Safety and Efficacy of Immune Checkpoint Inhibitors in Advanced Cancer patients with Autoimmune Disease: a Meta-Analysis

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Research Article

Keywords: cancer, autoimmune disease, immune checkpoint inhibitors, immune-related adverse events, progression-free survival, overall survival

Posted Date: May 11th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1537689/v3

Abstract

Background: Cancer patients with autoimmune disease (AID) are usually excluded from clinical trials involving immune checkpoint inhibitors (ICIs); their safety and effectiveness remain uncertainty.

Methods: The available electronic databases were systematically searched. We recorded the incidence of immune-related adverse events (irAEs), progression-free survival (PFS), and overall survival (OS) of included studies.

Results: This meta-analysis included 11 studies comprising 5489 participants. The pooled risk ratio (RR) for any grade and grade ≥3 irAEs was 1.79 (95% confidence interval [CI]: 1.31-2.45) and 1.58 (95% CI: 1.06-2.36), respectively. The irAEs in the same system as the AID were referred to as AID-homogeneous irAEs, otherwise known as AID-heterogeneous irAEs. Subgroup analysis found that the higher risk of AID-homogeneous irAEs contributed to the higher risk of overall irAEs among patients with AID. The pooled hazard ratio (HR) for PFS and OS was 1.09 (95% CI: 0.96–1.25) and 1.10 (95% CI: 0.68–1.77), respectively. The results of PFS and OS subgroup analyses matched the overall results.

Conclusion: patients with AID had a significantly higher risk of developing any grade and ≥3 grade irAEs under ICI therapy, specifically AID-homogeneous irAEs; however, AID-heterogeneous irAEs were higher among patients with AID than in those without. No statistically significant differences in PFS and OS were observed between two groups.

1. Introduction

The therapeutic outlook for many malignancies has fundamentally changed owing to the advent of immune checkpoints inhibitors (ICIs)[1–3], a radical transformation of the antitumor concept that directly kills tumor cells to regulate the immune microenvironment. ICIs aim to block negative co-stimulation of T lymphocytes, which can activate anergic T cells, thus restoring their antitumor effects[4]. This differs from chemotherapy and targeted therapies. However, immune-related side events caused by ICIs have gradually attracted the attention of clinicians.

To distinguish between self and non-self, the immune system was finely tuned to maintain host integrity[5]. Autoimmune disease (AID) occurs when the immune system overactivates autoantigens[6]. Varieties autoimmune diseases can occur in any body system. The common pathogenesis is the loss of tolerance to autoantigens, leading to attack of organs[7]. It is unclear whether the immunological and molecular mechanisms of each autoimmune disease are related to breakdown of tolerance to autoantigens[8]. The common clinical manifestations of autoimmune diseases are similar to the immunological side effects associated ICIs[9]. Fearing deterioration of preexisting AID, cancer patients with AID are often excluded from clinical trials involving ICIs[10, 11].

Individuals with AID are often at higher risk of tumorigenesis[12], which in turn increases the risk of AID[13]. Owing to abnormalities of immune system, it is unclear whether patients with AID will benefit from ICIs. A previous study reported that ICIs were effective in patients with AID, with often manageable immune-related adverse events (irAEs)[14]. However, this study did not compare progression-free survival (PFS) and overall survival (OS) between patients with and without AID. Based on this background, published data from several studies that treated AID patients with ICIs were systematically collected. We aim to assess the rate of irAEs, PFS, and OS of patients on ICI therapy.

2. Methods

2.1Literature search

Electronic databases, including PubMed, Web of Science, EMBASE, and Google Scholar from inception until February 2022, were searched to identify eligible studies without language restrictions. The medical subject headings (MeSH) are following: cancer, melanoma, leukemia, lymphoma, multiple myeloma, sarcoma, malignant mesothelioma, immune-related adverse event, irAEs, autoimmune disease, autoimmune disorder, lupus, interstitial lung disease, autoimmune thyroiditis, inflammatory bowel disease, rheumatoid arthritis, CTLA-4, ipilimumab, PD-1, nivolumab, pembrolizumab, cemiplimab, PD-L1, atezolizumab, durvalumab, avelumab, PFS, OS. In addition, the related bibliographies of the retrieved articles were also searched in case any articles were missing.

2.2 Eligibility criteria

Studies were eligible if the following conditions were met: (1) patients had advanced cancer or other malignant diseases; (2) patients had pre-existing autoimmune disease; (3) patients were treated with ICIs, including PD-1, PD-L1, CTLA-4 agents; and (4) studies reporting the incidence of irAEs, exact hazard ratio (HR) values, or survival curve for PFS and/or OS. Studies were excluded if (1) they only reported irAEs without PFS or OS; (2) they reported PFS and OS as survival rates in percentage terms; (3) they included patients diagnosed with autoimmune diseases after treatment of ICIs; (4) they discussed autoimmune antibodies instead of autoimmune diseases; and (5) they were case reports.

2.3Data extraction and quality assessment

Two authors (QC and GW H) reviewed and screened the content of all eligible studies using a predefined data extraction form. All the patients in each study were divided into AID (cancer patients with AID) and non-AID(cancer patients without AID) groups. We calculated the total number of patients in the AID group and non-AID groups, number of patients developing any grade or grade ≥ 3 irAEs, and incidence of irAEs, which was reported as risk ratio (RR). The outcome measures, PFS and OS, were assessed and consistently reported as HRs. The following information was collected independently: the first author's name, publication time, country, and patient characteristics, such as number of patients, proportion of sex, type of autoimmune disease, class of malignancy, and category of immunotherapy. The New Castle–Ottawa Scale was used to evaluate the quality of each study. Any disagreement was resolved by an experienced reviewer (FY Z) or through discussions.

