Factors associated with immune-related severe adverse events (Review)

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Abstract. Immune checkpoint inhibitors (ICIs) are frequently used in cancer treatment. Despite their clinical benefits, they can also cause a wide range of immune-related adverse events (ir-AEs). The overall incidence of irAEs in cancer patients treated with immunotherapy ranges from 70-90%, while that of immune-related severe adverse events (ir-SAEs) is 10-43%. ir-SAEs pose a significant risk to patient safety as they are extremely frequent and lethal. Due to non-specific manifestations, rapid progression and significant morbidity, it is essential to identify factors associated with ir-SAEs early to predict high-risk groups for treatment safety. However, less information is available on the factors causing ir-SAEs, and further research is needed. The present study reviews the factors associated with ir-SAEs in terms of demographic characteristics, disease-related information and laboratory examinations to provide a clinical reference. In terms of demographic characteristics, age, body mass index, smoking, ethnicity and cancer family history may influence the incidence of ir-SAEs. Regarding disease-related information, the risks factors associated with ir-SAEs may include disease history, treatment regimen and cancer type. For laboratory examinations, risk factors associated with ir-SAEs include the laboratory examination parameters of peripheral blood cells, immunocytes, cytokines/chemokines, genetics, gut microbia, proteins and brain injury markers. All of these risk factors can stimulate the body's inflammatory response, leading to over proliferation of T cells and other inflammatory factors. In addition, the use of ICIs may disrupt gut microbial homeostasis and dysregulate the pre-existing intestinal ecology, which may therefore trigger inflammatory signaling pathways, affect overall immune function and increase the occurrence of ir-SAEs. In response to the aforementioned risk factors, it is recommended that medical professionals incorporate their analysis into routine patient testing for early identification of patient ir-SAEs and to create early individualized interventions to improve the safety for immunotherapy patients.

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Abbreviations: ICIs, immune checkpoint inhibitors; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; irAEs, immune-related adverse events; ir-SAEs, immune-related severe adverse events; BMI, body mass index; FHC, cancer family history; NSCLC, non-small cell lung cancer; ICI-AKI, ICI-related acute kidney injury; AD, autoimmune disease; TKIs, tyrosine kinase inhibitors; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio

Key words: ICIs, irAEs, PD-1, PDL1 inhibitors, CTLA4

Contents

1. Introduction

The immune checkpoint inhibitors (ICIs), represented by programmed cell death protein-1 (PD-1) and programmed death-ligand 1 (PD-L1), as well as cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), have greatly improved clinical the outcomes in patients with cancer in comparison to cytokine-based immunotherapies of more than a decade ago (1-3), but can cause a series of irAEs (4). In all patients who take ICIs, irAEs can affect almost every organ, with an overall incidence of 70-90% (5), while the incidence of immune-related severe adverse events (ir-SAEs) is between 10-43% (6,7). irAEs are classified according to the Common Terminology Criteria for Adverse Events version 5.0 (5), and

grades 3-5 are considered severe. Anti-PD-1 and -PD-L1 therapies cause 10 and 30.1% of ir-SAEs, manifested as pneumonitis, hepatitis and neurotoxicity, while the 31% of severe ir-SAEs caused by anti-CTLA-4 therapy manifest as colitis and diarrhea (6-9). ir-SAEs, including immune myocarditis, can lead to treatment interruption, poor prognosis and patient death.

The identification of ir-SAEs is further complicated by the fact that ICIs are often chosen in combination with chemotherapy, targeted therapy, radiotherapy and other therapies in current tumor treatment modalities (10-13). Determining that AEs are caused by ICIs rather than concurrent treatment modalities is challenging. In addition, the lack of distinct clinical manifestations of ir-SAEs in the early stages of treatment makes identification difficult for healthcare professionals, and early judgment can affect decisions about treatment approaches. For example, immune checkpoint-related pneumonia is similar to infectious pneumonia in terms of clinical symptoms and imaging, and immune-associated pneumonia has a mortality rate of 35% (9). If irAEs cannot be diagnosed accurately, it will delay the treatment of adverse reactions and antitumor therapy for patients, and in addition, the use of other incorrect agents will increase the toxicity of the drugs for patients, so that they will lose the chance of prolonged survival and a cure, which will lead to irreversible consequences.

