkpoint inhibitors (ICIs) has become the standard of care for non-small cell lung cancer. The purpose of this study was to systematically review the literature to determine whether the occurrence of immune-related adverse events (irAEs) following the use of ICIs predicts different clinical outcomes in non-small cell lung cancer (NSCLC).

Methods: Relevant studies from the time of database creation to July 20, 2023, were systematically searched to explore the differences in clinical outcomes in patients with advanced NSCLC with or without irAEs. The outcome indicators included the occurrence of irAEs, progression-free survival (PFS), and overall survival (OS).

Results: 25 studies met the inclusion criteria. Of these studies, 22 reported the effect on OS, and 19 reported the effect on PFS. The results showed that for patients with NSCLC, the occurrence of irAEs after receiving immunotherapy showed a statistically significant benefit over the absence of irAEs for OS (HR=0.55,95% CI=0.46–0.65) and PFS (HR=0.55 95% CI=0.48–0.64), but severe irAEs (grades 3–5) were associated with worse OS (HR=1.05, 95% CI=0.87–1.27). Compared with gastrointestinal, lung, and hepatitis, irAEs of the skin and endocrine system tend to predict better OS and PFS.

Conclusion: The occurrence of irAEs, especially mild and early irAEs, indicates better OS and PFS in patients with NSCLC treated with ICIs, irrespective of patient characteristics, type of ICIs, and irAEs. However, Grade 3 or higher toxicities resulted in worse OS.

Systematic review registration: https://www.crd.york.ac.uk/prospero/, identifier CRD42023409444.

KEYWORDS

immune related adverse effects (irAEs), survival & prognosis, non small cell lung cancer (NSCLC), immune check inhibitor (ICI), meta - analysis

Background

Lung cancer is a common type of thoracic neoplasm that ranks among the forefront of cancers in terms of incidence and mortality. However, its mortality rate has been decreasing annually, owing to early diagnosis and treatment of non-small cell lung cancer (NSCLC) (1).The two primary histological forms of NSCLC are adenocarcinoma (AC) and squamous cell carcinoma (SCC) (2). Locally advanced NSCLC is the initial diagnosis for about 70% of patients with NSCLC, and the 5-year survival rate is less than 3% (3). Previously, patients with advanced NSCLC were usually treated with chemotherapy, radiotherapy, and targeted therapy, but presented poor outcomes with an OS of approximately 12–18 months and a median PFS of only 4–8 months (4, 5).

In contrast, immunotherapy developed by ICIs has revolutionized the treatment strategy for non-small cell lung cancer in recent years (6), mainly including the anti-programmed cell death 1 (PD-1) drugs, Nivolumab and Pembrolizumab, and the anti-programmed cell death ligand 1 (PD-L1) drugs, Atezolizumab and Durvalumab (7). It can be leveraged to leverage the intrinsic immune response against tumor antigens by taking away the inhibitory effect that antigen-presenting cells (APCs) have on T-cell activation. Nevertheless, these drugs have the potential to stimulate T-cell attack on self-antigens through the same mechanism, leading to a clinical manifestation of distinct toxicities known as irAEs (5).With the widespread use of ICIs, irAEs such as skin damage, myocarditis, hepatitis, colitis, endocrine disorders, inflammatory arthritis, and pneumonitis, have been widely reported (8, 9). Most irAEs tend to be mild and self-limiting, while 2–18% of patients present with grade 3 or 4 irAEs that require prompt recognition and management (10).

The correlation between irAEs and improved clinical outcomes was first observed in patients with melanoma and, in recent years, with the widespread use of ICIs in NSCLC (11), several studies have shown that the occurrence of irAEs after the use of ICIs correlates with clinical outcome indicators. A systematic review of 30 studies revealed that irAEs, such as pulmonary, thyroid and gastrointestinal diseases, were associated with improved OS and PFS in patients with NSCLC and melanoma (12). However, the review did not provide separate data analysis for NSCLC patients. A robust and precise systemic review is required to evaluate the association between irAEs occurrence and the efficacy of ICIs in advanced NSCLC patients. Herein, we conducted a systematic review and meta-analysis to investigate whether OS and PFS are associated with the occurrence of irAEs in patients with advanced non-small cell lung cancer using ICIs.

Methods

Study objectives and inclusion criteria

The purpose of this systematic review was to summarize and provide a qualitative and quantitative review in the form of a meta-analysis to address the following research question: "Is there an improvement in survival among patients diagnosed with non-small cell lung cancer and treated with ICIs who develop irAEs?" We used the population-intervention-comparison-outcomes-study design (PICOS) framework to construct the research question and its corresponding literature search. This systematic review and meta-analysis was registered in the International Prospective Register of Systematic Reviews (CRD42023409444).

Literature search strategy

The study was based on the Preferred Reporting Items for systematic reviews and meta-analyses (PRISMA) statement for literature search, study inclusion, extraction of data, and consolidation of results. We identified eligible studies from databases, such as PubMed, ISI Web of Science database, and Cochrane Library from the time of its creation to July 20, 2023 (Supplementary Table S1). The search terms included the following subject terms and free terms: ((“immune checkpoint inhibitor” OR “Checkpoint Inhibitors, Immune” OR “immune checkpoint blockade” OR “Checkpoint Inhibitor, Immune” OR “immune

checkpoint blockades" OR "Checkpoint Blockers, Immune" OR "Checkpoint Blockade, Immune" OR "Immune Checkpoint Inhibition" OR "Checkpoint Inhibition, Immune" OR "PD-L1 Inhibitors" OR "PD L1 Inhibitors" OR "PD-L1 Inhibitor" OR "PD L1 Inhibitor" OR "Programmed Death-Ligand 1 Inhibitors" OR "Programmed Death Ligand 1 Inhibitors" OR "PD-1-PD-L1 Blockade" OR "Blockade, PD-1-PD-L1" OR "PD 1 PD L1 Blockade" OR "PD-1 Inhibitors" OR "PD 1 Inhibitors" OR "PD-1 Inhibitor" OR "Inhibitor, PD-1" OR "PD 1 Inhibitor" OR "Programmed Cell Death Protein 1 Inhibitor" OR "Programmed Cell Death Protein 1 Inhibitors") OR ("nivolumab" OR "pembrolizumab" OR "atezolizumab" OR "durvalumab" OR "avelumab" OR "ipilimumab" OR "cemiplimab" OR "Tislelizumab" OR "camrelizumab" OR "toripalimab")) AND ("Carcinoma, Non-Small-Cell Lung" OR "Lung Carcinoma, Non-Small-Cell" OR "Non-Small-Cell Lung Carcinomas" OR "Non-Small Cell Lung Cancer") AND (("immune-related") AND ("adverse" OR "adversely" OR "adverses") AND ("event" OR "event s" OR "events")).