2.4 Statistical analysis

R software (version 4.1.3) was used for data analyses. RR was used to reflect the incidence of irAEs of any grade and grade ≥ 3[15–21]. If the studies recorded HR for PFS or OS, we adopted the results. For some studies [15–19, 22] that lacked HR for PFS or OS values, we downloaded the Kaplan–Meier curves, used drawing tools to extract the curves' data, and estimate HR using Jayne F Tierney's spreadsheet[23]. Calculations were independently repeated twice to obtain precise results[24]. We reported pooled RR with 95% CI for irAEs and the pooled HR with 95% CI for PFS and OS. Forest plots were used to represent the pooled results. Statistical heterogeneity was estimated using I^2 test. I^2 < 50% and > 50%was considered as low and high heterogeneity, respectively. Statistical significance was set at $p < 0.05$.

3. Result

3.1 Literature search results

In total, 5754 relevant articles were initially retrieved from database searches; 5502 studies were excluded either because they were repetitive or did not meet the study's requirements after screening of titles and the abstracts. In total, 252 studies were considered eligible for further assessment. Eleven studies were included in the analysis. Details of the inclusion and exclusion process are presented as a flowchart (Fig. 1).

3.2 Characteristics of the selected studies

Eleven eligible citations were included, nine of which adopted a retrospective design, with only two cohort studies. All articles were published between 2014 and 2021. A total of 8,277 participants were included, of which 5156 (62.3%)were male; a detailed description of the patients' characteristics is contained in the meta-analysis presented in Table 1. Of these, 5489 participants were treated with ICIs. These studies mainly took place in Asia and Europe, with only one in the US. Among these, three studies were from Japan[15, 16, 22], one from Korea [17], two from the Italy [18, 25], one from Germany[26], one from the UK[19], one from Switzerland[20], one from Holland[27], and one from the US[21]. Seven studies focused on non-small cell lung cancer [15–17, 19, 22, 26], four reported melanoma[18, 21, 25, 27], and two involved in metastatic renal cell cancer and urothelial carcinoma[18, 20]. Among AIDs, pneumonic AID and endocrine AID were the most frequently mentioned. Specific information on irAEs, survival, and quality characteristics is presented in Tables 2,3,4, and 5, respectively.

Table 1
Detailed description of the characteristics of included studies

Author	Year	Gender Male(%) Female(%)	Age	Type of Autoimmune Disease	Type of Cancer	Immunotherapy Regimen
U. Bottoni et al.	2014	48(24.1%) 151(75.9%)	< 60 56.3% ≥ 60 43.7%	Autoimmune thyroiditis 55.1% Rheumatoid arthritis12.2% Others32.7%	melanoma	CTLA-4
Osamu Kanai et al.	2018	154(71.3%) 62(28.7%)	69 (30–89)	Interstitial lung disease	NSCLC	PD-1 (nivolumab)
Alessio Cortellini et al.	2019	499(66.4%) 252(33.6%)	69(24–92)	Thyroid disorders60% Dermatologic16.4% Rheumatologic11.8% Others 11.8%	NSCLC65.5% Melanoma21.2% Kidney cancer 12.5% Others0.8%	PD-1 (pembrolizumab) (nivolumab)
Ryota Shibaki et al.	2019	223(62.3%) 135(37.7%)	62(27–84)	Interstitial lung disease	NSCLC	PD-1 (nivolumab) (pembrolizumab)
Seonggyu Byeon et al.	2020	167(70.5%) 70(29.5%)	60(35–80)	Rheumatoid arthritis7.1% Behcet's disease7.1% Interstitial lung disease85.3%	NSCLC	PD-1 (pembrolizumab) (nivolumab)
Yuri Tasaka et al.	2020	337(73.1%) 124(26.9%)	69(34–88)	Interstitial lung disease	NSCLC	PD-1 (atezolizumab)
Yohann Loriot et al. [a]	2020	772(77.4%) 225(22.6%)	69(41–82) 68(34–93)	psoriasis	urinary tract carcinoma	PD-L1 (atezolizumab)
Martin Faehling et al.	2020	82(65.1%) 44(34.9%)	62.4(33.5–81.6)	NA	NSCLC	PD-L1 (durvalumab)
Sonam Ansel et al.	2020	41(50%) 41(50%)	65(60.6–73.2)	Rheumatoid Arthritis Psoriasis Idiopathic pulmonary fibrosis Raynaud's Disease Fibromyalgia Post-polio Syndrome Multiple sclerosis	NSCLC	PD-1 (pembrolizumab)

[a]: We chose baseline characteristics of cohort studies; NSCLC: non-small cell lung cancer; PD-1: programmed cell death protein 1; PD-L1: programmed cell death protein ligand 1; CTLA-4: cytotoxic T-lymphocyte–associated protein 4 ; NA: not available

Author	Year	Gender Male(%) Female(%)	Age	Type of Autoimmune Disease	Type of Cancer	Immunotherapy Regimen
Nicholas Gulati et al. [a]	2021	295(61.1%) 188(38.9%)	Mean 63.29	Asthma Inflammatory bowel dsease Psoriasis Rheumatoid arthritis Eczema Polymyalgia rheumatic Other	Melanoma	CTLA-4 CTLA-4 + PD-1 PD-1
van der Kooij et al.	2021	2538(58.1%) 1829(41.9%)	< 65 67.8% ≥ 65 32.2%	RheumatologicAID Endocrine AID Inflammatory bowel disease other	Melanoma	CTLA-4 (ipilimumab) PD-1 (pembrolizumab) (nivolumab) CTLA-4 + PD-1

[a]: We chose baseline characteristics of cohort studies; NSCLC: non-small cell lung cancer; PD-1: programmed cell death protein 1; PD-L1: programmed cell death protein ligand 1; CTLA-4: cytotoxic T-lymphocyte–associated protein 4 ; NA: not available