Risk factor studies are critical to improving patient safety by helping to identify ir-SAEs early, monitoring changes in irAEs and clarifying treatment regimens that lead to adverse events in patients on multiple lines and multi-drug therapy. However, fewer current studies have reported the risk factors associated with ir-SAEs than the predictors of ICI efficacy (14). There is a dearth of information on factors associated with ir-SAEs, and additional research is required to identify contributing factors. Therefore, the present review examines the factors that affect patients with ir-SAEs, including demographic characteristics, disease-related information, blood indices and biomarkers. The aim of the present review is to assist medical professionals in assessing and treating ir-SAEs, alleviating patients' physical and emotional strain, and ensuring treatment safety.

2. Factors associated with ir-SAEs

Risk factors associated with ir-SAEs include the demographic characteristics of age, body mass index (BMI), smoking, ethnicity and family history of cancer (FHC).

Age. Baldini *et al* (15) investigated 603 patients treated with anti-PD-1/PD-L1 and found a higher incidence of ir-SAEs in patients aged ≥70 years than in those aged <70 years (33 vs. 25%; P<0.05) (15). Elderly patients are a group of concern for ir-SAEs, as the immune system changes with age, exhibiting reduced infiltration of B cells, CD8 T cells and myeloid dendritic cells. When treated with ICIs, this change may activate more T cells, leading to increased immune responses in various organ systems and causing ir-SAEs (16,17). Therefore, when using immunotherapy in the elderly in the clinic, it is still necessary to assess the benefit, strictly monitor the process of use and be alert to the occurrence of ir-SAEs to ensure the safety of the drug. However, there have been inconsistent results with regard to age. Ksienski *et al* (18) retrospectively analyzed 302 patients with melanoma treated with anti-PD-1, comparing the incidence of irAEs between groups aged <75 and ≥75 years, and showed that the incidence of discontinuation due to immunotoxicity was similar (31.8 vs. 40.0%; P=0.50) (18). The reasons for the different findings might be attributed to differences in the study population or research methodology. Currently, there is still a lack of data on elderly patients with cancer in ICI clinical trials and real-world studies, and more elderly patients need to be included in future in-depth studies.

BMI. A meta-analysis confirmed that high BMI (≥25 kg/m^2) increased the risk of ir-SAEs [odds ratio (OR), 2.62] (19). It was suggested that obesity may play a key role in the induction of immunotherapeutic toxicity. Obese patients can produce a variety of adipocyte-derived molecules that are responsible for altering the inflammatory and immune landscapes, and this makes patients more susceptible to triggering ir-SAEs, as the immune response of the body is exacerbated by treatment with ICIs (20). Based on these results, the study by Cortellini *et al* (21) hypothesized that patients with a high BMI have a pro-inflammatory state, which affects the regulation of immune and inflammatory responses and can lead to ir-SAEs. Lowering the BMI appears to be one of the effective ways to reduce the incidence of ir-SAEs. Therefore, healthcare professionals need to be educated on this before patients are ready to start immunotherapy. However, De Filippi *et al* (22) investigated 133 patients with Hodgkin's lymphoma treated with nivolumab and found no association between BMI and ir-SAEs. Currently, aside from the aforementioned studies, there are still few studies on BMI with ir-SAEs and the results are inconsistent, which may be related to the fact that thresholds for BMI have been defined differently in different studies. Therefore, in the future, it is necessary to define the BMI threshold and use more large-sample, full-cancer population studies to explore the relationship between BMI and ir-SAEs to further explore the intrinsic connection.