Selection and data extraction

Two authors (HD and LL) independently retrieved the available literature to identify eligible studies. The studies were chosen based on the following criteria: (a) studies that only included patients with non-small cell lung cancer; (b) the primary efficacy outcomes with the occurrence of irAEs, progression-free survival (PFS), and overall survival (OS). (c) randomized controlled trials (RCTs) or retrospective experiments comparing non-small cell lung cancer patients with and without immune-related adverse events after immunotherapy. The exclusion criteria were as follows: (a) studies reporting incomplete or inconsistent outcomes; and (b) duplicate studies, studies reporting animal experiments, case reports, cohort studies, and review articles. Once the final set of included studies was identified, data were extracted independently by three authors (HD, LL, and CX) using a pre-designed form implemented in Microsoft Excel 2010 version, and any disagreements were resolved through consensus discussions.

The following information was collected from each study: first author, year of publication, study type, study population characteristics, immune checkpoint inhibitor type, total percentage of patients with irAEs, percentage with grade 1–2 irAEs, percentage with grade 3–5 irAEs, landmark analysis and the HR associated with prognostic outcomes (OS and/or PFS). If the HR and 95% CI were not directly provided in the original article, summary time-to-event data were included in the meta-analysis (13). In addition, if available, a multivariate analysis was preferable because it considers possible confounding factors (14).

Data analysis

All analyses were conducted using the STATA statistics software V16.0 and Review manager V5.3. First, the clinicopathological and prognostic significance of the occurrence of irAEs in locally advanced NSCLC was summarized using the HR and its associated 95% confidence interval (CI) as impact indicators. When available, the multivariate adjusted risk was used in each study. All eligible studies were included in the analyses. In addition, we tested for publication bias using funnel plots of Egger's and Begg's tests. If the *P*-value of the test was less than 0.05, it indicated publication bias. In addition, Egger's test is usually considered more sensitive than Begg's test (15). We chose the results of the Egger's test if they were inconsistent.

The Newcastle-Ottawa scale (NOS; range, 0–9)1 was used to assess the quality of each study. A score of > 6 was considered as high quality. Studies with a score ≤6 were excluded.

We evaluated the statistical heterogeneity among the studies using the X^2-based Q test and I^2 statistics. When $P > 0.05$ for the Q test and $I^2<50\%$, the fixed-effect model with the Mantel-Haenszel technique was applied; otherwise, the random-effect model with the inverse-variance method was utilized, and the pooled HRs and 95% CIs for all included studies were calculated. Subgroup and meta-regression analyses were used to explore heterogeneity, if necessary. Sensitivity analysis was also conducted to ensure the stability of the results; all statistical analyses were two-sided, and a *P* value less than 0.05 was considered statistically significant.

Results

Study selection

The online database search identified 1986 studies. The removal of duplicate and irrelevant articles left 1729 records. Removing nonhuman and nonclinical trial articles resulted in 258 abstracts that met the screening criteria. The full texts of these 258 articles, including additional appendices, were reviewed. Of the 258 studies, 25 met all the inclusion criteria (16–40) detailed data are provided in Table 1. 22 of these studies reported effects on OS (16–21, 23–28, 30–37, 39, 40), and 19 reported effects on PFS (16–18, 21–24, 26–29, 31, 32, 34–37, 39, 40). We have also summarized the incidence and effectiveness of different types of irAEs in a new table (Supplementary Table S2). A PRISMA flowchart was developed to summarize the study selection process along with a quality evaluation of the included literature (Figures 1, 2). The incidence of adverse reactions after receiving immunotherapy was extracted from each study, including the overall incidence and the incidence of grade 1–2 mild and grade 3–5 severe. The hazard ratios and 95% confidence intervals for OS and PFS for the occurrence of irAEs compared to the absence of irAEs were extracted, and 7 studies by Denis et al. (18) and Nadia et al. (25) provided data on the association between OS and severe immune adverse reactions.

Correlation between irAEs and OS

A total of 22 studies with OS data were obtained (16–21, 23–28, 30–37, 39, 40), and overall hazard ratios, including the occurrence and absence of irAEs, were observed. The occurrence of irAEs in patients with advanced NSCLC treated with immunotherapy

TABLE 1 Summary of study characteristics and efficacy of all included cohort studies.

Author	Study type	immune checkpoint inhibitor type	Initial irAEs			Overall survival hazard ratio (95% CI)	Progression-free survival hazard ratio (95% CI)	Grade 3–5 irAEs Overall survival hazard ratio (95% CI)	Landmark analysis	Trial design
			Total	Low grade (1–2)	High grade (3–5)					
Koji Haratani 2018 (23)	M	PD-1(Nivolumab)	69/134	57/134	12/134	0.28 (0.10–0.79)	0.52 (0.29–0.96)	NA	6 weeks	R
J.C. Osorio 2017 (21)	M	PD-1 (Pembrolizumab)	10/48	9/48	1/48	0.29 (0.09–0.93)	0.58 (0.27–1.25)	NA	NA	P
Doran Ksienski 2019 (33)	S	PD-1 (Pembrolizumab, Nivolumab)	100/230	77/230	23/230	0.85 (0.50–1.42)	NA	2.29 (1.05–4.99)	6 weeks	R
R.Dupont 2020 (26)	M	PD-1(Nivolumab)	58/191	49/191	9/191	0.58 (0.41–0.82)	0.36 (0.26–0.50)	NA	12 weeks	R
Yukihiro TOI 2018 (29)	S	PD-1(Nivolumab)	42/70	41/70	1/70	NA	0.43 (0.21–0.88)	NA	NA	R
Wenxian Wang 2022 (27)	S	PD-(L)1	79/222	59/222	20/222	0.76 (0.53–1.09)	0.65 (0.48–0.88)	NA	6 weeks	R
Koichi Sato 2018 (22)	S	PD-1(Nivolumab)	11/38	10/38	1/38	NA	0.10 (0.02–0.50)	NA	60 days	R
Lea Daniello 2021 (24)	M	PD-(L)1	232/894	121/894	111/894	0.38 (0.27–0.53)	0.65 (0.48–0.88)	NA	14 weeks	R
Biagio Ricciuti 2019 (16)	S	PD-1(Nivolumab)	85/195	70/195	15/195	0.55(0.33–0.92) 0.4(0.26–0.59)	0.69(0.45–1.05) 0.48(0.34–0.69)	NA	6 weeks 12 weeks	R
Ana Ortega-Franco 2022 (30)	S	PD-1	47/113	33/113	14/113	0.51 (0.31–0.84)	NA	NA	NA	R
David Conde-Estévez 2021 (17)	S	PD-(L)1	31/70	26/70	5/70	0.46 (0.25–0.85)	0.63 (0.33–1.20)	NA	NA	R
Denis Maillet 2020 (18)	M	PD-(L)1	104/304	80/304	24/304	0.50 (0.36–0.69)	0.58 (0.43–0.78)	1.10 (0.57–2.12)	NA	R
Yahua Wu 2022 (28)	S	PD-(L)1	45/101	37/101	8/101	0.52 (0.29–0.93)	0.57 (0.34–0.96)	NA	12 weeks	R