Table 2
Detailed information of irAEs of included studies

Author	Sum AID	Any irAEs (%)	≥G3 irAEs (%)	Sum non-AID	Any irAEs (%)	≥G3 irAEs (%)
Osamu Kanai et al.	26	8(31%)	5(19%)	190	22(12%)	10(5%)
Alessio Cortellini et al.	85	56(65.9%)	8(9.4%)	666	266(39.9%)	59(8.8%)
Ryota Shibaki et al.	14	4(29%)	1(7.1%)	196	22(11%)	8(4.1%)
Yuri Tasaka et al.	49	15(30.6%)	NA	412	39(9.5%)	NA
Yohann Loriot et al.	35	24(69%)	9(26%)	962	506(53%)	112(12%)
Sonam Ansel et al.	10	9(90%)	1(10%)	72	51(70.8%)	5(6.9%)
van der Kooij et al. [b]	187	NA	31(16.6%)	1540	NA	206(13.4%)

[b]: We chose the patients treated with anti-PD-1 because they are the most in this study; AID: autoimmune disease; irAEs: immune-related adverse events; G3: grade 3; NA: not available.

Table 3
Detailed information for PFS and OS of included studies

Author	Country	Patients AID (%) Non-AID (%)	PFS(month) (AID: Non AID)	OS(month) (AID: Non AID)	HR for PFS (95%CI)	HR for OS (95%CI)	Quality
U. Bottoni et al.	Italy	49 24.6% 150 75.4%	NA	109:187	NA	3.01 (1.26–7.19)	7
Osamu Kanai et al.	Japan	26 12% 190 88%	2.7:2.9	NA	2.99 (1.04–8.62)	NA	7
Alessio Cortellini et al.	Italy	85 11.3 666 88.7%	6.8:8.0	9.8:16.5	2.31 (1.19–4.45)	1.04 (0.73–1.48)	6
Ryota Shibaki et al.	Japan	14 6.6% 196 93.4%	4.3:5.3	NA	0.97 (0.67–1.44)	NA	6
Seonggyu Byeon et al.	Korea	14 5.9% 223 94.1%	3.6:2.3	NA	1.28 (0.61–2.69)	NA	6
Yuri Tasaka et al.	Japan	49 10.6% 412 89.4%	5.9:3.5	27.8:25.2	0.94 (0.63–1.42)	1.70 (0.75–3.82)	6
Yohann Loriot et al.	Switzerland	35 3.5% 962 96.5%	NA	8.2:8.8	NA	1.80 (0.85–3.81)	7
Martin Faehling et al.	Germany	9 7.1% 116 92.9% 1 UN	NA	NA	1.01 (0.41–2.54)	1.34 (0.42–4.28)	7
Sonam Ansel et al.	UK	10 12% 72 88%	33.32:6.4	42:10.7	1.68 (0.15–18.22)	0.5 (0.19–1.3)	6
Nicholas Gulati et al.	US	74 15.3% 409 84.7%	NA	NA	0.49 (0.26–0.91)	0.21 (0.07–0.65)	8
van der Kooij et al. [b]	Holland	187 10.8% 1540 89.2%	NA	NA	1.11 (0.92–1.34)	1.08 (0.87–1.34)	8

[b]: We chose the patients treated with anti-PD-1 they are the most in this study; UN: whether he/she had AID or not was uncertain; UK: the united kingdom; US: the united states; NA: not available.

Table 4
Quality assessment of the included retrospective studies with New Castle –Ottawa quality assessment scale

Study	Case definition adequate	Representativeness of the case	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Assessment of exposure	Same method of ascertainment for cases and controls	Non-Response rate
U. Bottoni et al.	√	√	√	√	√		√	
Osamu Kanai et al.	√	√	√	√	√		√	
Alessio Cortellini et al.	√	√	√	√	√			
Ryota Shibaki et al.		√	√	√	√		√	
Seonggyu Byeon et al.		√	√	√	√	√		
Yuri Tasaka et al.		√	√	√	√	√		
Martin Faehling et al.	√	√	√	√	√			√
Sonam Ansel et al.		√	√	√	√	√		
van der Kooij et al.	√	√	√	√	√	√	√	
√ Adequacy of criteria and its absence represents inadequacy								

Table 5
Quality assessment of the included cohort studies with New Castle –Ottawa quality assessment scale

Study	Representativeness of exposed cohort	Selection of Non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up completion of cohorts
Yohann Loriot et al.	√	√	√	√	√			√
Nicholas Gulati et al.	√	√	√	√	√	√	√	
√ Adequacy of criteria and its absence represents inadequacy								

3.3 Safety

Seven studies reported irAEs, including 406 and 4038 patients in the AID and non-AID groups, respectively. Six studies reported irAEs of any grade, six of which were grade ≥ 3 irAEs. Two studies reported ICI-induced mortality. The incidence of irAEs of any grade ranged from 29–90% in the AID group and 9.5–70.8% in the non-AID group, whereas the incidence of grade ≥ 3 irAEs ranged from 7.1–26% in AID group and 4.1–13.4% in non-AID group. The AID group (RR: 1.79, 95%CI 1.31–2.45, $p < 0.01$, Fig. 2) was significantly associated with higher risk of developing irAEs; nevertheless, significant heterogeneity was detected ($I^2 = 69.0\%$, $p < 0.01$). The incidence of grade ≥ 3 irAEs (RR, 1.58; 95%CI 1.06–2.36, $p = 0.01$; Fig. 3) was also higher in AID group, and low heterogeneity was found ($I^2 = 27.3\%$; $p = 0.23$).