Smoking. A study by Wood *et al* (23) on 153 patients with advanced non-small cell lung cancer (NSCLC) treated with pembrolizumab found that failure to quit smoking early in treatment was also associated with ir-SAEs (OR, 2.27) (23). This condition may be related to the negative effects on the immune system of the chemicals in tobacco, such as nicotine, which not only increase the risk of inflammation and infection in the body, but also cause hyperactivation of the inflammatory system during treatment with ICIs, increasing the incidence of ir-SAEs (24). Therefore, medical staff need to advise and supervise patients who start immunotherapy but still have smoking habits, and observe them closely to detect signs of ir-SAEs as early as possible and deal with them promptly.

Ethnicity. Abdelrahim *et al* (25) found that compared with Caucasian populations, the Asian population was more susceptible to ICI-related acute kidney injury (ICI-AKI) [hazard ratio (HR), 5.970]. Consistent with the ethnic differences in their study, there were differences between ethnicities in the global prevalence of kidney injury-like diseases (such as chronic kidney disease and uremia), with Asian populations having a higher prevalence (26). The underlying mechanisms linking

ethnicity to prior ir-SAEs are unclear due to a lack of research, and the fact that relevant studies included samples of <1% of non-caucasian patients makes the conclusions much less credible. Larger sample studies are needed to explore this finding in the future.

FHC. FHC was categorized into three different types by direct and collateral branches, namely FHC-high (in cases where cancer was diagnosed in both the immediate and lateral line), FHC-low (in cases where cancer was diagnosed in only one family line) and FHC-negative. A multicenter study investigating 822 patients found that FHC-high patients were more likely to develop ir-SAEs compared with FHC-negative patients (P=0.012) (27). This result provided a link between FHC burden and the occurrence of ir-SAEs. This may be related to the higher immunosensitivity and more active immune system when treated with ICIs. Therefore, medical professionals need to pay specific attention to FHC-high patients when administering immunotherapy to patients with cancer. However, only the aforementioned study discussed the association between FHC and ir-SAEs (27), which is an area that future studies could focus on.

3. Disease-related information associated with ir-SAEs

Risk factors associated with ir-SAEs include the disease-related information of disease history, treatment regimen and cancer type.

Disease history. Risk factors associated with ir-SAEs include a disease history of autoimmune diseases (ADs) and cardiovascular disease.

AD. In early clinical trials of ICIs, patients with AD were mostly excluded, but they are not excluded from treatment by the U.S. Food and Drug Administration With the widespread use of ICIs, there is a growing need for more reliable data for patients with AD combined with cancer who require ICI therapy. Several studies have confirmed increased ICI-associated risk of ir-SAEs in patients with AD due to abnormal immune function. Sorah *et al* (28) investigated 14 patients and found that a history of AD was a significant predictor of ICI-AKI (14%). Akturk *et al* (29) reported 2 cases of ir-SAEs in patients with AD treated with anti-PD-1 therapy, suggesting that physicians should be cautious in treating such patients with ICIs. This may occur as pre-existing AD in the context of immunotherapy causes T cells and other immune cells to be activated, which can lead to a high susceptibility to ir-SAEs (30). However, Tang *et al* (31) investigated patients with cancer treated with PD-1/PD-L1 and found that patients with a history of AD had no increased risk of death from ir-SAEs (HR, 1.03). Although this is excellent news for patients with cancer suffering from AD, the large variations in sample size and tumor type between studies are still not eliminated based on the safety of the life of the patient.