(Continued)

10.3389/fonc.2024.1281645

TABLE 1 Continued

Author	Study type	immune checkpoint inhibitor type	Initial irAEs			Overall survival hazard ratio (95% CI)	Progression-free survival hazard ratio (95% CI)	Grade 3–5 irAEs Overall survival hazard ratio (95% CI)	Landmark analysis	Trial design
			Total	Low grade (1–2)	High grade (3–5)					
Nadia Guezour2022 (25)	M	PD-(L)1	119/201	83/201	36/201	0.48 (0.19–1.23)	NA	3.00 (1.80–5.00)	NA	P
Fernando C. Santini 2017	M	PD-(L)1	68/482	35/482	33/482	0.24 (0.09–0.62)	0.46 (0.21–1.01)	NA	12 weeks	R
J. Rogado 2019 (20)	S	PD-1 (Pembrolizumab, Nivolumab)	40/77	30/77	10/77	1.10 (0.70–1.73)	NA	2.30 (1.40–3.78)	NA	R
Kim 2017 (32)	S	PD-1 (Pembrolizumab, Nivolumab)	19/58	19/58	0/58	0.11 (0.01–0.92)	0.38 (0.17–0.85)	NA	NA	R
Ahn 2019 (37)	S	PD-1 (Pembrolizumab, Nivolumab)	73/155	65/155	8/155	0.40(0.25–0.65)	0.36(0.23–0.56)	NA	6 weeks	R
Bjørnhart 2019 (38)	S	PD-(L)1	NA	NA	25/118	NA	NA	0.47 (0.21–1.05)	NA	R
Cortellini 2019 (39)	M	PD-1 (Pembrolizumab, Nivolumab)	231/559	181/559	50/559	0.55 (0.41–0.72)	0.59 (0.47–0.76)	0.53 (0.41–0.69)	6 weeks	R
Grangeon 2019 (40)	S	PD-(L)1	124/270	NA	NA	0.29 (0.18–0.46)	0.42 (0.32–0.57)	NA	NA	R
Lee 2023 (34)	M	PD-L1 (Atezolizumab)	275/300	139/300	136/300	0.78 (0.63 - 0.97)	0.87 (0.70 -1.07)	NA	NA	P
Lesueur 2018 (35)	M	PD-1(Nivolumab)	62/104	52/104	10/104	0.64 (0.38–1.09)	0.66 (0.43–1.1)	NA	NA	R
Lisberg 2018 (36)	S	PD-1 (Pembrolizumab)	28/97	NA	NA	0.72 (0.49–1.05)	0.75 (0.56–0.99)	NA	NA	R
Owen 2018 (19)	S	PD-(L)1	27/91	21/91	6/91	0.90(0.72–1.13)	NA	1.20 (0.76–1.92)	3 months	R

ICIs, immune checkpoint inhibitors; irAEs, immune-related adverse events; M, Multicenter study; S, Single-center study; PD-1, programmed cell death protein-1; PD-L1, programmed cell death protein ligand-1; P, Prospective; R, Retrospective; NA, not applicable.

10.3389/fonc.2024.1281645

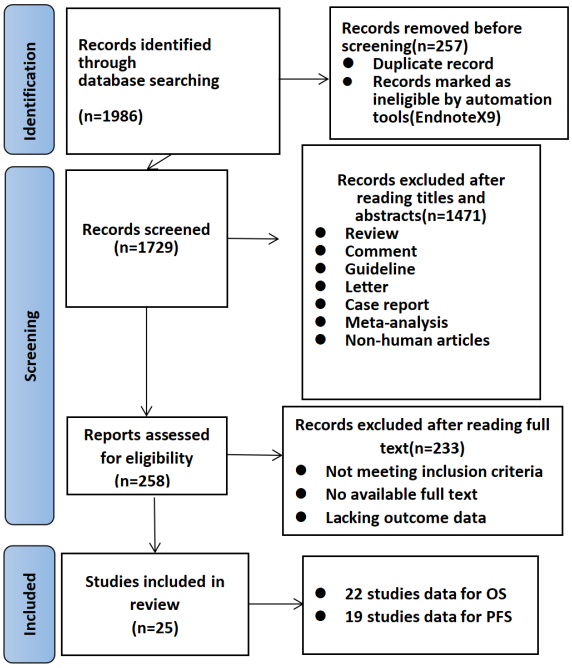


FIGURE 1
Flow diagram of the literature search and article evaluation process.

reduced the risk of death by 45% when compared to the non-occurrence of irAEs(HR=0.55, 95% CI=0.46–0.65; Figure 3). The percentage of the total heterogeneity/total variability was high (I^2 = 68%). In addition, from the subgroup analysis, we found that some of the subgroups did not have significant differences, such as group of sample size and ICI types but other subgroups showed subtle differences. For example, in Figure 4A, we showed that multicenter studies (HR=0.52, 95% CI=0.41–0.66)predict better OS than single-center studies (HR=0.58, 95% CI=0.45–0.75). Also in the landmark analysis, we concluded that the clinical outcome of patients with irAES at less than or equal to 6 weeks(HR=0.53, 95% CI=0.40–0.70) was better than that at more than 6 weeks(HR=0.62, 95% CI=0.46–0.84).

7 studies by Denis et al. reported a relationship between severe adverse immune reactions (grade 3 irAEs) and OS (18–20, 25, 33, 38, 39). In Figure 4A, we observed the association between grade 3–5 irAEs and OS (HR = 1.05, 95% CI = 0.87–1.27). This illustrates that severe adverse immunotherapeutic effects (grade 3 irAEs) lead to decreased OS in patients with advanced NSCLC and are detrimental to patient prognosis.

As shown in Supplementary Table S2, irAEs mainly occurred in the skin, digestive system, pulmonary, endocrine system, and hepatobiliary system. Skin and endocrine irAEs were the most common. In addition, 11 studies reported the relationship between different types of irAEs and survival (16, 17, 21–24, 26, 32, 37, 39, 40). From Figure 4B, we concluded that skin irAEs (HR=0.42 95% CI=0.31–0.57)and endocrine irAEs(HR=0.56 95% CI=0.47–0.67) indicate better prognosis than other irAEs. However, pulmonary irAEs (HR=1.01 95% CI=0.66– 1.55) was a relatively poor type.

Correlation between irAEs and PFS

19 studies reported PFS (16–18, 21–24, 26–29, 31, 32, 34–37, 39, 40) with a Random-effects model for the 2-group comparison using HR as an effect indicator. The results of the meta-analysis (Figure 5) showed that the risk of disease progression with irAEs in patients with advanced NSCLC receiving ICIs was 45% of that in patients without irAEs. This difference was statistically significant (HR=0.55; 95% CI = 0.48–0.64). This result suggested that the occurrence of irAEs in patients with advanced NSCLC receiving ICIs prolongs the PFS of their disease.