Subsequently, a subgroup analysis for irAEs of any grade was carried out to determine the reason for the high heterogeneity. We found that AIDs tended to aggravate irAEs in the same systems as them, but generally did not exacerbate irAEs in other systems. When irAEs occurred in the same system as the AID, we were referred to as AID-homogeneous irAE; otherwise, they were AID-heterogeneous irAEs. For example, there studies mainly discussed interstitial lung disease, and pneumonitis-related side effects were higher than non-interstitial lung disease group (RR = 2.93, 95%CI 2.01–4.27). When the AID was psoriasis, the cutaneous side effects were AID-homogeneous irAEs (RR = 1.64, 95%CI 1.10–2.47). For AID-unrelated

irAEs, the pneumonitis-side effects (RR = 1.78, 95%CI 0.75–4.22) and endocrine side effects (RR = 0.91, 95%CI 0.38–2.19) were observed. Detailed information is presented in Fig. 4.

3.4 Efficacy

Nine and eight studies reported PFS and OS, respectively. In total, 5489 participants were treated with ICIs, of these, 4293 participants were treated for PFS and 4826 participants were treated for OS. There was no significant difference in PFS (HR: 1.09, 95% CI 0.96–1.25) and OS (HR: 1.10, 95% CI 0.68–1.77) between AID and non-AID when they were treated with ICIs. There was low heterogeneity (I^2 = 30.8%; p = 0.17) in PFS; however, high heterogeneity was found (I^2 = 63.6%; p < 0.01) in OS. Forest plots of these outcomes are shown in Figs. 5 and 6, respectively.

Furthermore, we analyzed sources of heterogeneity using a subgroup analysis, such as cancer type, regional factors, and quality characteristics of these studies. For example, for cancer type in PFS, the pooled HR was 1.09(95% CI 0.86–1.37) in the NSCLC group and 0.95(95% CI 0.57–1.59) for melanoma. The results of each subgroup matched the overall results. Forest plots of the subgroup analyses are shown in Fig. 7.

3.5 Publication bias and sensitivity analysis

Publication bias was verified using a funnel plot (Supplemental Material: Figure S1) and Egger's linear regression test. There was no obvious publication bias for any grade irAEs(t = 1.66, p = 0.17), grade ≥ 3 irAEs(t = 0.68, p = 0.53), PFS (t = − 0.18, p = 0.86), or OS (t = − 0.02, p = 0.99). However, funnel plots for irAEs of any grade and OS were asymmetrical on visual inspection, indicating that the underlying publication bias should be considered. From the sensitivity analysis, our study results were reliable because the pooled results of any grade irAEs, grade ≥ 3 irAEs, PFS, and OS remained significant regardless of the study omitted. Forest plots of sensitivity analysis are shown in Figure S2.

4. Discussion

From our findings, the incidence of irAEs was higher in the AID group than in the non-AID group treated with ICIs. Specifically, AID-homogeneous irAEs are more likely to occur in the AID group than in the non-AID group, whereas no significant difference was detected for AID-heterogeneous irAEs. Survival outcomes in the AID group were almost unaffected compared to those in the non-AID group. To the best of our knowledge, we are the first to study types of irAEs that AID patients are prone to, and compare PFS and OS in cancer patients with and without AID on ICI therapy, thus filling a gap in previous studies of this kind.

As mentioned above, close relationship exists between cancer, autoimmune diseases, and immune-related adverse events[28]. Immune checkpoints are a class of immunosuppressive molecules expressed on immune cells to regulate the degree of immune activation[29]. Normally, the effector function of $CD4^+$ T cells remains stable owing to the presence of immune checkpoints[30]. Once the negative signal regulating T-cell activation is suppressed, T cells killing function is strengthen. Simultaneously, this may also enhance the immune response in normal body tissues[31]. This process resembles that of AIDs recognized by existing theories, although the pathogenesis of AIDs is not fully understood. Hence, the fear of exacerbating AIDs during ICI administration is valid. Owing to abnormalities in the immune system of patients with AID, T cell activation levels are higher than those in normal individuals. ICIs further promote T cell function such that the balance of immune system is disrupted, which can easily cause irAEs to occur. This may partly explain the high incidence of irAEs in patients with AIDs.

The major pathological and clinical manifestations of AIDs mainly manifest in the system, indicating that the immune cells of this system are in an abnormal activation state. The immune cells of other systems are generally in a normal state; hence, the frequency of irAEs is similar to that in normal people. Clinicians should pay more attention to irAEs of the same system as pre-existing AID.

Although patients with AID are at a higher risk of developing irAEs, no statistically significant reduction in PFS and OS were observed in AID group compared to the non-AID group. Meanwhile, the curative effect of ICIs in patients with AID is worthy of affirmation. This may suggest that the abnormal immune system in AID does not affect the killing function of tumor cells by T lymphocytes, or aggravation of irAEs does not shorten survival of AID patients. Considering the fatality of some irAEs, means of controlling the occurrence of irAEs during treatment is yet to be determined. Clinically, immunosuppressants such as steroids are commonly used to control irAEs. Since only two studies have discussed the use of immunosuppressants to control irAEs, we cannot rely on the limited data to accurately analyze results[15, 19]. Zhang et al. found that the OS and PFS were significantly shortened in the administration of corticosteroids [32]. However, Fausto et al. indicated that the use of steroids in cancer patients to control irAEs did not shorten OS[33, 34]. There are no definitive answers on whether, when and how steroids should be used in treatment with ICIs. Therefore, it is necessary to perform patient stratification strategies based on the severity of irAEs to determine subsequent treatment[35].