Cardiovascular disease. By reviewing 3,326 oncology patients undergoing ICIs in the Mayo Clinic from March 2010 to July 2019 to analyze the clinical relationship between cardiovascular disease and patients receiving immunotherapy, Oren *et al* (32) demonstrated the association of hypertension with ir-SAEs (OR, 4.3; HR, 1.32) (32). Noseda *et al* (33), using the VigiBase database, found that drugs labeled for the treatment of cardiovascular disease were risk factors for severe ICI-associated myocarditis when selecting 108 cases of ICI-associated myocarditis and 108 non-myocarditis irAEs controls (Cramer's coefficient of effect size: φ=0.214) (33). Many electronic databases, such as VigiBase, are unable to provide comprehensive information on whether patients had comorbidities before treatment. The databases only provide information on concomitant medications and their indications for use. Accordingly, it can be hypothesized that patients with cardiovascular disease have a higher risk of developing ir-SAEs, which is also associated with an increased inflammatory response in the body that is exacerbated by the stimulation of the immune system by ICIs during immunotherapy. Despite the paucity of information related to the disease history, considering the clinical complexity surrounding disease history development, healthcare professionals should do a thorough job of asking questions and fully understanding the history of the disease to achieve early prevention. By constructing a large database of adverse events to assist medical personnel in making accurate judgments about medication choices for this population, and by strengthening close observation before, during and after the treatment process, it is believed that ICIs are equally promising for oncology populations with AD, hypertension and cardiovascular disease history.

Treatment regimen. Risk factors associated with ir-SAEs include a treatment regimen of combination therapy. Kim *et al* (34) employed a systematic review and meta-analysis to explore whether treatment regimens for patients with melanoma receiving ICIs had an impact on irAEs and found that a higher incidence of ir-SAEs occurred in combination therapy than in monotherapy (34). In the study, the incidence of ir-SAEs was 24.5% when patients were treated with a single ICI drug, while the incidence was 41.0% with the combination of two ICIs. Regardless of the type of cancer, including melanoma, lung cancer, gastric cancer and colorectal cancer, patients treated with a CTLA-4 inhibitor in combination with PD-1/PD-L1 had a higher risk of ir-SAEs than those treated with just PD-1/PD-L1 (14,35,36). Regarding the combination of chemotherapy with ICIs, a meta-analysis by Huang *et al* (37) observed that CTLA-4 inhibition combined with chemotherapy had the highest risk of ir-SAEs, with the most common being severe diarrhea (37). Furthermore, the study by Zheng *et al* (38) revealed that ICIs in combination with dacarbazine, paclitaxel or carboplatin would increase the incidence of ir-SAEs (38). This increased incidence of ir-SAEs was the same in patients who were administered ICIs combined with radiotherapy (13 vs. 1%) (39). Another type of cancer treatment is targeted therapy including tyrosine kinase inhibitors (TKIs) and macromolecular monoclonal antibodies. A number of widely known drugs, such as osimertinib, anlotinib and lenvatinib, belong to the TKI family. In a meta-analysis of pancreatic immunotherapy for renal cell carcinoma, the combination of lenvatinib plus pembrolizumab was associated with a significantly higher likelihood of ir-SAEs (40). In a retrospective study of 126 patients with NSCLC treated with osimertinib and ICIs inhibitors, Schoenfeld *et al* (41) found that the use of osimertinib was associated with an increased

incidence of ir-SAEs. Similarly, in patients with SCLC, combination therapy of anlotinib with ICIs has been found to be associated with severe immune-related pneumonia and thyroiditis (42). Macromolecular monoclonal antibodies, such as bevacizumab, were likewise found by Zhang and Xu (43) to increase the risk of ir-SAEs in patients with ovarian cancer when used in combination with PD-1/PD-L1 inhibitors. A new therapy, phototherapy, including photodynamic therapy and photothermal therapy, has also increasingly been used in various patients with cancer, such as patients with breast cancer and melanoma, with an increased efficacy as well as an increased incidence of ir-SAEs when combined with ICIs (44). A possible reason for the association of combination treatments with an increased incidence of ir-SAEs is that these treatments differentially enhance T-cell-mediated tumor cell killing, which, when combined with ICIs, leads to an increased immune status and susceptibility of the organism to ir-SAEs (44-48).