For different types of irAEs, skin irAEs (HR=0.47 95% CI=0.34–0.65) and endocrine irAEs (PFS : HR=0.50 95%CI=0.41–0.61) indicated better PFS than other irAEs. However, hepatobiliary irAEs (HR=0.78 95% CI=0.53–1.14) and pulmonary irAEs(PFS : HR=0.81 95% CI=0.54–1.22)were not significantly associated with a favorable PFS.

Different from the results of OS, in the subgroup analysis of ICI types, we showed obvious differences in the study results of Pembrolizumab(HR=0.73 95% CI=0.55–0.97) and Nivolumab (HR=0.46 95% CI=0.35–0.60), but we believed that it may be related to the heterogeneity caused by the small sample size of Pembrolizumab. Further clinical studies are needed to prove this.

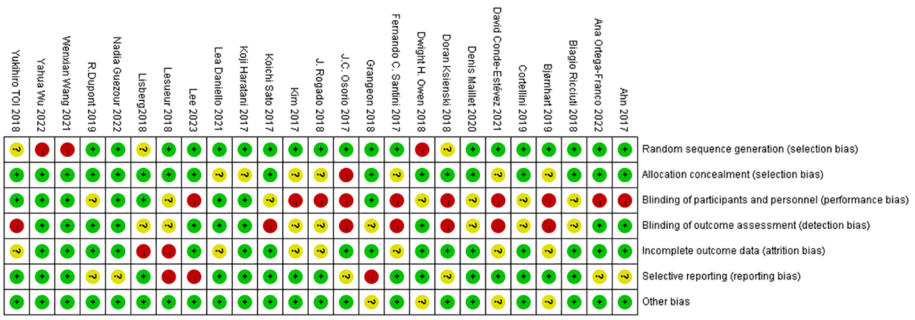


FIGURE 2
Bias from seven key sources assessed with the Cochrane Risk Bias Assessment Tool, with green representing low risk, yellow representing medium risk, and red representing high risk.

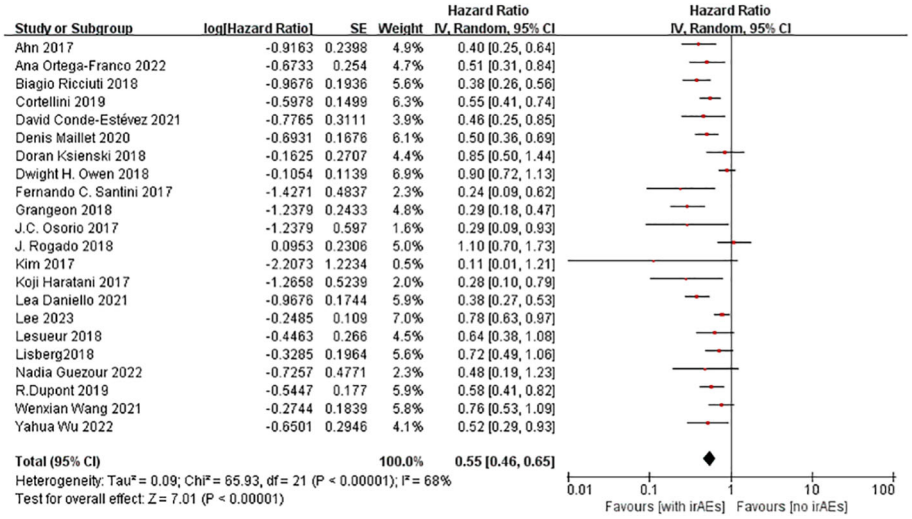


FIGURE 3
Forest plot of OS in NSCLC patients.

Sensitivity analysis and publication bias

In the sensitivity analysis, regardless of whatever trial was removed, the combined results for OS and PFS remained significant, showing that there was a strong correlation between the incidence of irAE and the effectiveness of ICIs in NSCLC patients. Publication bias in this meta-analysis was indicated by Egger's and Begg's tests (Figures 6, 7; Table 2). The results revealed no significant publication bias in the included studies.

Discussion

Given the emergence of immune checkpoint inhibitors (ICIs) as a therapeutic strategy for non-small cell lung cancer (NSCLC) in recent years, there has been a concerted effort to identify reliable biomarkers that can predict response to ICIs through intensive research (40). Early clinical studies exploring immunotherapy have suggested a potential association between the occurrence of immune-related adverse events (irAEs) and prognosis in NSCLC patients. A systematic review performed by Zhou et al. summarized the studies investigating the association between irAEs and ICIs efficacy in patients with cancer (12). It was reported that irAEs predicted better OS and PFS regardless of tumor type. However, whether for global OS or PFS, as well as different types of irAEs, the relevant data of NSCLC were not listed separately in the article. Therefore, we conducted this meta-analysis to investigate whether the presence of irAEs impacts overall survival (OS) or progression-free survival (PFS) in advanced NSCLC patients. Our study corroborated previous findings with 25 literature sources and an enrollment of 5213 patients. The overall incidence rate of irAEs was found to be 35.6%, with mild immune adverse reactions (Grade 1–2) occurring at a rate of 25.1% and severe immune responses at a rate of 9.7%. The hazard ratio for total OS was calculated as 0.55, with a confidence interval (CI) of 0.46–0.65, while the hazard ratio for total PFS was determined as 0.55 with a CI of 0.48–0.64; these results unequivocally demonstrated that the occurrence of irAEs, particularly mild and early ones, conferred benefits on both OS and PFS outcomes in advanced NSCLC patients.

However, our understanding of the mechanisms behind the genesis of irAEs is still lacking. Several mechanisms have been suggested to contribute to the occurrence of irAEs, according to prior reports. These include homologous antigens/epitopes present in both normal tissues and tumor cells, autoantibody production, direct binding of ICIs to immune checkpoint molecules expressed on the surface of normal cells or complement activation, and elevated levels of inflammatory factors (41). Therefore, the most likely mechanism for the development of irAEs could be the abnormal activation of T cells that are specific to a target tissue, and that activation of T cells would cause the production of inflammatory components. For example, PD-(L)1 inhibitors act in the T-cell effector phase, mainly activating T cells in peripheral tissues, thereby increasing the specificity of irAEs (8).