Previous studies reported that irAEs significantly correlated with better curative effect in cancer patients[36–40]. Therefore, some clinicians doubt that patients with AID may benefit more from ICIs because of their immune-activated tendency[41]. Although our findings showed that patients with AID were at higher risk of developing irAEs, we did not conclude that the survival would be prolonged in the AID group. All the above studies were conducted in non-AID cancer patients, unlike the population we studied. Moreover, several factors can affect final PFS and OS. First, regarding the ECOG status of cancer patients, it is necessary to evaluate the survival time separately, according to the performance of ECOG

status. Second, various AIDs may have mild or severe effects on the body. For instance, systemic lupus erythematosus (SLE) can affect nearly all organs and produces multiple autoantibodies[42], whereas psoriasis causes relatively minor impairments in other systems.

This study has some limitations. First, because most studies did not use ICIs in patients with AID, the number of included studies was insufficient. Second, most data collected were from retrospective studies rather than prospective clinical trials; therefore, the veracity of the information may not be sufficiently objective. Third, the included studies were mainly conducted in Asia and Europe; therefore, geographical and ethnic differences could not be excluded. Fourth, most of the malignancies included in the study were NSCLC and melanoma, with only few other cancers involved. Furthermore, six studies only reported survival curves; hence, HR was estimated from the survival curve using specialized tools. Thus, there may be a certain degree of deviation from the actual situation.

Conclusions

In summary, patients with AID were at a higher risk of developing irAEs, and AID-homogeneous irAEs were higher in the AID group than in the non-AID group, whereas no significant difference was detected for AID-heterogeneous irAEs. No statistically significant reduction in PFS and OS was observed in cancer patients with AID. Therefore, the indications of ICIs treatment can be broaden to include AID populations in routine clinic practice. Further large-scale prospective studies are required to validate our findings.

Abbreviations

ICIs	immune checkpoint inhibitors
AID	autoimmune disease
irAEs	immune-related adverse events
EMBASE	Excerpta Medica Database
PFS	progression-free survival
OS	overall survival
CI	confidence interval
RR	risk ratio
HR	hazard ratio
PD-1	programmed cell death protein 1
PD-L1	programmed cell death protein ligand 1
CTLA-4	cytotoxic T-lymphocyte–associated protein 4
MeSH	medical subject headings
NSCLC	Non-small cell lung cancer
ECOG	Eastern Cooperative Oncology Group
SLE	systemic lupus erythematosus

Declarations

Acknowledgments

The authors would like to acknowledge Prof. Peng Chen and Tianjin Medical University Cancer Institute and Hospital

and thank Editage (www.editage.cn) for English language editing.

Authors' contributions

QC and GW H conducted literature search, data extraction, risk of bias assessment. QC performed statistical analysis and wrote the original manuscript. GW H revised the manuscript and rectified some information of tables and Figs. FY Z resolved differences in data collection and revised the manuscript critically. P Y and DQ Y advised on the writing and revised the manuscript critically. All authors read and approved the final manuscript.

Funding

None.

Conflict of interests

The authors declare no conflict of interest.

Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figures

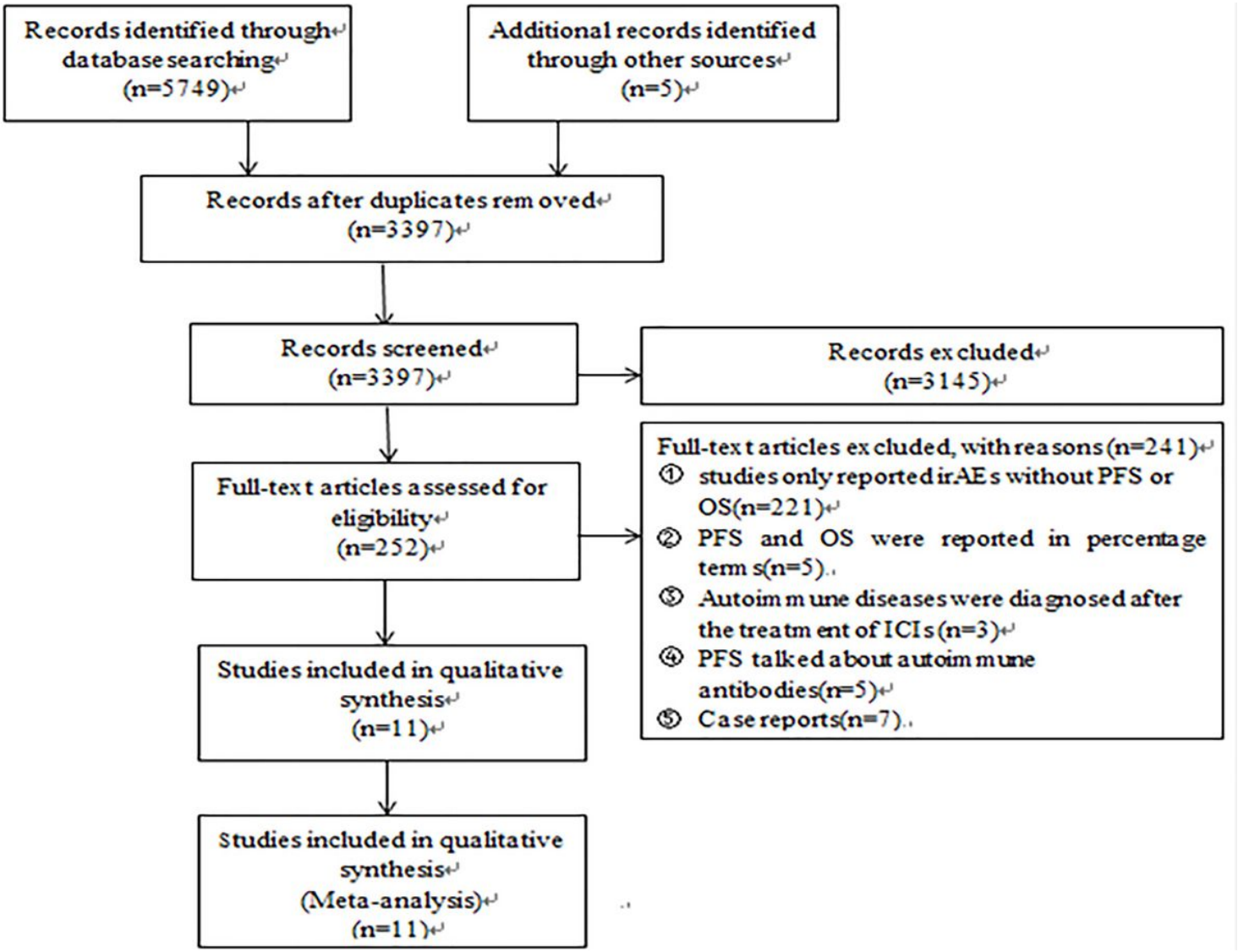

Figure 1

Selection process for the studies included in the meta-analysis.