In summary, the high level of difficulty in antitumor therapy and the low immunity of patients with tumors put patients on combination regimens at higher risk for SAEs. Therefore, health education and disease observation should be strengthened for patients on combination therapy.

Cancer type. Risk factors associated with ir-SAEs include the cancer types of superficial spreading melanoma, lung cancer (especially NSCLC), breast cancer and renal cell carcinoma.

L'Orphelin *et al* (49) conducted a study using data from the RicMel database and linked the previous history of cancer and treatment with anticancer drugs to the late onset (>1 year) of ir-SAEs in patients with superficial spreading melanoma (OR, 5.23) (49). Using data from the REISAMIC database of 1,187 patients receiving ICIs, Ruste *et al* (50) found lung tumors to be a risk factor for developing ICI in patients with ir-SAEs. With regard to lung cancer histological types, according to the study by Brumberger *et al* (51), patients with NSCLC are more likely to develop ir-SAEs than those with SCLC. A meta-analysis study comprising 11 trials showed that among patients with cancer using pembrolizumab, patients with breast cancer were most likely to develop ir-SAEs (52). After further analysis of the different types of ir-SAEs, Khoja *et al* (6) observed that patients with renal cell carcinoma were more susceptible to ir-SAEs in the lungs at the time of immunotherapy compared with patients with melanoma, whereas patients with melanoma were more susceptible to skin and gastrointestinal tract ir-SAEs (6). Although the exact mechanistic role of histology remains elusive, these findings may be interpreted as the differences in the immune microenvironment between different cancer types driving tissue-specific ir-SAEs (6). Regarding common cancer types, while 20-50% of patients with liver or gastric cancer have been reported to develop ir-SAEs following immunotherapy, whether these cancers are associated with a higher overall frequency of ir-SAEs has been rarely explored (53). Only one study by Lou *et al* (54) investigated the relationship between hepatocellular carcinoma subtypes and the occurrence of ir-SAEs. However, the study found no difference in the incidence of ir-SAEs when analyzing the toxicity profiles of ICIs in patients with different types of hepatocellular carcinoma (54). The current analysis primarily included the association between lung cancer and melanoma patients and the incidence of ir-SAEs, and rarely addressed other populations. As patients with a wide range of cancer types are enrolled in ICI treatments, future studies will need to add analyses of more cancer types. Based on the widespread use of ICIs in various solid cancer types, multiple subgroup analyses could be conducted in future studies with large samples to explore whether cancer type can be used as a risk factor for ir-SAEs.

4. Laboratory examinations associated with ir-SAEs

Risk factors associated with ir-SAEs include the laboratory examination parameters of peripheral blood cells, immunocytes, cytokines/chemokines, genetics, gut microbia, proteins and brain injury markers (Fig. 1).

Peripheral blood cells. Studies have confirmed the association between baseline neutrophil-to-lymphocyte ratio (NLR) levels and the occurrence of ir-SAEs. Liu *et al* (55) investigated 150 patients with NSCLC treated with anti-PD-1 therapy and found that low baseline NLR was associated with ir-SAEs. Zhao *et al* (56) observed the association of ir-SAEs with a baseline NLR of >6 in 832 patients treated with PD-1 (OR, 1.16). However, the NLR values were not consistent. Takada *et al* (57) observed that, in 73 patients with gastric and renal cancer treated with nivolumab, the risk of developing ir-SAEs was reduced when baseline NLR was <4.3. Regardless of the threshold, various studies have shown that imbalances in the NLR are associated with a higher incidence of ir-SAEs. The NLR is a general immune response marker to various stress stimuli, and an imbalance in the NLR directly reduces the antitumor immune response, which can lead to an overactive body immune response when treated with ICIs, thereby increasing the incidence of ir-SAEs (58).