In general, irAEs are mild and manageable (42). As reported previously, most irAEs are cutaneous disorders, with rashes being the most prevalent (17). For example, reactive cutaneous capillary endothelial proliferation (RCCEP) is the most common skin-related immune-related adverse reaction to the PD-1 inhibitor camrelizumab, with an incidence of approximately 78.8% (834/1059) and occurs mainly in the superficial skin of the face and trunk, and is characterized by capillary hyperplasia in the skin dermis. RCCEP mostly appears 2–4 weeks after the first dose of ICIs, does not increase in size at 3–4 months, and can atrophy, recede, or become necrotic 1–2 months after the termination of ICIs. Very few patients present in the oral, nasal, or oculofacial mucosa; however, to date, it has not occurred in the respiratory and gastrointestinal mucosa. Therefore, RCCEP can be used as a clinical indicator to predict the efficacy of camrelizumab monotherapy (43). In addition to skin diseases, irAEs usually manifest as thyroid disease, colitis, pneumonitis, and hepatitis (17). Zhou et al. reported that the occurrence of endocrine and skin irAEs predicted better OS and PFS. Nevertheless, the occurrence of pulmonary and hepatobiliary irAEs was not significantly associated

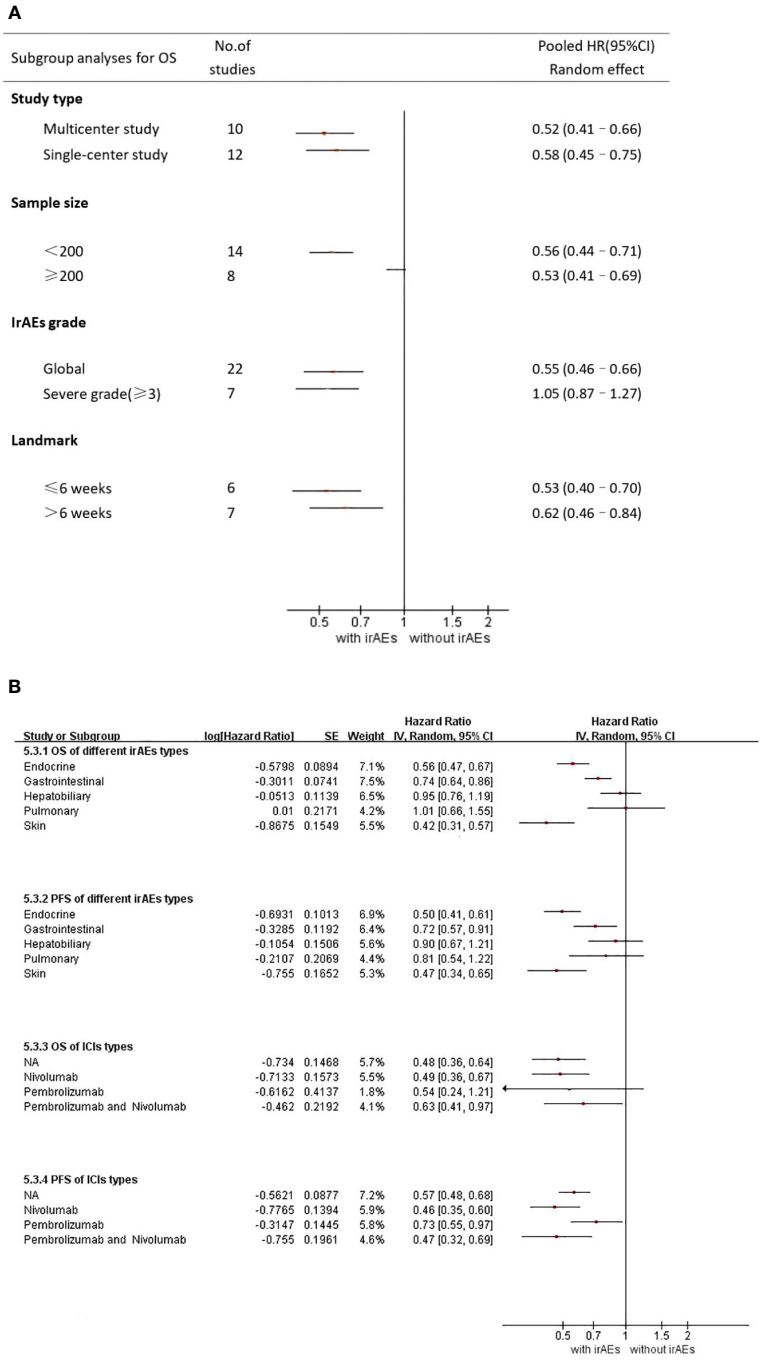


FIGURE 4
(A) Subgroup analysis of the association between irAEs and OS **(B)** Subgroup analysis of irAEs types and ICI types NA, not applicable.

with favorable OS and PFS (12). This is consistent with our findings. We supposed that the observed outcome may be attributed to other irAEs such as thyroid and skin diseases, which typically have a self-limiting nature and milder symptoms. However, checkpoint inhibitor pneumonitis(CIP) could lead to various degrees of lung damage, ranging from the acute stage (acute interstitial pneumonia [AIP]) to the tissue stage (histological pneumonia [OP]) and the fibrotic stage (nonspecific interstitial pneumonia [NSIP]). The majority of CIP cases represent severe irAEs necessitating high doses of oral or parenteral steroids. A comprehensive retrospective cohort study revealed that 86% of patients with CIP demonstrated improvement following corticosteroid therapy. However, a notable 14% of CIP patients did not show any signs of improvement post-treatment and exhibited limited response to alternative immunosuppressants, ultimately leading to unfavorable patient outcomes (44, 45).

For the correlation between severe immune adverse reactions (grade 3–5) and clinical outcomes, we observed that grade 3–5 irAEs were unfavorable for OS (HR=1.05, 95% CI=0.87–1.27), while the sample size for PFS results was too small; only Denis et al. showed that grade 3–5 irAEs were also favorable for PFS (HR=0.66,

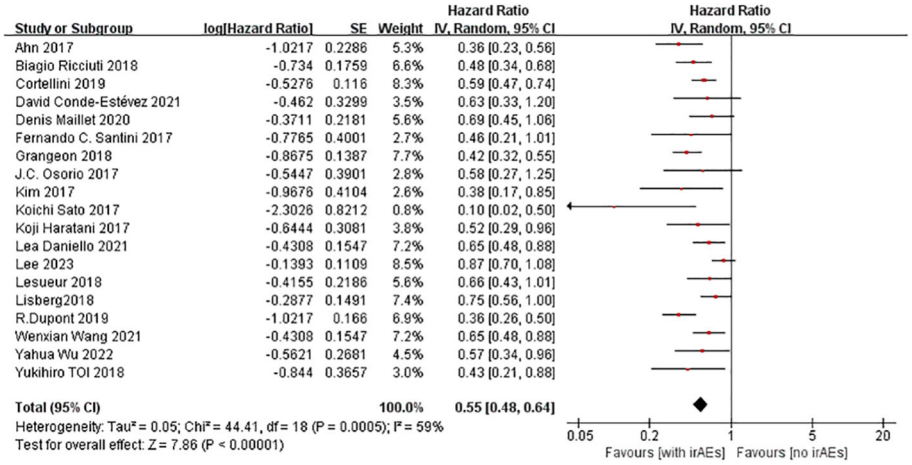


FIGURE 5
Forest plot of PFS in NSCLC patients.

