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Review Article

Occurrence of irAEs after Immune Checkpoint Inhibitor Rechallenge: An Updated Meta-Analysis

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What Is Known? and Objective. Immune checkpoint inhibitors (ICIs) play an important role in various cancers. The efficacy and safety of rechallenge with ICIs after immune-related adverse events (irAEs) were not well known. Accumulating studies report inconsistent findings. Thus, we conducted an updated meta-analysis by including more studies. *Methods*. We searched PubMed, Web of Science, Embase, and Cochrane Library for studies reporting the rechallenge of ICIs after irAEs. The evaluation outcomes included the incidence of irAEs, objective response rate (ORR), and disease control rate (DCR). *Results and Discussion*. A total of 896 ICI rechallenge cases from 24 studies were included. Compared to the initial treatment with ICIs, rechallenge showed a higher incidence of all-grade irAEs (OR, 2.78; 95% CI, 1.51–5.10; $p = 0.001$) and high-grade irAEs (OR, 1.88; 95% CI, 1.27–2.78; $p = 0.002$), but ORR (OR, 1.01; 95% CI, 0.55–1.84; $p = 0.97$) and DCR (OR, 1.21; 95% CI, 0.68–2.15; $p = 0.52$) were not further improved after the rechallenge of ICIs. *What Is New? and Conclusion*. More studies are included in this paper to compare and analyze the efficacy and safety of ICIs after rechallenge, so as to update the previous meta-analyses, and finally get different conclusions from the previous meta-analyses in terms of safety. Our results suggest that rechallenged ICIs after irAEs showed similar efficacy and lower safety than initial ICIs. However, these results need to be further verified by high-quality studies with large samples. In addition, we added subgroup analysis not available in previous meta-analyses to explore the association of cancer type, age, and gender factors with the incidence of irAE after ICI rechallenge.

1. Introduction

In recent years, immune checkpoint inhibitors (ICIs) directed targeting programmed cell death protein-1 (PD-1)/ programmed cell death protein ligand-1 (PD-L1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) become emerging therapies to improve the survival of patients with malignancies [1, 2]. Currently, ICIs have shown unprecedented clinical efficacy in a variety of tumors such as melanoma, lymphoma, lung cancer, uroepithelial carcinoma, and gastrointestinal tract tumors [3–7]. However, the treatment of ICIs is a "double-edged sword," as it may cause excessive enhancement of immune response or immune imbalance, resulting in immune-related adverse events (irAEs) in all major systems of the body, which can theoretically occur in any tissue and organ. Common irAEs are fatigue, pruritus, diarrhea, and rash [8], with the incidence of fatigue ranging from 16% to 20% and the probability of pruritus and rash being approximately 10.6% and 9.3%. Most of these adverse reactions are mild and manageable and resolve on their own after discontinuation without special treatment, but there are still some serious and even fatal toxic reactions, such as immune-related pneumonia, immune-related neurotoxicity, and fatal diarrhea, which can lead to treatment discontinuation. irAE occurrence is varied due to different ICIs. The incidence of grade 3 or 4 irAEs associated with anti-PD-1/ PD-L1 and anti-CTLA-4 monotherapy is approximately 14%

[9] and 23% [10], respectively; yet, severe irAEs after combination therapy are up to 53% [11].

When irAEs are fully recovered, the question of whether to rechallenge is crucial. Practical guidelines of irAE management are based on clinical observations and expert consensus, and the possibility of rechallenge is not discussed. When ICIs are discontinued due to irAEs, once irAEs are fully recovered, restarting ICIs may control tumor growth; on the other hand, this may also increase the risk of the same or different irAEs [12, 13]. Several recent studies have shown that the rechallenge of ICIs is safe, effective, and reasonable [14–20]. In the study by Santini et al., patients with no observed partial responses prior to irAEs had PFS and OS that lasted longer after rechallenge with ICIs and may benefit [18]. According to Plazy et al., irAEs at resumption were severe (grade 3-4) in 18%– 62% of cases, which were really similar or even less severe than what was reported during the first ICI, suggesting that toxicity during ICI resumption seems manageable once irAEs have recovered [21]. However, other studies suggest that the incidence of irAEs after rechallenged ICIs is even higher [22, 23]. For example, in the study by Pollack et al., patients who discontinued CTLA-4/PD-1 blockade for severe irAEs had relatively high rates of recurrent or distinct toxicities with anti-PD-1 resumption [22].

Recently, several meta-analyses about the safety of ICI rechallenge have been reported, but the results are not completely consistent. Several new cohort studies are exploring the safety of ICI rechallenge [24]. Therefore, we further conducted an updated meta-analysis to clarify the safety and efficacy of rechallenged ICIs and provide an objective reference for the clinical reuse of ICIs.

2. Materials and Methods

2.1. Literature Search Strategy. PubMed, Embase, Web of Science, and Cochrane Library were searched to retrieve relevant studies published from the database inception to January 20, 2022. The key retrieve terms in the search strategy included immune checkpoint inhibitors (anti-PD-1, anti-PD-L1, and anti-CTLA-4), specific ICI names (nivolumab, pembrolizumab, ipilimumab, atezolizumab, avelumab, durvalumab, and cemiplimab), and some expressions related to "rechallenge" (retreat, readministrate, restart, reinitiate, resume, and reinduce).

2.2. Inclusion and Exclusion Criteria. Studies were considered eligible if all of the following criteria were included: (1) the study subjects were cancer patients with a clear diagnosis, (2) patients were treated with ICIs, and (3) the same or a different type of ICIs were resumed after a previous interruption for irAEs. Exclusion criteria were as follows: (1) studies that did not meet the inclusion criteria, (2) review and meta-analyses, case reports, editorials, and letters to the editors, (3) the number of cases was less than 10, and (4) duplicate studies and incomplete or unusable original study data. Two researchers independently screened the title and abstract of each search retrieved to identify all studies that might meet the inclusion criteria and then read the full text of all potentially eligible studies for further screening. The two researchers solved any discrepancies in study selection through discussion and in-depth reading of the search, consulting a noninterested third party for judgment when necessary.