Besides the NLR, there are other blood cell parameters that have been reported to be associated with ir-SAEs, such as the platelet-to-lymphocyte ratio (PLR) and neutrophil levels. The study by Liu *et al* (55) included 150 patients with NSCLC receiving PD-1 inhibitors and analyzed the association of peripheral blood markers with ir-SAEs. It was concluded that low PLR and low baseline neutrophil levels were significantly associated with the development of ir-SAEs (P-values of 0.0016 and 0.009, respectively) (55). As first-line cells responding to inflammatory reactions, neutrophils play an important role in the defense against invading pathogens during infectious inflammation in the body (59). The increase in PLR also reflects a relative increase in platelet count, and studies have shown that platelets can release anti-inflammatory factors in addition to being involved in hemostasis. In an inflammatory state, platelets balance the body's inflammatory response by releasing anti-inflammatory factors (60). However, the complexity of the relationships in hematological indices will require future large-scale, well-designed randomized controlled studies to analyze the relationship between blood cells and ir-SAEs. Peripheral blood cells have the advantages of easy access and low cost to assess, especially NLR and PLR, which can reflect the inflammatory state and have gained the attention of physicians. It is believed that more related studies will be reported in the future.

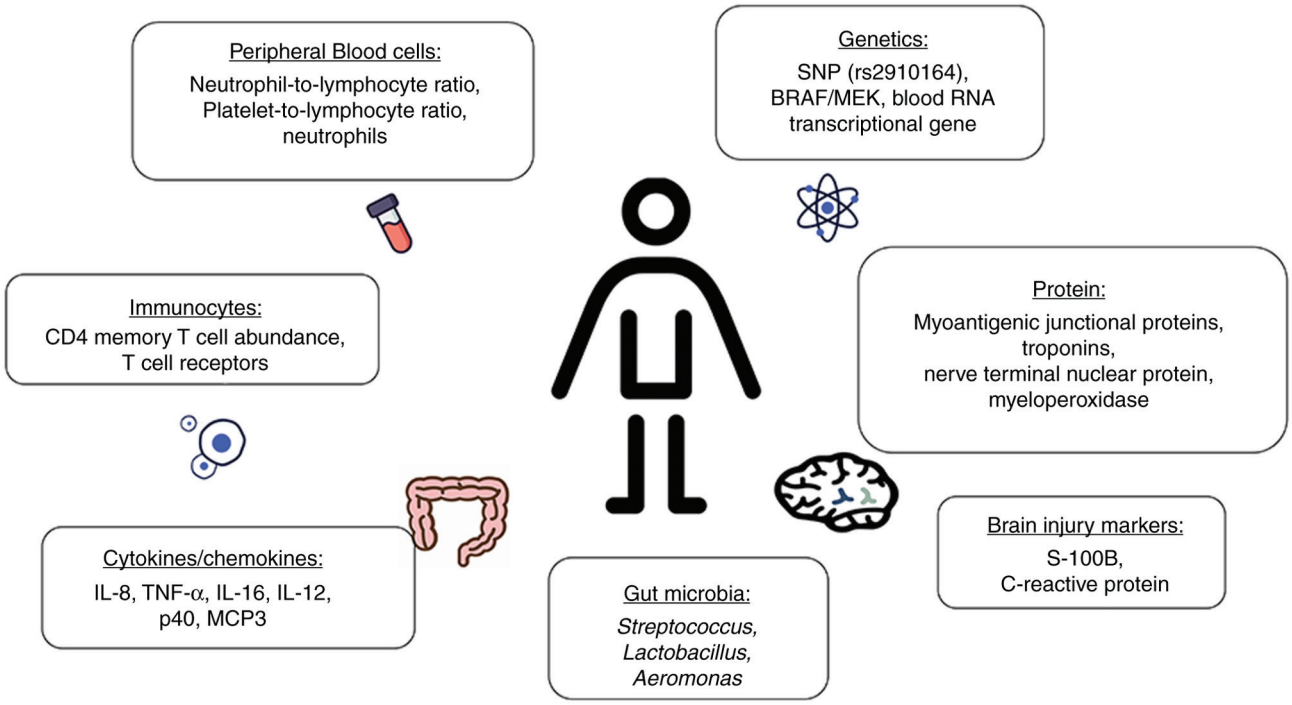

Figure 1. Components of the laboratory examination associated with immune-related severe adverse events.