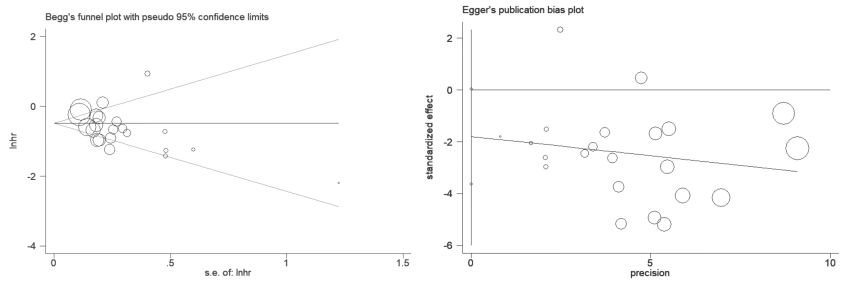


FIGURE 6
Egger ' s test and Begg ' s test for OS.

95% CI=0.40–1.08) (18). This might be related to the following reasons. Large doses of steroids are needed for early severe irAEs, which reduces the effectiveness of ICIs. Furthermore, immunotherapy may be interrupted by severe irAEs, which could impact the prognosis. In addition, a few studies have suggested that the interaction between tumor cells and T cells, cytokines, and antibodies may be linked to significant adverse events and worse clinical outcomes. When using PD-1/PD-L1 inhibitors, macrophage regulatory T cells can exert antibody-dependent cellular phagocytosis through Fc receptors (FcR) and T cell antigen receptors, stimulating the growth of certain cells while suppressing the proliferation of other cells. The anti-tumor activity of immune cells exerts a potent tumor-promoting effect (27, 46).

Numerous studies have shown that systemic immunotherapy should be discontinued when grade 3–5 irAEs occurs (25, 47) because severe adverse effects such as pneumonitis and thrombocytopenia may

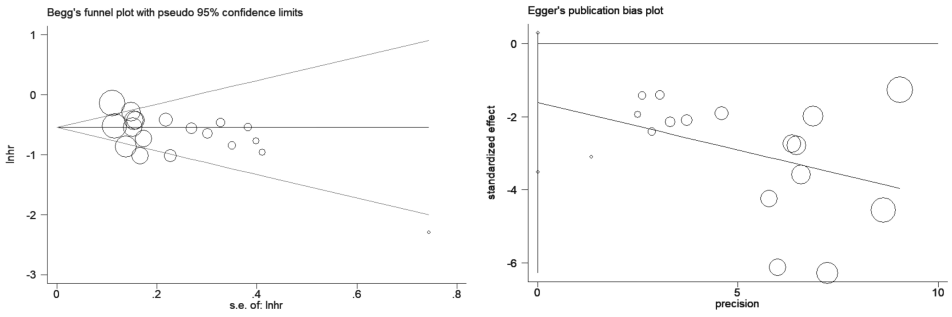


FIGURE 7
Egger ' s test and Begg ' s test for PFS.

TABLE 2 Result of publication bias.

Item	Egger's test	Begg's test
OS	0.195	0.063
PFS	0.074	0.093

directly lead to patient death, which may affect prognostic outcome indicators (27). In addition, there is a meta-analysis on Tocilizumab that allows continuation of immunotherapy in the presence of severe irAEs with significant efficacy, but this still needs to be confirmed in controlled prospective studies (48). Petrelli (49) confirmed a significantly worse prognosis in patients receiving steroids during treatment with ICIs (HR = 1.54, 95% CI:1.24–1.91, $p < 0.0001$). In addition, Wang (27) showed that regardless of the early or late appearance of irAEs, patients who did not require systemic glucocorticoid therapy affecting thyroid function, skin, and other adverse effects had a better prognosis than patients with pneumonitis abnormal liver function, and other adverse effects requiring systemic glucocorticoid therapy because they required less frequent and cumulative measures of steroids. However, R. Dupont reported that anti-PD1 outcomes are similar in patients treated with steroids for irAEs and patients experiencing irAEs who do not require the use of steroids. Additionally, they discovered that PFS was negatively impacted by steroids used to manage irAEs, but not OS (48). We hypothesize that this might be connected to the kind of steroid medication, when treatment is administered, and the kind of tumor, but more investigation is required to validate this. In addition, it has been proposed that the presence of 2 irAEs may suggest better clinical outcomes than the occurrence of 1 irAE (19).

Limitations

This meta-analysis has several limitations, and it is preferable to rely on published outcomes rather than individual patient data. Using a random-effects model, we assumed that these 25 studies represented a random sample of all hypothetical studies wherein there was a treatment effect on the outcome measures. Thus, the pooled effect represents the average effect in the entire study population. Second, chemoimmunotherapy combination therapy has become a routine treatment for NSCLC, and the effects of the type, dose, and frequency of chemotherapeutic agents on clinical outcome indicators are also under consideration. Moreover, although quality assessment was performed, most of the studies were retrospective, and the included studies for PD-1 drugs were mainly focused on Pembrolizumab and Nivolumab; there were fewer data for other PD-1 drugs, such as Camrelizumab or Tislelizumab. Therefore, it is difficult to apply the study findings to all patients.

Conclusion

Overall, the occurrence of irAEs, particularly mild and early irAEs, positively correlated with PFS and OS in patients with advanced NSCLC treated with ICIs. However, irAEs of grade 3 and above resulted in a poorer OS. For different irAEs types, skin and endocrine irAES predicted better OS and PFS than pulmonary and hepatobiliary irAEs. As the use of ICIs continues to expand, early detection and management of these irAEs will become even more important to maximize the duration of treatment while minimizing toxicity to patients. Simultaneously, we think it's critical to find indicators that can recognize and forecast adverse reactions, identify people at risk for severe adverse reactions, and evaluate the prognosis of patients in advance.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Author contributions

YL: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. HX: Data curation, Methodology, Writing – review & editing. FL: Methodology, Supervision, Writing – review & editing. LL: Methodology, Software, Writing – review & editing. CL: Data curation, Methodology, Writing – review & editing. YZ: Methodology, Supervision, Writing – review & editing. NW: Formal analysis, Resources, Writing – review & editing. LW: Resources, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This research was funded by the Key R&D Program of Hebei Province, grant number 213777105D and Natural Science Foundation of Hebei Province, grant number H2022206391.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1281645/full#supplementary-material

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA Cancer J Clin*. (2021) 71:7–33. doi: 10.3322/caac.21654

2. Bodor JN, Boumber Y, Borghaei H. Biomarkers for immune checkpoint inhibition in non-small cell lung cancer (NSCLC). *Cancer*. (2020) 126:260–70. doi: 10.1002/cncr.32468

3. Ozkaya S, Findik S, Dirican A, Atici AG. Long-term survival rates of patients with stage IIIB and IV non-small cell lung cancer treated with cisplatin plus vinorelbine or gemcitabine. *Exp Ther Med*. (2012) 4:1035–8. doi: 10.3892/etm.2012.714

4. Bradley JD, Hu C, Komaki RR, Masters GA, Blumenschein GR, Schild SE, et al. Long-term results of NRG oncology RTOG 0617: standard- versus high-dose chemoradiotherapy with or without cetuximab for unresectable stage III non-small-cell lung cancer. *J Clin Oncol*. (2020) 38:706–14. doi: 10.1200/JCO.19.01162