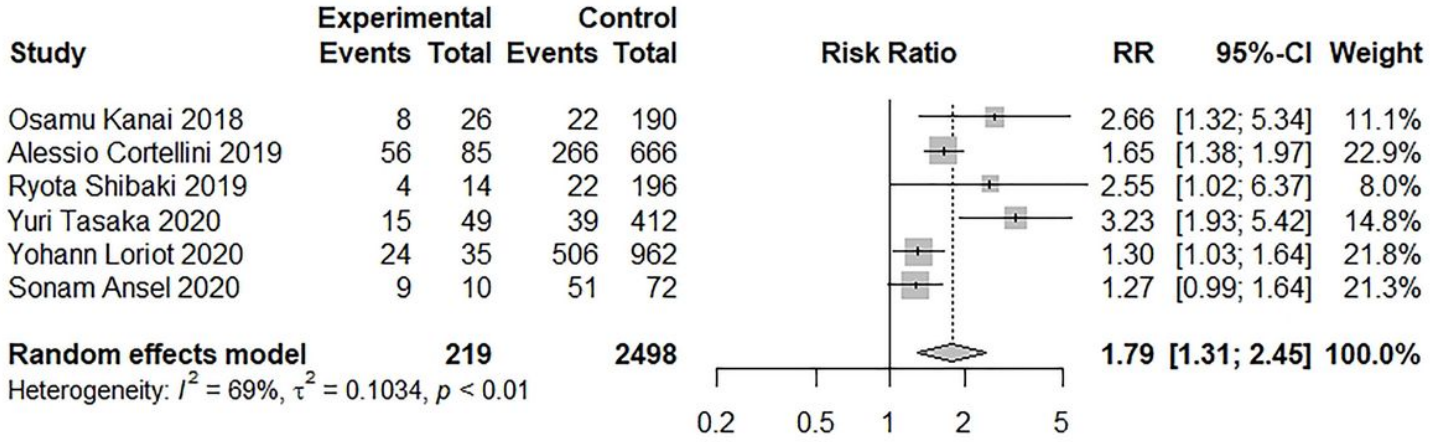

Figure 2

Forest plot of any grade irAEs in patients with and without AID receiving ICIs

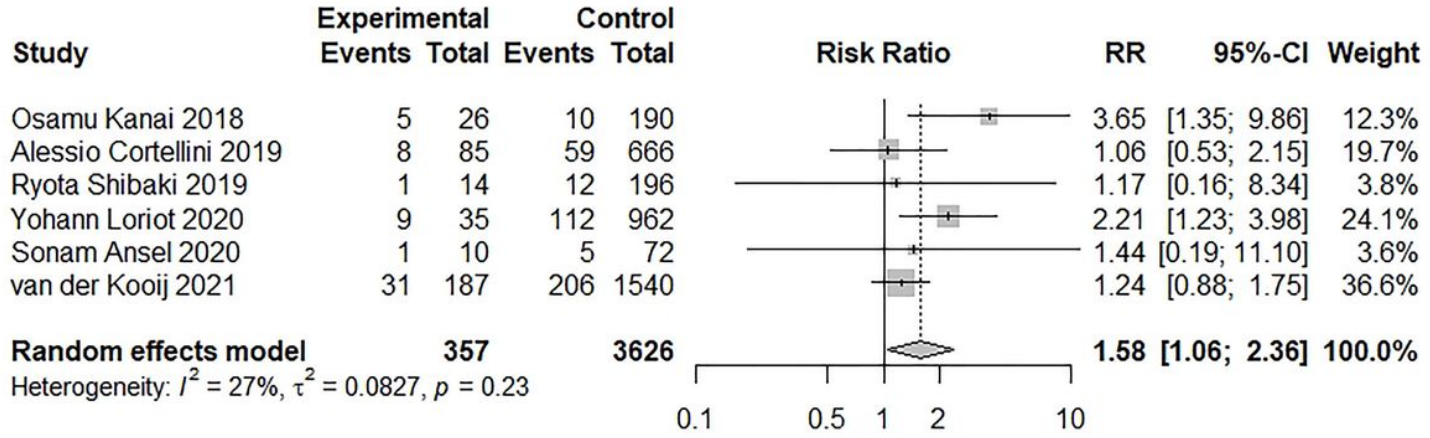

Figure 3

Forest plot of grade ≥3 irAEs in patients with and without AID receiving ICIs

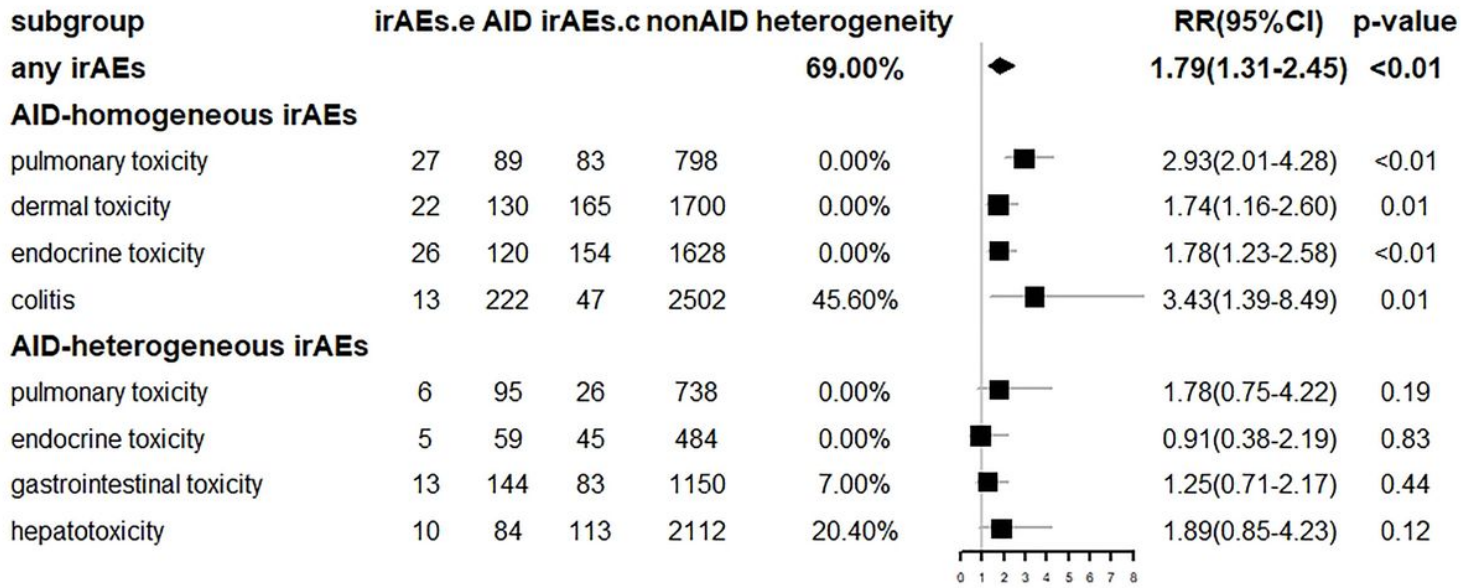

Figure 4

Forest plot of AID- homogeneous and AID-heterogeneous irAEs in patients with and without AID receiving ICIs

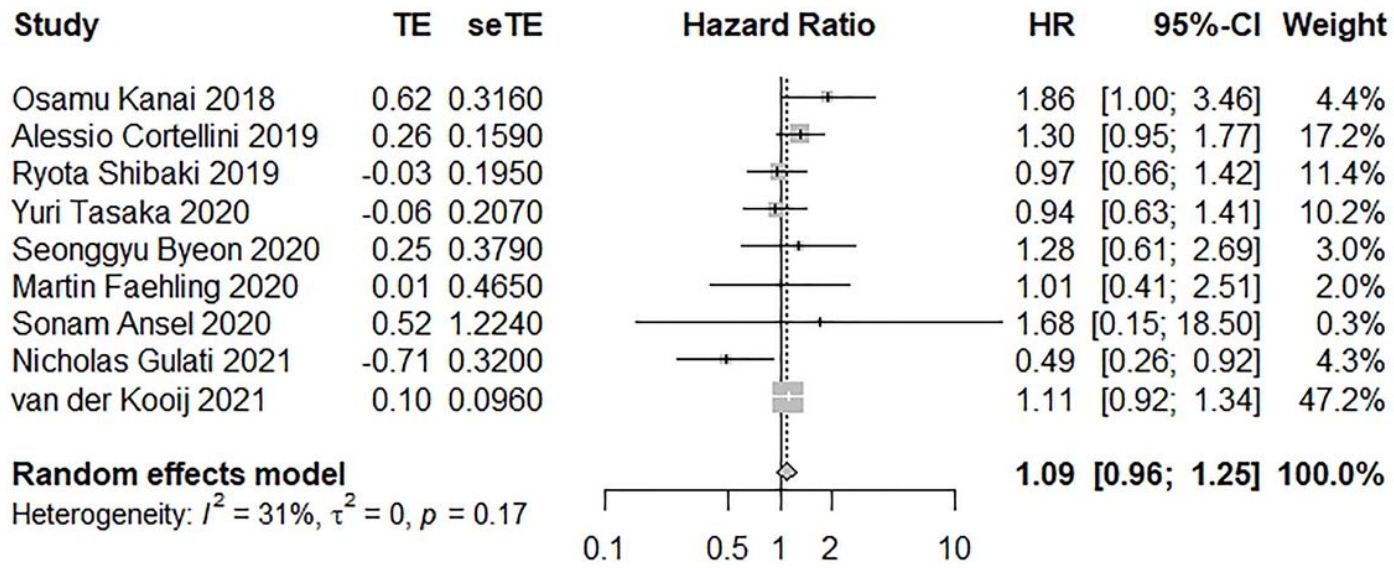

Figure 5

Forest plot of PFS in patients with and without AID receiving ICIs

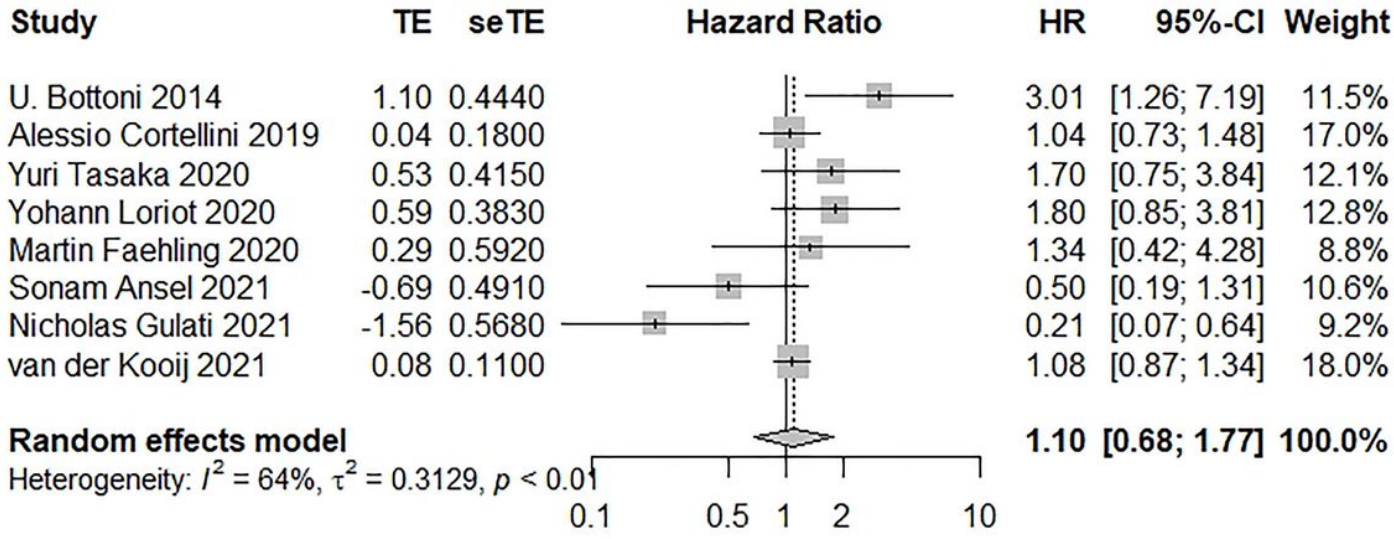

Figure 6

Forest plot of OS in patients with and without AID receiving ICIs

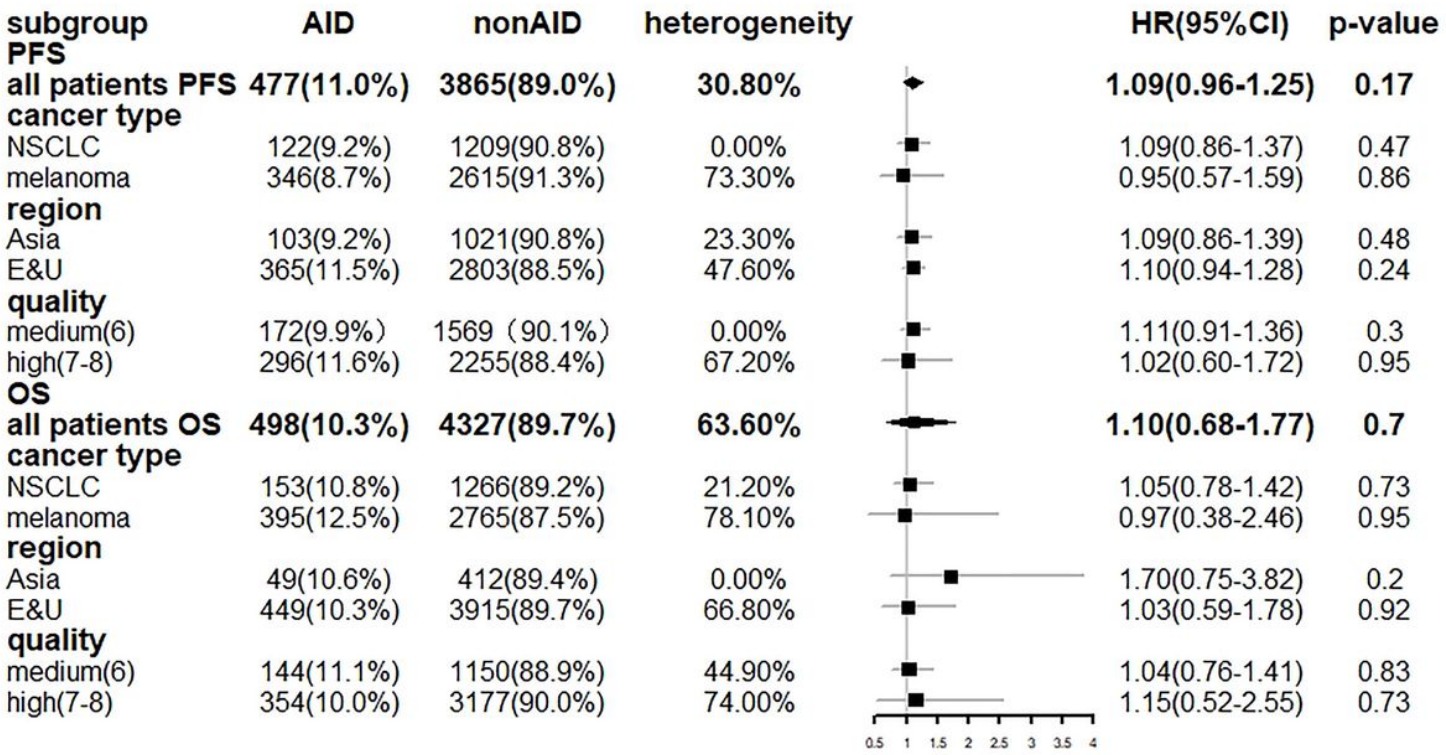

Figure 7

Forest plot of PFS and OS in cancer types, regional factors and quality characteristics subgroup analysis

Supplementary Files

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- supplementarymaterials.pdf