Immunocytes. Activated CD4 memory T-cell abundance and more diverse T-cell receptors in the peripheral blood before treatment were associated with ir-SAEs in 164 patients with melanoma treated with ICIs [area under the curve (AUC)=0.90 and AUC=0.80] (61). Meanwhile, enrichment of regulatory T cells in colitic lesions showed a close association with severe immune-associated colitis. A study involving 209 patients with cancer from global pharmacovigilance databases found an association between increased $CD4^+$ T cells and immune-associated encephalitis (62). By including a comparison of 28 healthy people and 87 advanced patients with NSCLC treated with ICIs, Zamora *et al* (63) concluded that patients in the $CD4^+PLT^+$ low and $CD14^+PLT^+$ high percentage groups presented with a higher rate of ir-SAE (63). Das *et al* (64) analyzed changes in circulating B cells before and after the first cycle of treatment in 39 patients with advanced melanoma who underwent immune checkpoint blockade, concluding that patients with early B-cell alterations experienced a higher incidence of ir-SAEs ($P<0.001$). The increased levels of inflammatory factors are mainly related to the mechanism of irAEs. The application of ICIs enhances the activity of T cells against antigens present in tumors and healthy tissue, and increases the levels of pre-existing autoantibodies and inflammatory factors (4). This indicates the involvement of inflammatory factors in the development of irAEs. Since CTLA-4 and PD-1 are involved in the regulation of B-cell and T-cell tolerance (64), anti-CTLA-4 and anti-PD-1 cause B-cell alterations and increase the risk of autoimmunity. Although the mechanism of irAEs is not clear yet, immune cells may be potential predictors of ir-SAEs and can help healthcare professionals gain a deeper understanding of the mechanisms.

Cytokines/chemokines. The study by Chao *et al* (65), which included 164 patients with NSCLC undergoing ICIs, revealed that higher baseline levels of IL-8 were associated with a lower incidence of checkpoint inhibitor pneumonitis in patients with NSCLC (OR, 0.758) (65). The study conducted by Costantini *et al* (66) analyzed the plasma of 35 patients with NSCLC and found that higher levels of TNF-α ($P=0.036$), IL-16 ($P=0.040$), IL-12p40 ($P=0.015$) and MCP3 ($P=0.025$) were all predictive biomarkers of ir-SAEs. Cytokines are a class of small molecule proteins that have a wide range of biological activities and play a key role in life activities by regulating intrinsic immunity, adaptive immunity and repairing damaged tissues (67). A previous study revealed that cytokines are associated with a variety of ADs, including thyroiditis, inflammatory bowel disease and systemic sclerosis (68). Therefore, cytokines are recognized as risk factors that are strongly associated with ir-SAEs. However, the diversity of ir-SAEs with a wide range of cytokines also provides challenges for future studies. In addition, with the progressive development of cytokine inhibitors in the treatment of ir-SAEs, exploring which cytokine inhibitors are effective in overcoming tissue-specific ir-SAEs is a key to future research.

Genetics. Patient genetic background is a crucial predictor of irAE susceptibility. A single nucleotide polymorphism (rs2910164) responsible for reduced miR-146a expression was associated with ir-SAEs in 167 patients with cancer (69). Huang *et al* (37) included 25 randomized controlled trials (12,925 patients with advanced melanoma) and found that ir-SAEs were associated with a high incidence of overall BRAF/MEK expression (32.11%) (37). Analysis of 360 patients with melanoma revealed that whole blood RNA transcriptional gene markers were associated with severe immune-related diarrhea (AUC=0.785) (70). Expression of these genes may be associated with hypersensitivity of the

immune system. In addition, genes that are simultaneously expressed on the surface of specific organs and tumor cells contribute to the high incidence of ir-SAEs (71). The identified genetic variants can be used to construct polygenic risk scores, thus providing patients and clinicians with personalized scores that measure the risk of ir-SAEs. In the future, more genomic prediction models should be developed that are more accurate and suitable for clinical use and measurement to facilitate the timely identification of populations at risk for ir-SAEs.