5. Suresh K, Naidoo J, Lin CT, Danoff S. Immune checkpoint immunotherapy for non-small cell lung cancer: benefits and pulmonary toxicities. *Chest*. (2018) 154:1416–23. doi: 10.1016/j.chest.2018.08.1048

6. Overman MJ, McDermott R, Leach JL, Lonardi S, Lenz HJ, Morse MA, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol*. (2017) 18(9):1182–91. doi: 10.1016/S1470-2045(17)30422-9

7. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med*. (2017) 377:1345–56. doi: 10.1056/NEJMc1714339

8. Hahn AW, Gill DM, Agarwal N, Maughan BL. PD-1 checkpoint inhibition: Toxicities and management. *Urol Oncol*. (2017) 35:701–7. doi: 10.1016/j.urolonc.2017.08.005

9. Brahmer JR, Govindan R, Anders RA, Antonia SJ, Sagorsky S, Davies MJ, et al. The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of non-small cell lung cancer (NSCLC). *J Immunother Cancer*. (2018) 6:75. doi: 10.1186/s40425-018-0382-2

10. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. (2012) 366:2443–54. doi: 10.1056/NEJMoa1200690

11. Weber JS, Hodi FS, Wolchok JD, Topalian SL, Schadendorf D, Larkin J, et al. Safety profile of nivolumab monotherapy: A pooled analysis of patients with advanced melanoma. *J Clin Oncol*. (2017) 35:785–92. doi: 10.1200/JCO.2015.66.1389

12. Zhou X, Yao Z, Yang H, Liang N, Zhang X, Zhang F. Are immune-related adverse events associated with the efficacy of immune checkpoint inhibitors in patients with cancer? A systematic review and meta-analysis. *BMC Med*. (2020) 18(1):87. doi: 10.1186/s12916-020-01549-2

13. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials*. (2007) 8:16. doi: 10.1186/1745-6215-8-16

14. Royston P, Parmar MK. Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. *BMC Med Res Methodol*. (2013) 13:152. doi: 10.1186/1471-2288-13-152

15. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. (1994) 50:1088–101. doi: 10.2307/2533446

16. Ricciuti B, Genova C, De Giglio A, Bassanelli M, Dal Bello MG, Metro G, et al. Impact of immune-related adverse events on survival in patients with advanced non-small cell lung cancer treated with nivolumab: long-term outcomes from a multi-institutional analysis. *J Cancer Res Clin Oncol*. (2019) 145:479–85. doi: 10.1007/s00432-018-2805-3

17. Conde-Estevez D, Monge-Escartín I, Ríos-Hoyo A, Monzonis X, Echeverría-Esnal D, Moliner L, et al. Prognostic factors and effect on survival of immune-related adverse events in patients with non-small-cell lung cancer treated with immune checkpoint blockage. *J Chemother*. (2021) 33(1):32–9. doi: 10.1080/1120009X.2020.1849488

18. Maillet D, Corbaux P, Stelmes JJ, Dalle S, Locatelli-Sanchez M, Perier-Muzet M, et al. Association between immune-related adverse events and long-term survival outcomes in patients treated with immune checkpoint inhibitors. *Eur J Cancer*. (2020) 132:61–70. doi: 10.1016/j.ejca.2020.03.017

19. Owen DH, Wei L, Bertino EM, Edd T, Villalona-Calero MA, He K, et al. Incidence, risk factors, and effect on survival of immune-related adverse events in patients with non-small-cell lung cancer. *Clin Lung Cancer*. (2018) 19:e893–e900. doi: 10.1016/j.cllc.2018.08.008

20. Rogado J, Sánchez-Torres JM, Romero-Laorden N, Ballesteros AI, Pacheco-Barcia V, Ramos-Levi A, et al. Immune-related adverse events predict the therapeutic efficacy of anti-PD-1 antibodies in cancer patients. *Eur J Cancer*. (2019) 109:21–7. doi: 10.1016/j.ejca.2018.10.014

21. Osorio JC, Ni A, Chaft JE, Pollina R, Kasler MK, Stephens D, et al. Antibody-mediated thyroid dysfunction during T-cell checkpoint blockade in patients with non-small-cell lung cancer. *Ann Oncol*. (2017) 28:583–9. doi: 10.1093/annonc/mdw640

22. Sato K, Akamatsu H, Murakami E, Sasaki S, Kanai K, Hayata A, et al. Correlation between immune-related adverse events and efficacy in non-small cell lung cancer treated with nivolumab. *Lung Cancer*. (2018) 115:71–4. doi: 10.1016/j.lungcan.2017.11.019

23. Haratani K, Hayashi H, Chiba Y, Kudo K, Yonesaka K, Kato R, et al. Association of immune-related adverse events with nivolumab efficacy in non-small-cell lung cancer. *JAMA Oncol*. (2018) 4:374–8. doi: 10.1001/jamaoncol.2017.2925

24. Daniello L, Elshiaty M, Bozorgmehr F, Kuon J, Kazdal D, Schindler H, et al. Therapeutic and prognostic implications of immune-related adverse events in advanced non-small-cell lung cancer. *Front Oncol*. (2021) 11:703893. doi: 10.3389/fonc.2021.703893

25. Guezour N, Soussi G, Brosseau S, Abbar B, Naltet C, Vauchier C, et al. Grade 3–4 immune-related adverse events induced by immune checkpoint inhibitors in non-small-cell lung cancer (NSCLC) patients are correlated with better outcome: A real-life observational study. *Cancers (Basel)*. (2022) 14:3878. doi: 10.3390/cancers14163878

26. Dupont R, Bérard E, Puisset F, Comont T, Delord JP, Guimbaud R, et al. The prognostic impact of immune-related adverse events during anti-PD1 treatment in melanoma and non-small-cell lung cancer: a real-life retrospective study. *Oncoimmunology*. (2019) 9:1682383. doi: 10.1080/2162402X.2019.1682383

27. Wang W, Gu X, Wang L, Pu X, Feng H, Xu C, et al. The prognostic impact of mild and severe immune-related adverse events in non-small cell lung cancer treated with immune checkpoint inhibitors: a multicenter retrospective study. *Cancer Immunol Immunother*. (2022) 71:1693–703. doi: 10.1007/s00262-021-03115-y

28. Wu Y, Wu H, Lin M, Liu T, Li J. Factors associated with immunotherapy respond and survival in advanced non-small cell lung cancer patients. *Transl Oncol*. (2022) 15:101268. doi: 10.1016/j.tranon.2021.101268

29. Toi Y, Sugawara S, Kawashima Y, Aiba T, Kawana S, Saito R, et al. Association of immune-related adverse events with clinical benefit in patients with advanced non-small-cell lung cancer treated with nivolumab. *Oncologist*. (2018) 23:1358–65. doi: 10.1634/theoncologist.2017-0384