2.3. Data Collection and Quality Assessment. All data were collected independently by two noninterfering investigators following a predetermined procedure, and extracted data included (1) literature-related information: author, publication year, study design, cancer type, total study population, type of initial and rechallenged ICIs, rechallenge ratios, the type and number of occurrence of initial and rechallenged irAEs, and the number of occurrence of initial and rechallenged low-grade irAEs (grade 1-2) and high-grade irAEs (≥grade 3), respectively, and (2) study event indicators: objective response rate (ORR) and disease control rate (DCR). The same two independent researchers assessed the methodological quality of all included studies using the Newcastle-Ottawa Scale (NOS) criteria [25].

2.4. Outcomes. Safety assessment included the incidence of all-grade rechallenged irAEs and the incidence of high-grade rechallenged irAEs. According to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 5, the severity of irAEs was classified as grades 1–5, with grade ≥3 being high-grade irAEs and grade 1 or 2 being low-grade irAEs. Efficacy assessment included ORR and DCR after ICI rechallenge. ORR was defined as the rate of patients who had a complete response or partial response, while DCR was defined as the rate of patients who had a complete response, partial response, or stable disease.

2.5. Statistical Analysis. We employed Review Manager 5.4 (Cochrane Community, London, UK) for statistical analyses and plotting. Synthesis of all-grade and high-grade rechallenged irAEs, ORR, and DCR was conducted via a meta-analysis using pooled odds ratios (ORs), with 95% confidence intervals (CIs) calculated via the Mantel–Haenszel model. Since the vast majority of the studies included in this meta-analysis were retrospective studies, considering significant heterogeneity, we used the random-effects model with the Mantel–Haenszel model and then validated it by the Q-test and I-squared (I^2) test. When $p > 0.05$ or $I^2 < 50\%$, no heterogeneity or mild heterogeneity among studies could be considered, and when $p \leq 0.05$ or $I^2 \geq 50\%$, statistical heterogeneity among studies was suggested. The Z test was used to determine whether the combined effect sizes were statistically different, and when $p < 0.05$, it was suggested that the combined effect sizes of multiple studies were statistically significant; conversely, when $p \geq 0.05$, it was suggested that they were not statistically significant. In addition, we performed subgroup analyses using accessible data (here mainly for cancer types) and sensitivity analyses by sequentially omitting one study to determine the stability of the combined results.

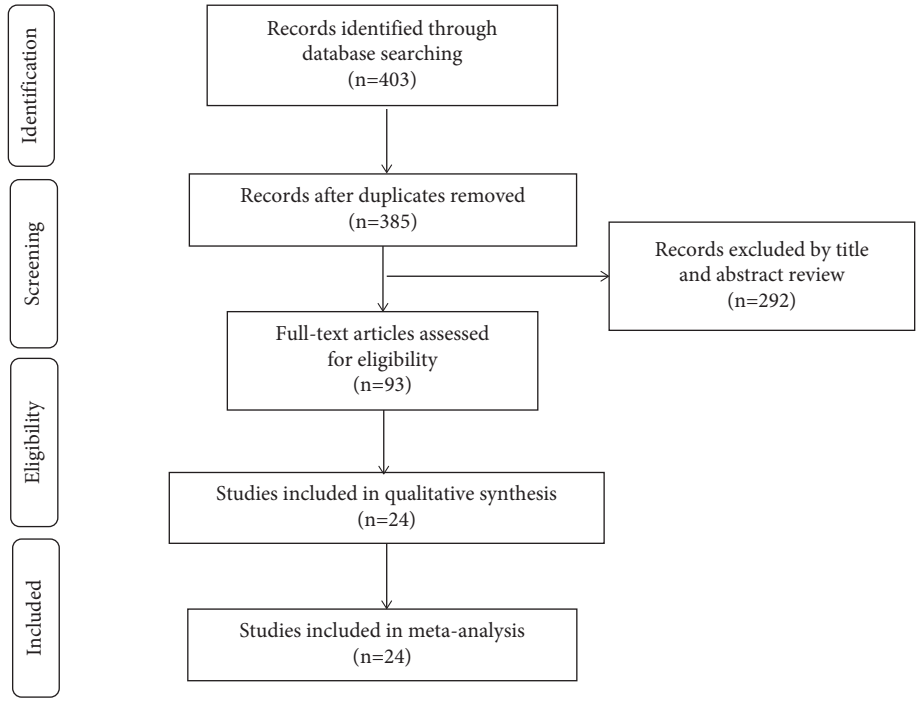


Figure 1: Flowchart of the included studies. "*n*" represents the number of studies.

3. Results

3.1. Eligible Studies and Characteristics. We retrieved a total of 403 relevant articles, 18 duplicates were removed, and 292 were excluded after the title and abstract review for not meeting the selection criteria. 93 were left for full-text reading, and 69 were removed after reading the full text; finally, 24 cohort studies [14, 18, 22, 23, 26–44] containing 896 patients were included for qualitative and meta-analysis. The literature screening process is shown in Figure 1. Characteristics of the included studies are reported in Table 1.

3.2. Safety Analysis. Sixteen studies [18, 26–30, 33, 34, 36–43] were included in the safety analysis, fifteen [18, 26–30, 33, 34, 36, 38–43] of which were used for the combined analysis of differences in the incidence of all-grade irAEs, and eleven [18, 27–29, 33, 36, 37, 39–41, 43] were used for the analysis of differences in the incidence of high-grade irAEs. The results showed ICI rechallenge was associated with a significantly higher incidence of all-grade irAEs than initial ICIs (OR, 2.78; 95% CI, 1.51–5.10; $p = 0.001$; $I^2 = 86\%$) (see Figure 2(a)), as well as a significantly higher risk of high-grade irAEs (OR, 1.88; 95% CI, 1.27–2.78; $p = 0.002$; $I^2 = 23\%$) (see Figure 2(b)).

3.3. Efficacy Analysis. Seven studies [18, 23, 27, 28, 36, 37, 40] were included for the pooled analysis of ORR with 529 patients. Four [23, 28, 36, 37] of them were included for the pooled analysis of ORR with 332 patients. The results illustrate that neither ORR (OR, 1.01; 95% CI, 0.55–1.84; $p = 0.97$; $I^2 = 60\%$) (see Figure 3(a)) nor DCR (OR, 1.21; 95% CI, 0.68–2.15; $p = 0.52$; $I^2 = 20\%$) (see Figure 3(b)) was further improved in the ICI rechallenge population.

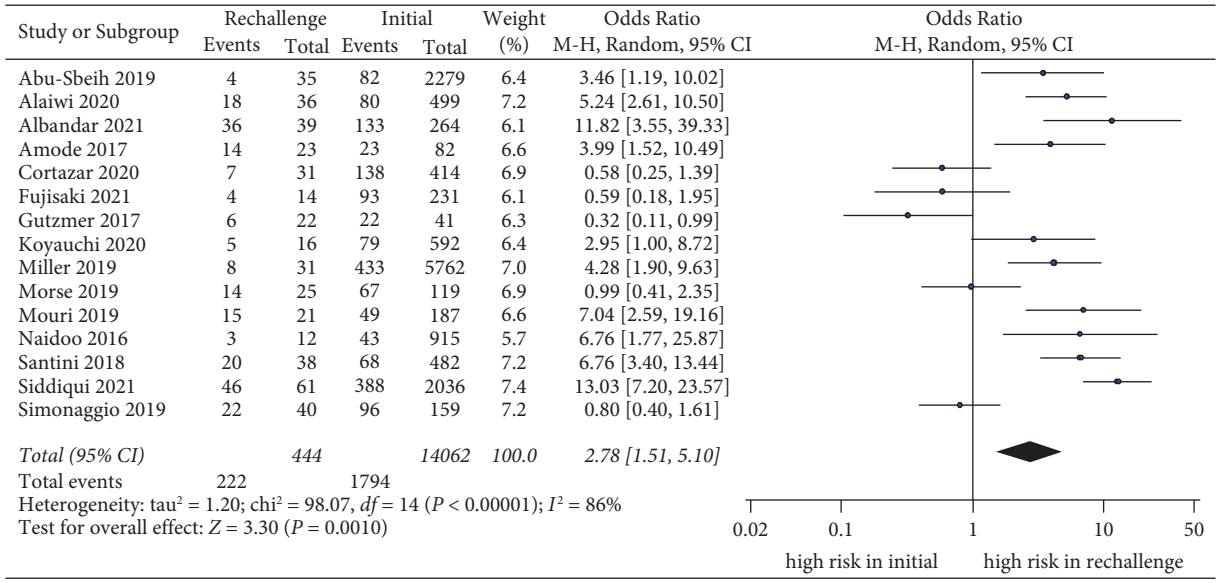
3.4. Subgroup Analysis. The results of subgroup analyses for cancer types are displayed in Figures 4(a) and 4(b). Cohorts enrolled with melanoma showed no significant difference in the incidence of all-grade irAEs and high-grade irAEs in ICI rechallenge. Patients with NSCLC had a higher incidence of all-grade rechallenged irAEs (OR, 3.22; 95% CI, 1.13–9.14; $p = 0.003$; $I^2 = 78\%$) (see Figure 4(a)), but no significant difference existed in high-grade irAEs (OR, 1.29; 95% CI, 0.38–4.45; $p = 0.69$; $I^2 = 47\%$) (see Figure 4(b)).

Further subgroup analysis was performed for age and gender stratification. The results showed that patients with a median age <65 years had a higher incidence of high-grade rechallenged irAEs (OR, 2.08; 95% CI, 1.22–3.54; $p = 0.007$; $I^2 = 30\%$), whereas no significant difference existed in patients with a median age ≥65 years (OR, 1.78; 95% CI, 0.84–3.76; $p = 0.13$; $I^2 = 25\%$) (see Figure 5(a)). On the other hand, in the predominantly male study population (male ≥50%), patients had a higher incidence of high-grade rechallenged irAEs (OR, 2.38; 95% CI, 1.45–3.91; $p = 0.0006$; $I^2 = 20\%$), whereas no significant difference existed in the predominantly female study population (female ≥50%) (OR, 1.34; 95% CI, 0.72–2.50; $p = 0.36$; $I^2 = 0\%$) (see Figure 5(b)).

Table 1: Characteristics of the included studies.

Author (year)	Type of study	Disease	N° pts	Initial ICI type			Initial irAEs				Rechallenge ratios	Type of rechallenged ICIs			Rechallenged irAEs				Disease response after rechallenge		Quality (NOS score)
				PD-1 (PD-L1)	CTLA-4	Combo	Type	Total irAEs	Low-grade irAEs	High-grade irAEs		PD-1 (PD-L1)	CTLA-4	Combo	Type	Total irAEs	Low-grade irAEs	High-grade irAEs	ORR (%)	DCR	
Abu-Sbeih et al. (2019) [14]	Retrospective	Various	NA	79	47	41	Diarrhea and/or colitis	167	105	62	167/167	135	32	0	Diarrhea and/or colitis	57	51	6	—	—	6
Abu-Sbeih et al. (2019) [26]	Retrospective	Various	2279	1434	627	218	Pancreatic injury	82	41	41	35/82	NA	NA	NA	Pancreatic injury	4	NA	NA	—	—	6
Abou Alaiwi et al. (2020) [27]	Retrospective	mRCC	499	NA	NA	NA	Global	80	37	43	36/80	32	0	4	Global	18	11	7	44	—	8
Albandar et al. (2021) [28]	Retrospective	Various	264	224	19	21	Global	133	70	45	39/133	NA	NA	NA	Global	36	19	17	41	24/39	6
Amode et al. (2017) [29]	Observational	Melanoma	82	0	82	0	NA	23	13	10	23/23	23	0	0	Global	14	10	4	21.7	8/23	7
Cortazar et al. (2020) [30]	Retrospective	Various	414	400	92	74	Acute kidney injury	138	NA	NA	31/138	NA	NA	NA	Acute kidney injury	7	NA	NA	—	—	7
Delyon et al. (2019) [31]	Prospective cohort	Melanoma	NA	NA	NA	NA	Diarrhea and/or colitis	25	NA	NA	11/25	8	2	1	Diarrhea and/or colitis	1	0	1	—	—	8
Dubey et al. (2020) [32]	Retrospective	Various	1834	1215	186	433	Neurological	NA	NA	28	10/28	NA	NA	NA	Neurological	6	NA	NA	—	—	6
Fujisaki et al. (2021) [33]	Retrospective	NSCLC	231	231	0	0	Global	93	68	25	14/93	14	0	0	Global	4	3	1	—	—	8
Fujita et al. (2019) [23]	Retrospective	NSCLC	18	18	0	0	Global	NA	NA	NA	18/18	18	0	0	Global	NA	NA	NA	0	7/18	5
Gutzmer et al. (2017) [34]	Retrospective	Melanoma	41	0	41	0	Global	22	10	12	22/22	22	0	0	NA	6	NA	NA	45.4	16/22	6
Kartolo et al. (2021) [35]	Retrospective	Various	NA	65	6	8	Global	85	64	21	40/85	NA	NA	NA	Global	31	NA	NA	—	—	5
Koyauchi et al. (2020) [36]	Retrospective	NSCLC	592	592	0	0	Pneumonitis	79	49	30	16/79	16	0	0	Pneumonitis	5	5	0	50	14/16	8
Li et al. (2020) [37]	Retrospective	Melanoma	1913	NA	NA	NA	Hepatitis	NA	NA	102	31/102	29	2	0	Hepatitis (4) others (11)	15	12	3	64.5	23/31	8
Miller et al. (2019) [38]	Retrospective	Various	5762	4001	1446	315	Hepatotoxicity	433	333	100	31/433	25	5	1	Hepatotoxicity	8	NA	NA	—	—	6
Morse et al. (2019) [39]	Retrospective	mCRC	119	0	0	119	Global	67	38	29	25/67	0	0	25	Global	14	8	6	—	—	7
Mouri et al. (2019) [40]	Retrospective	NSCLC	187	187	0	0	Global	49	34	15	21/49	21	0	0	Global	15	14	1	15	18/21	5
Naidoo et al. (2016) [41]	Retrospective	Various	915	716	0	199	Pneumonitis	43	31	12	12/43	NA	NA	NA	Pneumonitis	3	3	0	—	—	6
Pollack et al. (2017) [22]	Retrospective	Melanoma	NA	0	0	80	Global	80	25	55	80/80	80	0	0	Global	40	26	14	70	71/80	7
Santini et al. (2018) [18]	Retrospective	NSCLC	482	432	0	50	Global	68	35	33	38/68	38	0	0	Global	20	12	8	47.4	31/38	6
Siddiqui et al. (2021) [42]	Retrospective	GU cancers	2036	NA	NA	NA	Global	388	NA	NA	61/388	27	10	24	Global	46	32	14	36.1	46/61	6
Simonaggio et al. (2019) [43]	Cohort study	Various	159	NA	NA	NA	Global	96	46	50	40/96	35	0	4	Global	22	8	14	32.5	28/40	7
Weill et al. (2021) [44]	Retrospective	Various	NA	18	0	2	Myositis	20	NA	NA	9/20	8	1	0	Colitis	1	0	1	66.7	7/9	6
Williams et al. (2017) [45]	Retrospective	Various	NA	59	28	16	Global	103	78	25	86/103	NA	NA	NA	NA	86	73	13	—	—	6

CTLA-4, cytotoxic T-lymphocyte antigen-4; DCR, disease control rate; ICIs, immune checkpoint inhibitors; irAEs, immune-related adverse events; mCRC, metastatic colorectal cancer; mRCC, metastatic renal cell carcinoma; NA, not applicable; NSCLC, non-small-cell lung cancer; ORR, objective response rate; PD-1, programmed cell death protein-1; PD-L1, programmed cell death protein ligand-1.



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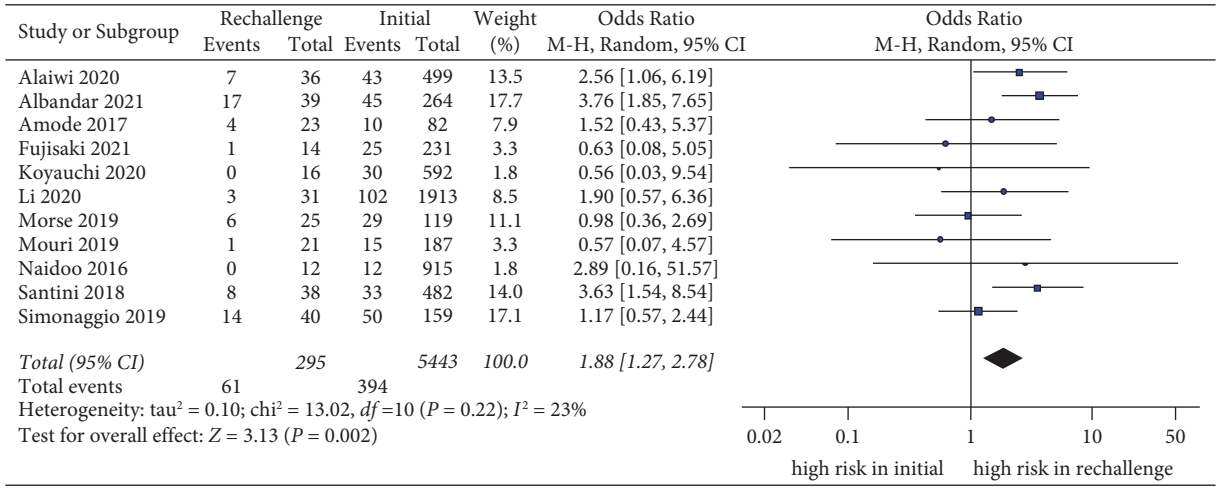

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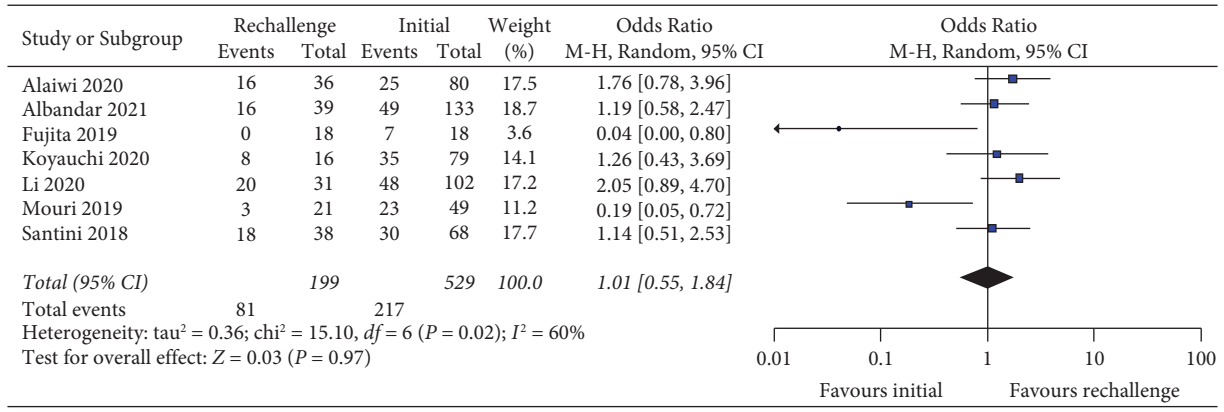
Figure 2: (a) Forest plot (random-effects model) of the association between ICI rechallenge and all-grade irAEs occurrence after ICI rechallenge. CI, confidence interval; ICIs, immune checkpoint inhibitors; irAEs, immune-related adverse events; M-H, Mantel–Haenszel model. The sizes of the squares indicate the weight of the study. (b) Forest plot (random-effects model) of the association between ICI rechallenge and high-grade irAE occurrence after ICI rechallenge. CI, confidence interval; ICIs, immune checkpoint inhibitors; irAEs, immune-related adverse events; M-H, Mantel–Haenszel model. The sizes of the squares indicate the weight of the study. High-grade was considered grade ≥3.

3.5. Sensitivity Analysis. In the sensitivity analysis, the pooled results for all-grade irAEs, high-grade irAEs, ORR, and DCR remained stable, regardless of which study was removed, indicating a robust correlation of the combined results.

4. Discussion

To the best of our knowledge, this updated meta-analysis is the latest and relatively comprehensive study on the safety and efficacy of ICI rechallenge in people who have discontinued ICI treatment due to irAEs previously. Our findings suggest that, in terms of safety, ICI rechallenge patients had overall higher risks of all-grade and high-grade irAEs than initial ICIs. In the previous meta-analysis, Zhao et al. [46] found a higher incidence of all-grade irAEs after ICI rechallenge, but there was no significant difference in the incidence of high-grade irAEs. This differs from our results. The discrepancy may be due to relatively large cohort studies enrolled in our safety analysis ($n = 11$ vs. $n = 6$). Inno et al. [47] conducted a meta-analysis of ICI rechallenge that showed a similar incidence of all-grade and high-grade irAEs between initial and rechallenged ICIs, which included all patients who discontinued ICIs due to disease progression and toxicity. Our results differ from those of that study because we focused on the population who



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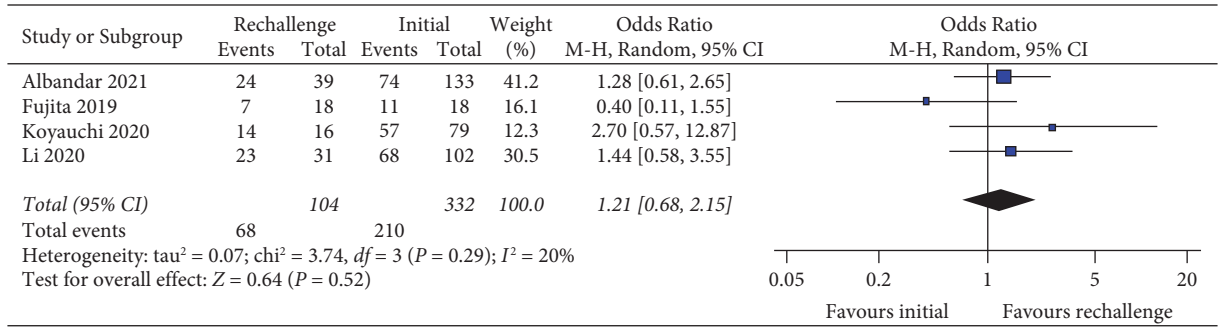


(b)

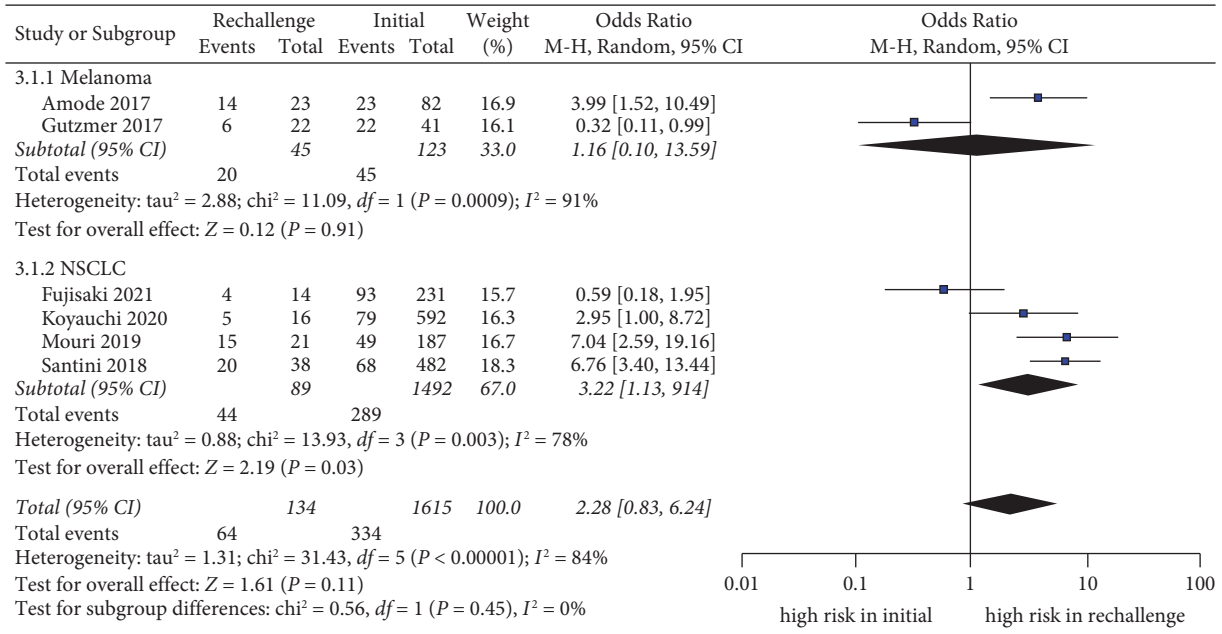
Figure 3: (a) Forest plot (random-effects model) of the association between ICI rechallenge and ORR after ICI rechallenge. CI, confidence interval; ICIs, immune checkpoint inhibitors; irAEs, immune-related adverse events; M-H, Mantel–Haenszel model; ORR, objective response rate. The sizes of the squares indicate the weight of the study. (b) Forest plot (random-effects model) of the association between ICI rechallenge and DCR after ICI rechallenge. CI, confidence interval; DCR, disease control rate; ICIs, immune checkpoint inhibitors; irAEs, immune-related adverse events; M-H, Mantel–Haenszel model. The sizes of the squares indicate the weight of the study.

discontinued ICIs due to irAEs. In terms of efficacy, there was no significant difference in ORR and DCR between initial and rechallenged ICIs, which is consistent with the study published by Zhao et al. [46]. Given the limited pooled sample size, large prospective clinical trials are required to confirm the effect of ICI rechallenge treatment in various cancer types.

Relatively large heterogeneity was presented in the analysis of all-grade irAE incidence. To explore the source of heterogeneity, we further performed subgroup analysis according to cancer types. The results showed no significant difference in the incidence of all-grade and high-grade irAEs in ICI rechallenge based on melanoma. We found patients with NSCLC had a higher incidence of all-grade irAEs, but no significant difference existed in high-grade irAEs after ICI rechallenge. In each subgroup, heterogeneity remained, indicating that the cancer type was not the source of heterogeneity. Other potential sources of this heterogeneity may be due to different intervals from initial irAEs to rechallenged ICIs and dosing regimens among studies. Unfortunately, the available data for these variables were incomplete and could not be used here. A prior study on irAEs showed the recurrence of high-grade irAEs after ICI reintroduction is associated with a longer interval between initial irAEs and rechallenged ICIs and the initial use of anti-CTLA-4 antibodies [20, 46].

In addition, a recent review indicated that the higher risk of irAEs in the initial ICI treatment population is associated with age <60 years, high body mass index, women on CTLA-4 and men on PD-1/PD-L1 agents, and chronic smokers [48]. To explore whether these factors have the same impact on rechallenged irAEs, we also stratified age and gender into subgroup analysis based on currently available data. The results prompt that the predominantly male study population (male ≥50%) with a median age <65 years appears to be associated with a higher risk of high-grade rechallenged irAEs, while in the predominantly female study population (female ≥50%) with a median age ≥65 years, the incidence of high-grade irAEs is similar between the initial and rechallenged ICI groups. However, this conclusion has certain limitations due to the limited number of the included articles.

Our meta-analysis has several limitations: First, the number of prospective studies is small, which may have had some impact on the quality of the research results. Second, not all studies reported OS or PFS, so in our meta-analysis, we evaluated the efficacy of ICI rechallenge in terms of ORR and DCR. Third, the source of heterogeneity among the



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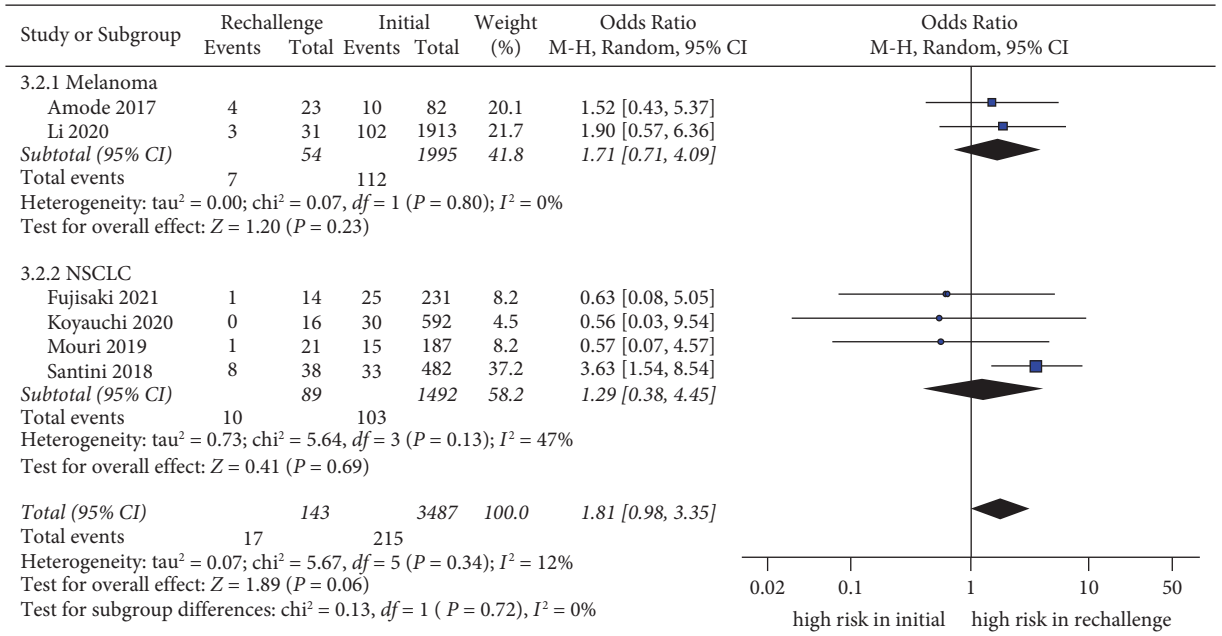
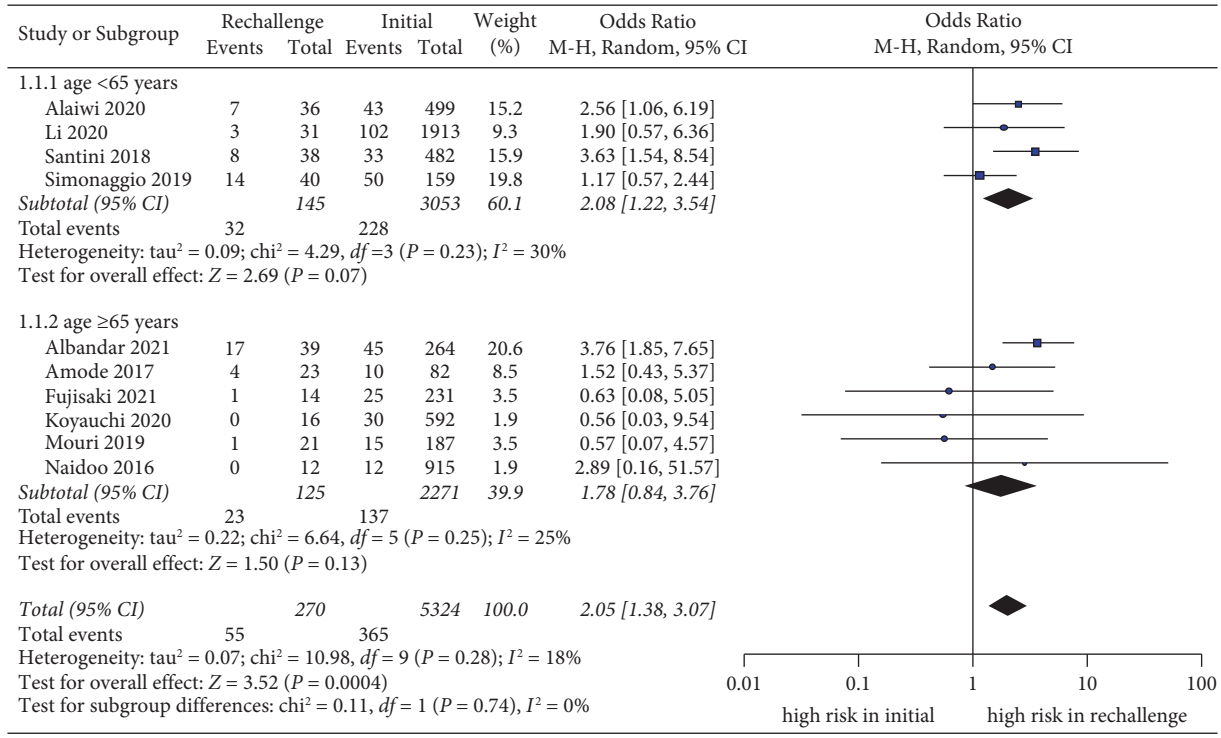


(b)

Figure 4: (a) Subgroup analyses of the association between ICI rechallenge and all-grade irAE occurrence after ICI rechallenge. CI, confidence interval; ICIs, immune checkpoint inhibitors; irAEs, immune-related adverse events; NSCLC, non-small-cell lung cancer; OR, odds ratio. (b) Subgroup analyses of the association between ICI rechallenge and high-grade irAE occurrence after ICI rechallenge. CI, confidence interval; ICIs, immune checkpoint inhibitors; irAEs, immune-related adverse events; NSCLC, non-small-cell lung cancer; OR, odds ratio. High-grade was considered grade ≥3.

studies could not be addressed. We performed subgroup analysis to decrease heterogeneity; however, the overall heterogeneity was not changed after subgroup analysis. Therefore, these results should be interpreted with caution, and additional well-designed studies are still needed to assess the safety and efficacy of ICI rechallenge in follow-up.



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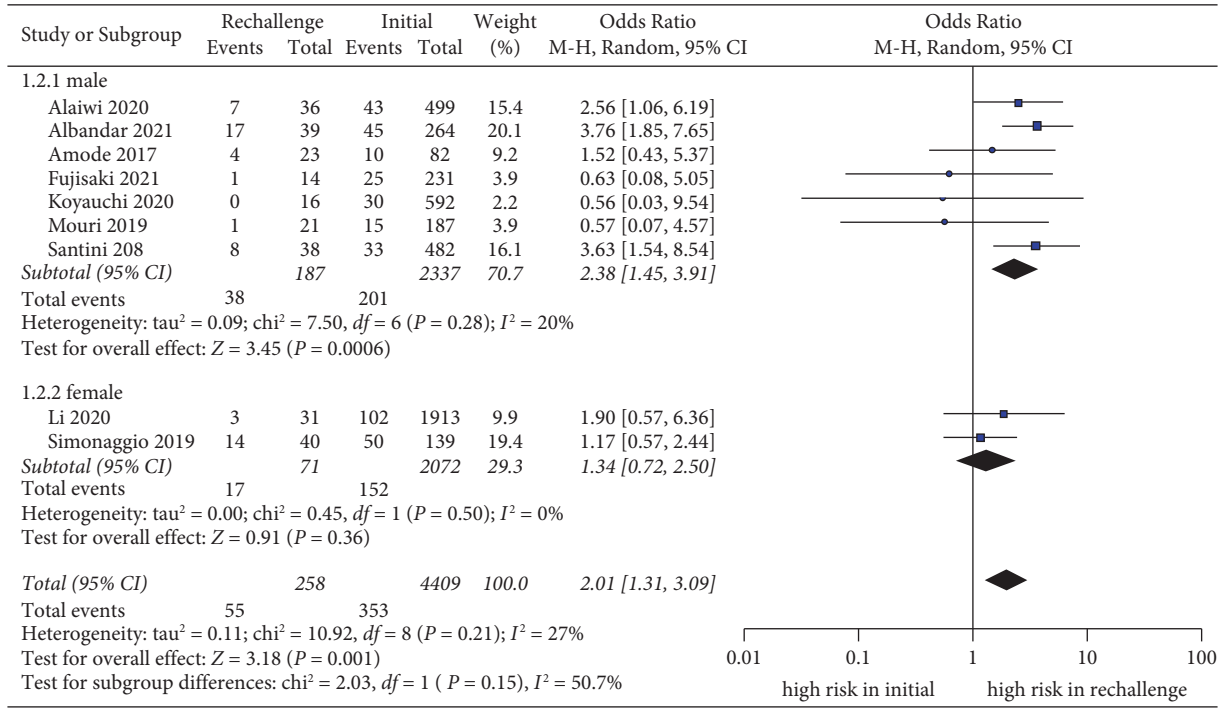

(b)

Figure 5: (a) Subgroup analyses of the association between ICI rechallenge and high-grade irAE occurrence after ICI rechallenge at different age stratification. CI, confidence interval; ICIs, immune checkpoint inhibitors; irAEs, immune-related adverse events; OR, odds ratio. High-grade was considered grade ≥3. (b) Subgroup analyses of the association between ICI rechallenge and high-grade irAE occurrence after ICI rechallenge at different gender stratification. The male subgroup is defined as males comprising more than 50% of the study population, and the female subgroup is defined as females comprising more than 50% of the study population. CI, confidence interval; ICIs, immune checkpoint inhibitors; irAEs, immune-related adverse events; OR, odds ratio. High-grade was considered grade ≥3.

5. Conclusion

More studies are included in this paper to compare and analyze the efficacy and safety of ICIs after rechallenge, so as to update the previous meta-analysis, and finally get different conclusions from the previous meta-analyses in terms of safety. Our study suggested that patients who rechallenged ICIs after irAEs were associated with similar efficacy and lower safety. Therefore, based on the conclusion of our current study, for cancer patients who have previously discontinued ICIs for irAEs, the option of rechallenged ICIs should be carefully weighed against benefits and risks after taking into account the patient's disease status, the response obtained, and the type and grade of adverse events previously experienced. In addition, more large-scale prospective studies are needed to validate our conclusion and further elucidate the role of ICIs after disease progression or toxicity.

Data Availability

The data supporting this meta-analysis are from previously reported studies, which have been cited. All data generated or analyzed are included in this article. Further information can be available from the corresponding author upon reasonable request.

Disclosure

Jiaqin Cai and Wenhua Wu are listed as joint first authors.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

JC and XW participated in the design of the study. JC and WW retrieved and selected the articles, analyzed and interpreted the data, and wrote the manuscript. WW and XW solved all disagreements and revised the manuscript. JZ, GZ, and HS supervised the study. All the authors contributed to the article and approved the final manuscript. Jiaqin Cai and Wenhua Wu contributed equally to this work.

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