Gut microbia. Liu *et al* (72) found that high concentrations of *Streptococcus*, *Lactobacillus* and narrow-feeding *Aeromonas* in baseline stool samples from 150 patients receiving anti-PD-1 therapy were associated with ir-SAEs (AUC=0.66) (72). The use of ICIs may disrupt gut microbial homeostasis and dysregulate the pre-existing intestinal ecology, which is typically characterized by a reduction in microbial diversity and/or substantial changes in resident species. In turn, ecological dysregulation in the gut may trigger inflammatory signaling pathways and affect overall immune function (73). This gives medical professionals hope that gut microbes can be used as predictive markers for ir-SAEs. Future work is needed to assess whether the effects of gut microbes are consistent across tumors and across drugs.

Protein. Okazaki *et al* (74) found that in PD-1-deficient mice that developed dilated cardiomyopathy, the cause of the cardiomyopathy was the production of anti-cardiac troponin I. The study also found myoantigenic junctional proteins and troponins expressed in primary tumors in myocardial tissues of immune-associated cardiomyopathies, concluding that these antigens may trigger immune responses to normal myocardial tissues (74). Elevated levels of troponin, nerve terminal nuclear protein (NT-proBNP) and myeloperoxidase are predictive factors of the development of ir-SAEs. The reason for this is that elevated levels of these proteins lead to a mechanism of inflammatory cell infiltration associated with cardiomyocyte degeneration/necrosis (75). However, studies on proteins in this context are still rare and more, large-sample, well-designed studies are needed to determine their role in increasing the incidence of ir-SAEs.

Brain injury markers. By analyzing 1 patient with melanoma who developed encephalitis after using ICIs, Bjursten *et al* (76) observed that brain injury markers S-100B and C-reactive protein increased before the appearance of signs or symptoms of encephalomyelitis; this suggests a potential role for the costimulatory receptor inducible T-cell costimulatory receptor on $CD4^+$ and $CD8^+$ T cells in mediating encephalomyelitis and other severe irAEs. In addition, brain damage markers in the blood could facilitate the early diagnosis of encephalitis (76). There is a very small number of studies on proteins and markers of brain injury, but it has been reported that such markers reappear after the onset of irAEs (76). Thus, these disease-related markers are not predictive but help medical personnel to observe and analyze ir-SAEs.

5. Conclusion

Immunotherapy increases the incidence of ir-SAEs, which can be fatal to patients receiving ICIs. Thus, the early detection of patients at high risk for ir-SAEs is essential for effective prevention of adverse outcomes and improvement of the safety of the treatment. The present review summarizes the factors associated with ir-SAEs in terms of demographic characteristics, disease-related information and laboratory examinations by consolidating data from various studies. Inconsistency in the results of studies related to risk factors such as age, BMI, disease history and cancer type may be due to differences in the types of cancer studied, the small sample sizes or the differences in the methodology of the studies. Future prospective studies should be conducted to validate these findings using larger cohorts and standardized methods. Collectively, the present review emphasizes the immense need for research on the determinant of ir-SAEs. Risk factors for predicting and tracking ir-SAEs in patients receiving immunotherapy could be used to facilitate tailored monitoring, early identification and intervention, and customized treatment. Healthcare professionals must be trained to recognize these risk factors, and high-risk individuals with risk factors must be closely monitored for ir-SAEs. For risk factors that can undergo intervention, such as smoking and abnormal BMI, medical professionals need to inform patients in good time and guide them to make adjustments in order to reduce the occurrence of ir-SAEs.

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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