30. Ortega-Franco A, Hodgson C, Raja H, Carter M, Lindsay C, Hughes S, et al. Real-world data on pembrolizumab for pretreated non-small-cell lung cancer: clinical outcome and relevance of the lung immune prognostic index. *Target Oncol*. (2022) 17:453–65. doi: 10.1007/s11523-022-00889-8

31. Santini FC, Rizvi H, Plodkowski AJ, Ni A, Lacouture ME, Gambarin-Gelwan M, et al. Safety and efficacy of re-treating with immunotherapy after immune-related adverse events in patients with NSCLC. *Cancer Immunol Res*. (2018) 6:1093–9. doi: 10.1158/2326-6066.CIR-17-0755

32. Kim HI, Kim M, Lee SH, Park SY, Kim YN, Kim H, et al. Development of thyroid dysfunction is associated with clinical response to PD-1 blockade treatment in patients with advanced non-small cell lung cancer. *OncoImmunology*. (2017) 7:e1375642. doi: 10.1080/2162402X.2017.1375642

33. Ksienski D, Wai ES, Croteau N, Fiorino L, Brooks E, Poonja Z, et al. Efficacy of nivolumab and pembrolizumab in patients with advanced non-small-cell lung cancer needing treatment interruption because of adverse events: A retrospective multicenter analysis. *Clin Lung Cancer*. (2019) 20:e97–e106. doi: 10.1016/j.cllc.2018.09.005

34. Lee SM, Schulz C, Prabhash K, Kowalski D, Szczesna A, Han B, et al. First-line atezolizumab monotherapy versus single-agent chemotherapy in patients with non-small-cell lung cancer ineligible for treatment with a platinum-containing regimen (IPSOS): a phase 3, global, multicentre, open-label, randomised controlled study. *Lancet*. (2023) 402:451–63. doi: 10.1016/S0140-6736(23)00774-2

35. Lesueur P, Escande A, Thariat J, Vauléon E, Monnet I, Cortot A, et al. Safety of combined PD-1 pathway inhibition and radiation therapy for non-small-cell lung cancer: A multicentric retrospective study from the GFPC. *Cancer Med*. (2018) 7:5505–13. doi: 10.1002/cam4.1825

36. Lisberg A, Tucker DA, Goldman JW, Wolf B, Carroll J, Hardy A, et al. Treatment-related adverse events predict improved clinical outcome in NSCLC patients on KEYNOTE-001 at a single center. *Cancer Immunol Res*. (2018) 6:288–94. doi: 10.1158/2326-6066.CIR-17-0063

37. Ahn B-C, Pyo KH, Xin CF, Jung D, Shim HS, Lee CY, et al. Comprehensive analysis of the characteristics and treatment outcomes of patients with non-small cell lung cancer treated with anti-PD-1 therapy in real-world practice. *J Cancer Res Clin Oncol*. (2019) 145:1613–23. doi: 10.1007/s00432-019-02899-y

38. Bjørnhart B, Hansen KH, Jørgensen TL, Herrstedt J, Schytte T. Efficacy and safety of immune checkpoint inhibitors in a Danish real life non-small cell lung cancer population: a retrospective cohort study. *Acta Oncol*. (2019) 58:953–61. doi: 10.1080/0284186X.2019.1615636

39. Cortellini A, Chiari R, Ricciuti B, Metro G, Perrone F, Tiseo M, et al. Correlations between the immune-related adverse events spectrum and efficacy of anti-PD1 immunotherapy in NSCLC patients. *Clin Lung Cancer*. (2019) 20:237–47.e231. doi: 10.1016/j.cllc.2019.02.006

40. Grangeon M, Tomasini P, Chaleat S, Jeanson A, Souquet-Bressand M, Khobta N, et al. Association between immune-related adverse events and efficacy of immune checkpoint inhibitors in non–small-cell lung cancer. *Clin Lung Cancer*. (2019) 20:201–7. doi: 10.1016/j.cllc.2018.10.002

41. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med*. (2018) 378:158–68. doi: 10.1056/NEJMra1703481

42. Brahmer JR, Lacchetti C, Thompson JA. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: american society of clinical oncology clinical practice guideline summary. *J Oncol Pract*. (2018) 14:247–9. doi: 10.1200/JOP.18.00005

43. Hussaini S, Chehade R, Boldt RG, Raphael J, Blanchette P, Maleki Vareki S, et al. Association between immune-related side effects and efficacy and benefit of immune checkpoint inhibitors - A systematic review and meta-analysis. *Cancer Treat Rev*. (2021) 92:102134. doi: 10.1016/j.ctrv.2020.102134

44. Frost N, Unger K, Blum TG, Misch D, Kurz S, Lüders H, et al. Management, risk factors and prognostic impact of checkpoint-inhibitor pneumonitis (CIP) in lung cancer - A multicenter observational analysis. *Lung Cancer*. (2023) 179:107184. doi: 10.1016/j.lungcan.2023.107184

45. Atchley WT, Alvarez C, Saxena-Beem S, Schwartz TA, Ishizawar RC, Patel KP, et al. Immune checkpoint inhibitor-related pneumonitis in lung cancer: real-world incidence, risk factors, and management practices across six health care centers in North Carolina. *Chest*. (2021) 160:731–42. doi: 10.1016/j.chest.2021.02.032

46. Teraoka S, Fujimoto D, Morimoto T, Kawachi H, Ito M, Sato Y, et al. Early immune-related adverse events and association with outcome in advanced non-small cell lung cancer patients treated with nivolumab: A prospective cohort study. *J Thorac Oncol*. (2017) 12:1798–805. doi: 10.1016/j.jtho.2017.08.022

47. Thompson JA, Schneider BJ, Brahmer J, Andrews S, Armand P, Bhatia S, et al. NCCN guidelines insights: management of immunotherapy-related toxicities, version 1.2020. *J Natl Compr Canc Netw*. (2020) 18:230–41. doi: 10.6004/jnccn.2020.0012

48. Campochiaro C, Farina N, Tomelleri A, Ferrara R, Lazzari C, De Luca G, et al. Tocilizumab for the treatment of immune-related adverse events: a systematic literature review and a multicentre case series. *Eur J Intern Med*. (2021) 93:87–94. doi: 10.1016/j.ejim.2021.07.016

49. Petrelli F, Signorelli D, Ghidini M, Ghidini A, Pizzutilo EG, Ruggieri L, et al. Association of steroids use with survival in patients treated with immune checkpoint inhibitors: A systematic review and meta-analysis. *Cancers (Basel)*. (2020) 12:546. doi: 10.3390/cancers12030546

Frontiers in Oncology

Advances knowledge of carcinogenesis and tumor progression for better treatment and management

The third most-cited oncology journal, which highlights research in carcinogenesis and tumor progression, bridging the gap between basic research and applications to imrpove diagnosis, therapeutics and management strategies.

Discover the latest Research Topics

See more →

Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact