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Immune checkpoint inhibitors related respiratory disorders in patients with lung cancer: A meta-analysis of randomized controlled trials

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Background: In recent years, immune checkpoint inhibitors (ICIs) had extremely rapid growth in anti-cancer and improved outcomes of many malignancies, specifically lung cancer. However, the incidence of ICIs-related adverse events also raised. Using this meta-analysis, ICIs-related respiratory disorders were investigated in lung cancer patients.

Methods: Using Cochrane Library, Embase, and PubMed databases, we performed an integrated search for randomized controlled trials (RCTs) to compare respiratory disorders among different regimens. The data was prepared with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline, and the quality of included studies was evaluated based on the Cochrane manual.

Results: In total, 22 RCTs were involved in this meta-analysis. Compared with ICIs, chemotherapy reduced the risk of interstitial lung disease ($p = 0.03$; SMD: 2.81; 95% CI: 1.08, 7.27), pleural effusion ($p = 0.002$; SMD: 2.12; 95% CI: 1.32, 3.42), and pneumonitis ($p < 0.00001$; SMD: 9.23; 95% CI: 4.57, 18.64). ICIs plus chemotherapy could provide a higher probability for patients to suffer pneumonitis than chemotherapy ($p = 0.01$; SMD: 1.96; 95% CI: 1.17, 3.28). In addition, single ICI brought a lower likelihood for patients suffering pneumonitis than double ICIs ($p = 0.004$; SMD: 2.17; 95% CI: 1.27, 3.69).

Conclusion: ICIs-based treatment, such as ICIs alone, ICIs plus chemotherapy and double ICIs, can raise the incidences of some respiratory disorders in patients with lung cancer. It suggests that ICIs should be conducted based on a comprehensive consideration to prevent ICIs-related respiratory disorders. To a certain degree, this study might be provided to the clinician as a reference for ICIs practice.

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KEYWORDS

immune checkpoint inhibitors (ICI), respiratory disorders, lung cancer, meta-analysis, randomized controlled trials (RCT)

Introduction

In most countries, cancer is currently the first or second most frequent cause of premature death. In 2022, the USA has experienced more than 1,900,000 new cancer cases and 600,000 cancer deaths, with lung cancer being the leading cause of these deaths (1). Fortunately, the survival rate of patients with lung cancer has improved, which may be related to the early screening of lung cancer. Furthermore, a significant progress in non-small cell lung cancer (NSCLC) treatment with the advent of targeted drugs, coupled with the approval of immunotherapy by the Food and Drug Administration (FDA) in 2015, has also contributed to the population-level improvement in lung cancer-specific survival (2).

Many treatments to control malignancies by mobilizing the immune system are under investigation, including cytokines, T cells (checkpoint inhibitors, co-stimulatory receptor agonists), T cell engineering, oncolytic viruses, and vaccines. Immune checkpoint inhibitor (ICI) therapy includes programmed death-1 (PD-1) and programmed cell death 1 ligand 1/2 (PD-L1/2), cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), lymphocyte-activation gene 3 (LAG3), and other potential targets. PD-1 is a transmembrane protein expressed in T, B, and NK cells and an inhibitory molecule that binds to PD-L1 and PD-L2. PD-L1 is represented on the cell surface of various tissue types, including many tumor and hematopoietic cells. Contrarily, PD-L2 is more restricted to hematopoietic cells. The combination of PD-1 and PD-L1/2 can directly inhibit tumor cell apoptosis and promote peripheral effector T cell depletion and conversion of effector T cells into Treg cells (3, 4). To date, the results of many large-scale randomized controlled trials (RCTs) of PD-1 inhibitors against lung cancer have confirmed the concept of durable antitumor responses and improved progression-free survival and overall survival (OS) (5). CTLA-4 was recognized as a negative regulator of T cell activation in the mid-1990s (6–8). CTLA-4 on the surface of CD4 + and CD8+ T cells can play a role by binding to the co-stimulatory receptors CD80 and CD86 on the surface of APCs with a higher affinity than the co-stimulatory receptor CD28 on the surface of T cells (9). Scientists believe CTLA-4 to be APC-triggered, acting as a brake on CD4+ and CD8+ T cell activation. LAG3 is expressed on B cells, specific T cells, NK cells, and tumor-infiltrating lymphocytes, where it regulates immune checkpoint pathways (10). With the deepening of the understanding of the immune mechanism, several other potential targets of immune checkpoint inhibition have been discovered, one after another, such as B and T lymphocyte attenuator, V-domain Ig suppressor of T cell activation, T cell immunoglobulin, and mucin domain-3. ICIs have become first-line treatments for various malignancies, with the addition of immunotherapy to surgery, radiotherapy, chemotherapy, and targeted therapy (11, 12).

Despite the favorable clinical benefits of checkpoint inhibition, it has side effects known as immune-related adverse events (irAEs) (13, 14). IrAEs include skin diseases, diarrhea, hepatotoxicity, and cardiotoxicity (15–19). Checkpoint inhibition may also cause fulminant or fatal toxic reactions (20). However, there is no comparative research to comprehensively discuss respiratory disorders caused by ICIs in lung cancer. Thus, we conducted this meta-analysis to identify potential respiratory diseases during ICI therapy for lung cancer to guide the selection of patients who should benefit from ICIs.

Materials and methods

Reporting standards

The meta-analysis for ICIs-related respiratory disorders in patients with lung cancer was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses reporting guideline (21).

Search strategy

A competent information specialist (HL) conducted an integrated search for RCTs between January 2000 and October 2022 using the Cochrane Library, Embase, and PubMed databases. According to the PICOS (participants, interventions, comparisons, outcomes, and study design) guidelines (22), "ICIs," "PD-1," "PD-1 inhibitors," "PD-L1," "PD-L1 inhibitors," "CTLA-4," "CTLA-4 inhibitor," "atezolizumab," "avelumab," "camrelizumab," "cemiplimab," "durvalumab," "ipilimumab," "nivolumab," "pembrolizumab," "sintilimab," "tislelizumab," "toripalimab," "tremelimumab," "lung cancer," "lung carcinoma," "neoplasms," "adverse reactions," "adverse events," and "randomized controlled trial" were entered as the Medical Subject Heading terms.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) RCT on lung cancer (phase II or III clinical trials); (2) ICI intervention, including PD-1/PD-L1 or CTLA-4 inhibitors; and (3) comparison between single-agent ICI plus chemotherapy and chemotherapy, single-agent ICI and chemotherapy, as well as single-agent and double-agent ICIs. The exclusion criteria were as follows: (1) no report of ICIs-related respiratory disorders; (2) publications not written in English; (3) abstracts, case reports, comments, editorials, letters, and reviews; and (4) duplicate, missing, and overlapping datasets.

Study selection

Two investigators (SL and JJ) independently reviewed the titles and abstracts of the articles to obtain the qualified studies. Furthermore, two investigators (SW and LS) identified the potentially relevant studies to determine if they were eligible based on the inclusion and exclusion

criteria. Disagreements as regards the study's selection were resolved through discussion and compromise.

Data extraction

Two investigators (HL and JJ) independently extracted the characteristic data, including publication year, first author name, number of clinical trial, drug name, clinical trial phase, lung cancer type, regiment of intervention, enrollment, and serious adverse events (SAEs), from the eligible studies. According to the analysis of SAEs, the top 10 most frequent ICIs-related respiratory disorders, including pneumonitis, dyspnea, pulmonary embolism, pleural effusion, chronic obstructive pulmonary disease, respiratory failure, hemoptysis, interstitial lung disease, pulmonary hemorrhage, and pneumothorax, were conducted as the main outcomes (Figure 1). Disagreements as regards data extraction were resolved through discussion and compromise.

Quality assessment

Based on the Cochrane manual, the bias risk of eligible studies, including allocation concealment, blinding of participants and personnel, blindness to outcome assessment, incomplete outcome data, random sequence generation, selective outcome reporting, and other bias, was independently evaluated by two investigators (SW and SL) (23). Funnel plot were performed to assess publication bias (24). Disagreements regarding quality assessment were resolved through discussion and compromise.

Data synthesis and statistical analysis

All statistical analyses were calculated using Review Manager (RevMan v5.3). ICIs-related respiratory disorders, including pneumonitis, dyspnea, pulmonary embolism, pleural effusion, chronic obstructive pulmonary disease, respiratory failure,

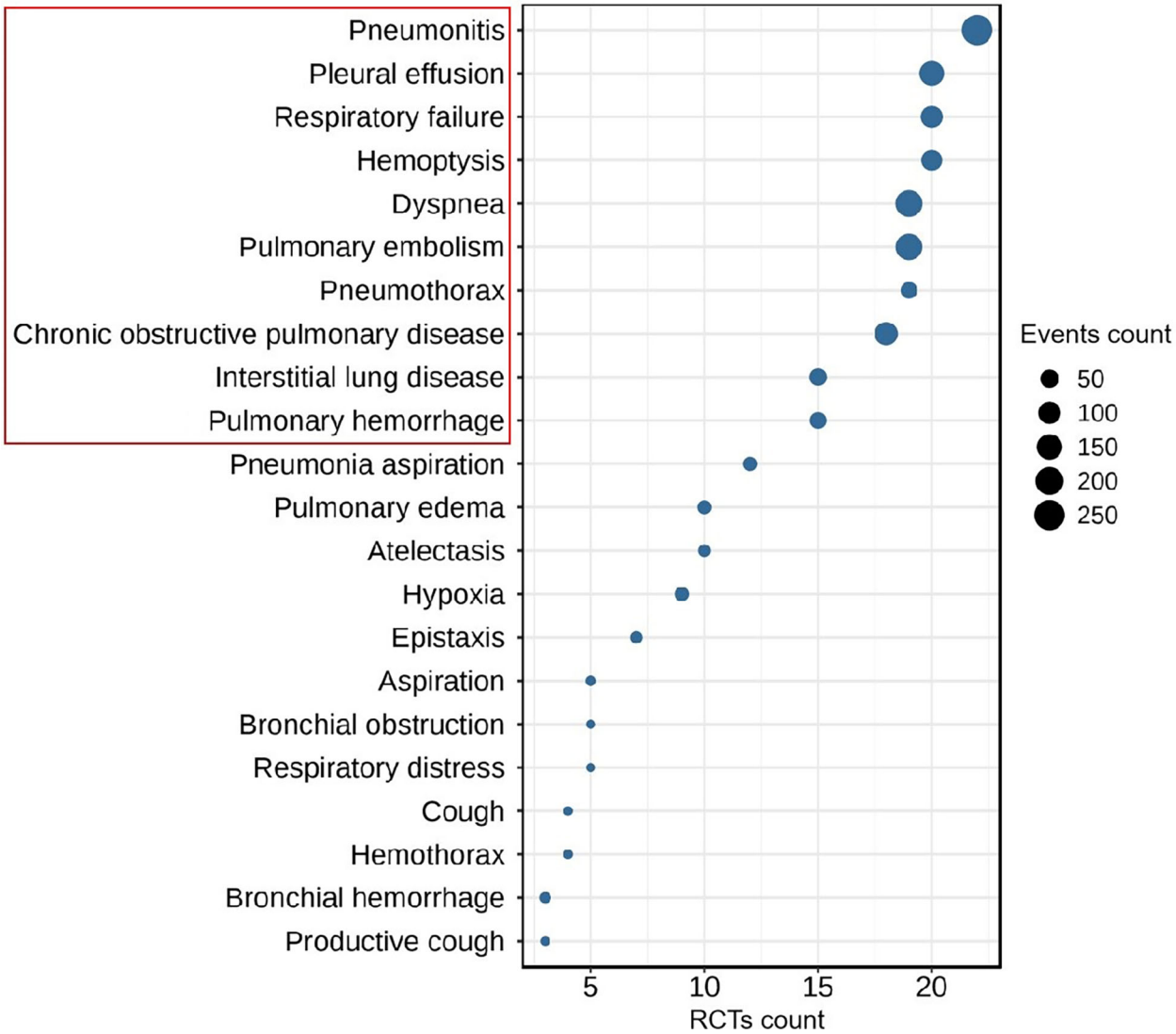

FIGURE 1
The Top-10 most frequent ICIs-related respiratory disorders in patients with lung cancer (RCTs count ≥ 3, event count ≥ 5).

hemoptysis, interstitial lung disease, pulmonary hemorrhage, and pneumothorax, were evaluated using the mean differences with 95% confidence intervals (CIs). Based on the Cochrane collaboration network, a fixed-effects model was used to pool studies, and the inconsistency index was used to access heterogeneity as low (I^2 < 30%), moderate (30% ≤ I^2 < 50%), or high (I^2 ≥ 50%) (25, 26). Subanalyses of the effects of the different intervention on ICIs-related respiratory disorders were conducted. A two-tailed *P*-value of <0.05 was considered statistically significant.

Results

Study selection

In total, 3884 potentially relevant studies were retrieved from databases as a result of the strategy performed in searching. 453 studies were recorded after duplicates removed. Then, 369 studies were excluded due to irrelevant topic, non ICIs-related or retrospective studies. The investigators removed 62 studies after screening the full texts. Four released updated results (27–30), and three did not report respiratory disorders (31–33). Finally, 22 studies were included as the flow diagram described in Figure 2 (34–55).

Study characteristics

The characteristics of 22 RCTs from the 22 included studies are presented in Table 1. The studies ranged in year of publication from 2015 to 2021. Enrollment of 22 RCTs was 11460. Eighteen RCTs included NSCLC and four included small cell lung cancer (SCLC). PD-1 inhibitors were administered in 16 RCTs, PD-L1 inhibitors in 6, and CTLA-4 inhibitors in 4. In the treatment regimens, 9 RCTs were conducted to compare ICIs plus chemotherapy vs. chemotherapy, 10 RCTs about ICIs vs. chemotherapy, and 3 RCTs about double ICIs vs. single ICI.

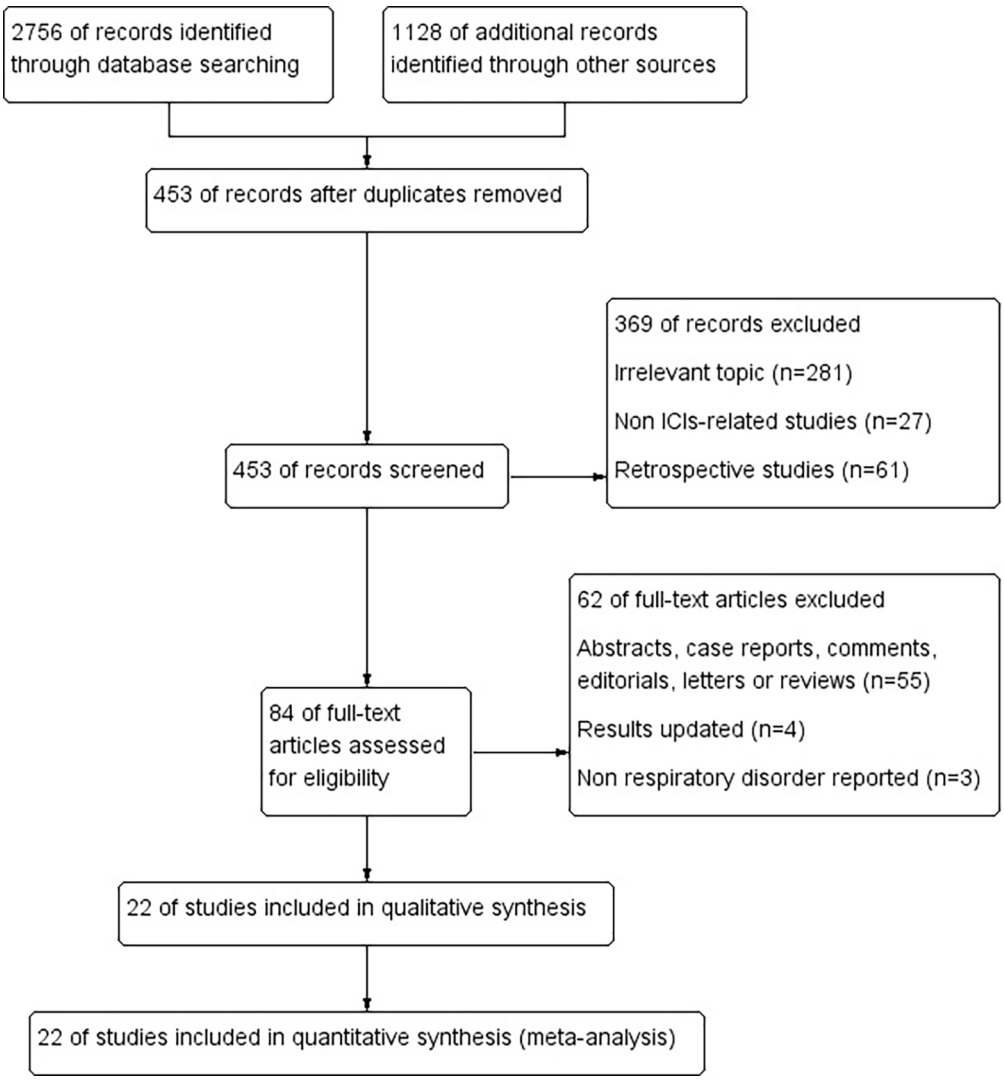

FIGURE 2
The flow diagram of the study identification and selection process.

TABLE 1 Characteristics of 22 studies included in analysis of ICIs-related respiratory disorders.

NO.	First Author Publication Year	Clinical Trial	Trial Phase	Cancer Type	Drug	Treatment Regimens	Enrollment
1	Arrieta, 2020 (34)	PROLUNG (NCT02574598)	II	NSCLC	Pembrolizumab (PD-1)	ICIs + Chemotherapy VS. Chemotherapy	78
2	Awad, 2021 (35)	KEYNOTE-021 (NCT02039674)	II	NSCLC	Pembrolizumab (PD-1)	ICIs + Chemotherapy VS. Chemotherapy	121
3	Barlesi, 2018 (36)	JAVELIN Lung 200 (NCT02395172)	III	NSCLC	Avelumab (PD-L1)	ICIs VS. Chemotherapy	758
4	Borghaei, 2015 (37)	CheckMate057 (NCT01673867)	III	NSCLC	Nivolumab (PD-1)	ICIs VS. Chemotherapy	555
5	Boyer, 2021 (38)	KEYNOTE-598 (NCT03302234)	III	NSCLC	Pembrolizumab (PD-1) Ipilimumab (CTLA-4)	Double ICIs VS. single ICI	563
6	Brahmer, 2015 (39)	CheckMate 017 (NCT01642004)	III	NSCLC	Nivolumab (PD-1)	ICIs VS. Chemotherapy	260
7	Carbone, 2017 (40)	CheckMate 026 (NCT02041533)	III	NSCLC	Nivolumab (PD-1)	ICIs VS. Chemotherapy	530
8	Gadgeel, 2020 (41)	KEYNOTE-189 (NCT02578680)	III	NSCLC	Pembrolizumab (PD-1)	ICIs + Chemotherapy VS. Chemotherapy	607
9	Gettinger, 2021 (42)	Lung-MAP 1400l (NCT02785952)	III	NSCLC	Nivolumab (PD-1) Ipilimumab (CTLA-4)	Double ICIs VS. single ICI	247
10	Goldman, 2021 (43)	CASPIAN (NCT03043872)	III	SCLC	Durvalumab (PD-L1) Tremelimumab (CTLA-4)	ICIs + Chemotherapy VS. Chemotherapy	531
11	Herbst, 2020a (44)	IMpower110 (NCT02409342)	III	NSCLC	Atezolizumab (PD-L1)	ICIs VS. Chemotherapy	549
12	Herbst, 2020b (45)	KEYNOTE-010 (NCT01905657)	III	NSCLC	Pembrolizumab (PD-1)	ICIs VS. Chemotherapy	991
13	Horn, 2018 (46)	IMpower133 (NCT02763579)	III	SCLC	Atezolizumab (PD-L1)	ICIs + Chemotherapy VS. Chemotherapy	394
14	Mok, 2019 (47)	KEYNOTE-042 (NCT02220894)	III	NSCLC	Pembrolizumab (PD-1)	ICIs VS. Chemotherapy	1251
15	Nishio, 2021 (48)	IMpower132 (NCT02657434)	III	NSCLC	Atezolizumab (PD-L1)	ICIs + Chemotherapy VS. Chemotherapy	565
16	Owonikoko, 2021 (49)	CheckMate 451 (NCT02538666)	III	SCLC	Nivolumab (PD-1) Ipilimumab (CTLA-4)	Double ICIs VS. single ICI	557

(Continued)

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TABLE 1 Continued

NO.	First Author Publication Year	Clinical Trial	Trial Phase	Cancer Type	Drug	Treatment Regimens	Enrollment
17	Paz-Ares,2020 (50)	KEYNOTE-407 (NCT02775435)	III	NSCLC	Pembrolizumab (PD-1)	ICIs + Chemotherapy VS. Chemotherapy	558
18	Reck, 2019 (51)	KEYNOTE-024 (NCT02142738)	III	NSCLC	Pembrolizumab (PD-1)	ICIs VS. Chemotherapy	304
19	Spigel, 2021 (52)	CheckMate 331 (NCT02481830)	III	SCLC	Nivolumab (PD-1)	ICIs VS. Chemotherapy	547
20	West, 2019 (53)	IMpower130 (NCT02367781)	III	NSCLC	Atezolizumab (PD-L1)	ICIs + Chemotherapy VS. Chemotherapy	604
21	Wu, 2019 (54)	CheckMate 078 (NCT02613507)	III	NSCLC	Nivolumab (PD-1)	ICIs VS. Chemotherapy	493
22	Yang, 2020 (55)	Orient-11 (NCT03607539)	III	NSCLC	Sintilimab (PD-1)	ICIs + Chemotherapy VS. Chemotherapy	397

Quality assessment

The quality assessment of the included studies is presented in Figure 3. In sum, all studies were randomized, with five presenting a high risk of bias in allocation concealment (selection bias). All studies showed low risks of blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), and selective reporting (reporting bias), with five studies demonstrating high risks of incomplete outcome data (attrition bias). Overall, the risk of other bias was low. The potential publication bias was evaluated through visual inspection of a funnel plot (Supplementary material).

Risk of ICIs-related respiratory disorders

The incidence of ICIs-related respiratory disorders in different treatment regimens is presented in Table 2. In total, the incidence rates of pneumonitis (2.14%), dyspnea (1.62%), and pulmonary embolism (1.51%) were the three highest than other respiratory disorders. Especially in double ICI treatment regimens, the incidence rates of pneumonitis and dyspnea were 6.43% and 3.65%, respectively. Compared with chemotherapy treatment regimens, the incidence rates of pneumonitis, interstitial lung disease, and pleural effusion increased by more than two-fold in ICI treatment regimens (2.84% vs. 0.22%, 0.69% vs. 0.15%, 1.68% vs. 0.83%).

Risk of chronic obstructive pulmonary disease

The different treatment regimens on the risk of chronic obstructive pulmonary disease were presented for 18 datasets (ICIs plus chemotherapy [n = 1969] vs. chemotherapy [n = 1411]; ICIs [n = 3118] vs. chemotherapy [n = 2627]; double ICIs [n = 560] vs. single ICI [n = 560]). Compared with chemotherapy, ICIs plus chemotherapy (P = 0.67; SMD: 0.87; 95% CI: 0.46, 1.64) or ICIs (P = 0.14; SMD: 1.52; 95% CI: 0.87, 2.64) did not significantly change the incidence of chronic obstructive pulmonary disease with low evidence of heterogeneity among the studies (I^2 = 0% and 10%). Double ICIs (P = 0.34; SMD: 0.45; 95% CI: 0.15, 1.30) did not significantly change the incidence of chronic obstructive pulmonary disease when compared with single ICI with low evidence of heterogeneity among the studies (I^2 = 0%) (Figure 4).

Risk of dyspnea

The different treatment regimens on the risk of dyspnea were presented for 19 datasets (ICIs plus chemotherapy [n = 2235] vs. chemotherapy [n = 1542]; ICIs [n = 3301] vs. chemotherapy [n = 2633]; double ICIs [n = 684] vs. single ICI [n = 683]). Compared with chemotherapy, ICIs plus chemotherapy (P = 0.29; SMD: 0.71; 95% CI: 0.38, 1.34) or ICIs (P = 0.36; SMD: 1.22; 95% CI: 0.80, 1.87) did not significantly change the incidence of dyspnea with low evidence of heterogeneity among the studies (I^2 = 0% and 0%). Double ICIs (P = 0.90; SMD: 1.04; 95% CI: 0.58, 1.87) did not significantly change the

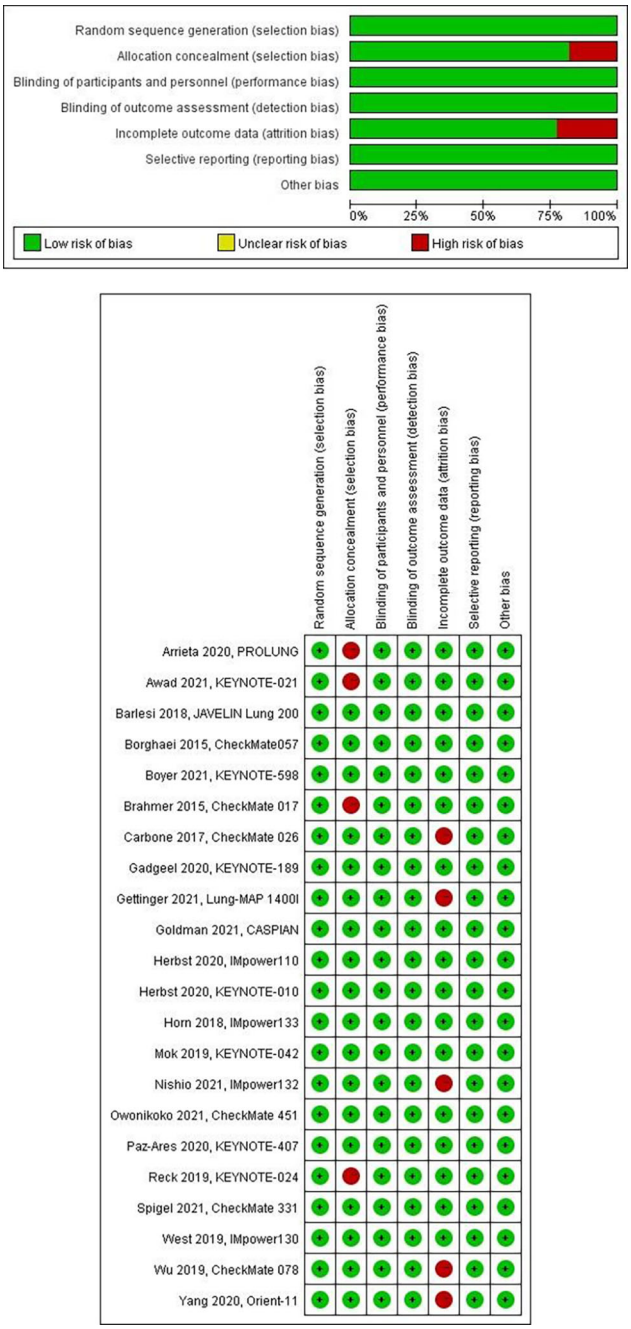

FIGURE 3
Assessment of bias risk, **(A)** risk of bias graph, **(B)** risk of bias summary.

incidence of dyspnea when compared with single ICI with moderate evidence of heterogeneity among the studies (I^2 = 41%) (Figure 5).

Risk of hemoptysis

The different treatment regimens on the risk of hemoptysis were presented for 20 datasets (ICIs plus chemotherapy [n = 2235] vs. chemotherapy [n = 1542]; ICIs [n = 3455] vs. chemotherapy [n = 2783]; double ICIs [n = 560] vs. single ICI [n = 560]). Compared with chemotherapy, ICIs plus chemotherapy (P = 0.88; SMD: 1.06; 95% CI: 0.53, 2.10) or ICIs (P = 0.99; SMD: 1.00; 95% CI: 0.55, 1.83) did not significantly change the incidence of hemoptysis with low evidence of heterogeneity among the studies (I^2 = 0% and 11%). Double ICIs (P = 1.00; SMD: 1.00; 95% CI: 0.14, 7.12) did not significantly change the incidence of hemoptysis compared with single ICI (Figure 6).

Risk of interstitial lung disease

The different treatment regimens on the risk of interstitial lung disease were presented for 15 datasets (ICIs plus chemotherapy [n =

TABLE 2 The incidence of ICIs-related respiratory disorders in different treatment regimens.

ICIs-related respiratory disorders	ICIs + Chemotherapy VS. Chemotherapy n/n (%)		ICIs VS. Chemotherapy n/n (%)		Double ICIs VS. single ICI n/n (%)		Total n/n (%)
	ICIs + Chemotherapy	Chemotherapy	ICIs	Chemotherapy	Double ICIs	single ICI	
Chronic obstructive pulmonary disease	26/1969 (1.32%)	16/1411 (1.13%)	35/3118 (1.12%)	20/2627 (0.76%)	5/560 (0.89%)	11/560 (1.96%)	113/10245 (1.10%)
Dyspnea	23/2235 (1.03%)	18/1542 (1.17%)	54/3301 (1.64%)	35/2633 (1.33%)	25/684 (3.65%)	24/683 (3.51%)	179/11078 (1.62%)
Hemoptysis	21/2235 (0.94%)	12/1542 (0.78%)	22/3455 (0.64%)	18/2783 (0.65%)	2/560 (0.36%)	2/560 (0.36%)	77/11135 (0.69%)
Interstitial lung disease	7/1573 (0.45%)	4/1082 (0.37%)	18/2622 (0.69%)	3/2005 (0.15%)	2/560 (0.36%)	2/560 (0.36%)	36/8402 (0.43%)
Pleural effusion	28/2235 (1.25%)	12/1542 (0.78%)	58/3455 (1.68%)	23/2783 (0.83%)	9/684 (1.32%)	8/683 (1.17%)	138/11382 (1.21%)
Pneumonitis	56/2275 (2.46%)	20/1580 (1.27%)	98/3455 (2.84%)	6/2783 (0.22%)	44/684 (6.43%)	21/683 (3.07%)	245/11460 (2.14%)
Pneumothorax	6/2235 (0.27%)	7/1542 (0.45%)	11/3168 (0.35%)	9/2515 (0.36%)	2/406 (0.49%)	2/404 (0.50%)	37/10270 (0.36%)
Pulmonary embolism	31/1969 (1.57%)	17/1411 (1.20%)	64/3455 (1.85%)	35/2783 (1.26%)	5/560 (0.89%)	10/560 (1.79%)	162/10738 (1.51%)
Pulmonary hemorrhage	2/1029 (0.19%)	1/671 (0.15%)	9/2776 (0.32%)	10/2155 (0.46%)	3/684 (0.44%)	6/683 (0.88%)	31/7998 (0.39%)
Respiratory failure	16/2235 (0.72%)	9/1559 (0.58%)	32/3455 (0.93%)	23/2783 (0.83%)	7/684 (1.02%)	6/683 (0.88%)	93/11399 (0.82%)

1573] vs. chemotherapy [n = 1082]; ICIs [n = 2622] vs. chemotherapy [n = 2005]; double ICIs [n = 560] vs. single ICI [n = 560]). Compared with chemotherapy, ICIs plus chemotherapy (P = 0.82; SMD: 1.14; 95% CI: 0.37, 3.57) did not significantly change the incidence of interstitial lung disease with low evidence of heterogeneity among the studies (I^2 = 0%). ICIs (P = 0.03; SMD: 2.81; 95% CI: 1.08, 7.27) significantly increased the risk of suffering interstitial lung disease with low evidence of heterogeneity among the studies (I^2 = 0%). Double ICIs (P = 1.00; SMD: 1.00; 95% CI: 0.17, 5.79) did not significantly change the incidence of interstitial lung disease when compared with single ICI with low evidence of heterogeneity among the studies (I^2 = 0%) (Figure 7).

Risk of pleural effusion

The different treatment regimens on the risk of pleural effusion were presented for 20 datasets (ICIs plus chemotherapy [n = 2235] vs. chemotherapy [n = 2542]; ICIs [n = 3455] vs. chemotherapy [n = 2783]; double ICIs [n = 684] vs. single ICI [n = 683]). Compared with chemotherapy, ICIs plus chemotherapy (P = 0.31; SMD: 1.41; 95% CI: 0.72, 2.75) did not significantly change the incidence of pleural effusion with low evidence of heterogeneity among the studies (I^2 = 0%). ICIs (P = 0.002; SMD: 2.12; 95% CI: 1.32, 3.42) significantly increased the risk of suffering pleural effusion with low evidence of heterogeneity among the studies (I^2 = 0%). Double ICIs (P = 0.82; SMD: 1.11; 95% CI: 0.44, 2.84) did not significantly change the incidence of pleural effusion when compared with single ICI with low evidence of heterogeneity among the studies (I^2 = 0%) (Figure 8).

Risk of pneumonitis

The different treatment regimens on the risk of pneumonitis were presented for 22 datasets (ICIs plus chemotherapy [n = 2275] vs. chemotherapy [n = 1580]; ICIs [n = 3455] vs. chemotherapy [n = 2783]; double ICIs [n = 684] vs. single ICI [n = 683]). Compared with chemotherapy, ICIs plus chemotherapy (P = 0.01; SMD: 1.96; 95% CI: 1.17, 3.28) and ICIs (P < 0.00001; SMD: 9.23; 95% CI: 4.57, 18.64) significantly increased the risk of suffering pneumonitis with low evidence of heterogeneity among the studies (I^2 = 0% and 0%). Double ICIs (P = 0.004; SMD: 2.17; 95% CI: 1.27, 3.69) significantly increased the risk of suffering pneumonitis with low evidence of heterogeneity among the studies (I^2 = 0%) (Figure 9).

Risk of pneumothorax

The different treatment regimens on the risk of pneumothorax were presented for 19 datasets (ICIs plus chemotherapy [n = 2235] vs. chemotherapy [n = 1542]; ICIs [n = 3168] vs. chemotherapy [n = 2515]; double ICIs [n = 406] vs. single ICI [n = 404]). Compared with chemotherapy, ICIs plus chemotherapy (P = 0.28; SMD: 0.60; 95% CI: 0.24, 1.51) or ICIs (P = 0.90; SMD: 0.95; 95% CI: 0.43, 2.11) did not significantly change the incidence of pneumothorax with

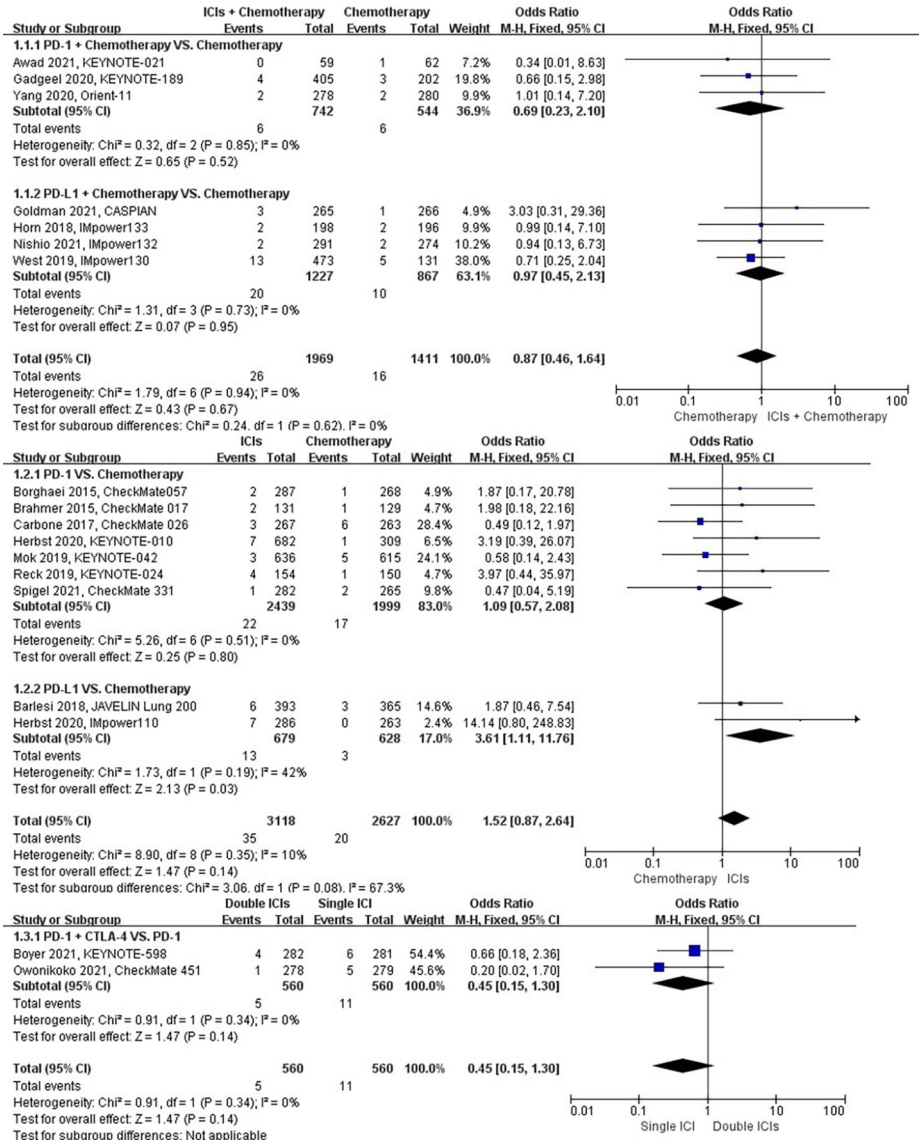

FIGURE 4
The forest plot of different treatment regimens on chronic obstructive pulmonary disease. Subgroup analyses investigated ICIs plus chemotherapy vs. chemotherapy, ICIs vs. chemotherapy and double ICIs vs. single ICI. CI, confidence interval.

low evidence of heterogeneity among the studies (I^2 = 0% and 0%). Double ICIs (P = 0.99; SMD: 0.99; 95% CI: 0.17, 5.77) did not significantly change the incidence of pneumothorax when compared with single ICI with low evidence of heterogeneity among the studies (I^2 = 0%) (Figure 10).

Risk of pulmonary embolism

The different treatment regimens on the risk of pulmonary embolism were presented for 19 datasets (ICIs plus chemotherapy [n = 1969] vs. chemotherapy [n = 1411]; ICIs [n = 3455] vs. chemotherapy [n = 2783]; double ICIs [n = 560] vs. single ICI [n = 560]). Compared with chemotherapy, ICIs plus chemotherapy (P = 0.94; SMD: 0.98; 95% CI: 0.53, 1.80) or ICIs (P = 0.06; SMD: 1.49; 95% CI: 0.98, 2.25) did not significantly change the incidence of pulmonary embolism with low evidence of heterogeneity among the studies (I^2 = 0% and 0%). Double ICIs (P = 0.21; SMD: 0.51; 95% CI: 0.18, 1.46) did not significantly change the incidence of pulmonary embolism when compared with single ICI with low evidence of heterogeneity among the studies (I^2 = 0%) (Figure 11).

Risk of pulmonary hemorrhage

The different treatment regimens on the risk of pulmonary hemorrhage were presented for 15 datasets (ICIs plus chemotherapy [n = 1029] vs. chemotherapy [n = 671]; ICIs [n =

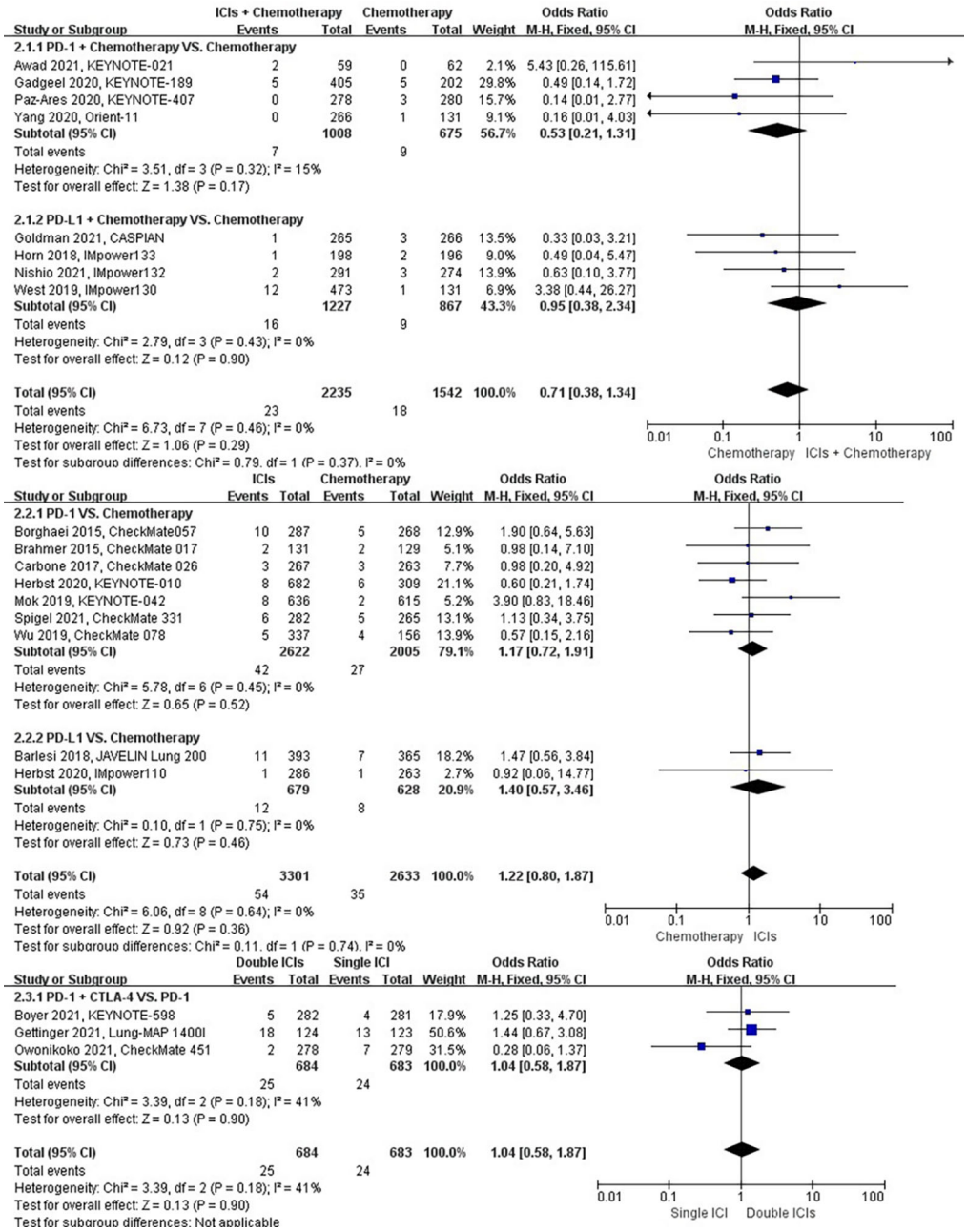

FIGURE 5
The forest plot of different treatment regimens on dyspnea. Subgroup analyses investigated ICIs plus chemotherapy vs. chemotherapy, ICIs vs. chemotherapy and double ICIs vs. single ICI. CI, confidence interval.

2776] vs. chemotherapy [n = 2155]; double ICIs [n = 684] vs. single ICI [n = 683]). Compared with chemotherapy, ICIs plus chemotherapy (P = 0.70; SMD: 0.68; 95% CI: 0.09, 4.82) or ICIs (P = 0.52; SMD: 0.77; 95% CI: 0.34, 1.71) did not significantly change the incidence of pulmonary hemorrhage with low evidence of heterogeneity among the studies (I^2 = 0% and 0%). Double ICIs (P = 0.34; SMD: 0.53; 95% CI: 0.14, 1.97) did not significantly change the incidence of pulmonary hemorrhage when compared with single ICI with low evidence of heterogeneity among the studies (I^2 = 0%) (Figure 12).

Risk of respiratory failure

The different treatment regimens on the risk of respiratory failure were presented for 20 datasets (ICIs plus chemotherapy [n = 2235] vs. chemotherapy [n = 1559]; ICIs [n = 3455] vs. chemotherapy [n = 2783]; double ICIs [n = 684] vs. single ICI [n = 683]). Compared with chemotherapy, ICIs plus chemotherapy (P = 0.97; SMD: 0.98; 95% CI: 0.45, 2.14) or ICIs (P = 0.52; SMD: 1.19; 95% CI: 0.70, 2.02) did not significantly change the incidence of respiratory failure with low evidence of heterogeneity among the

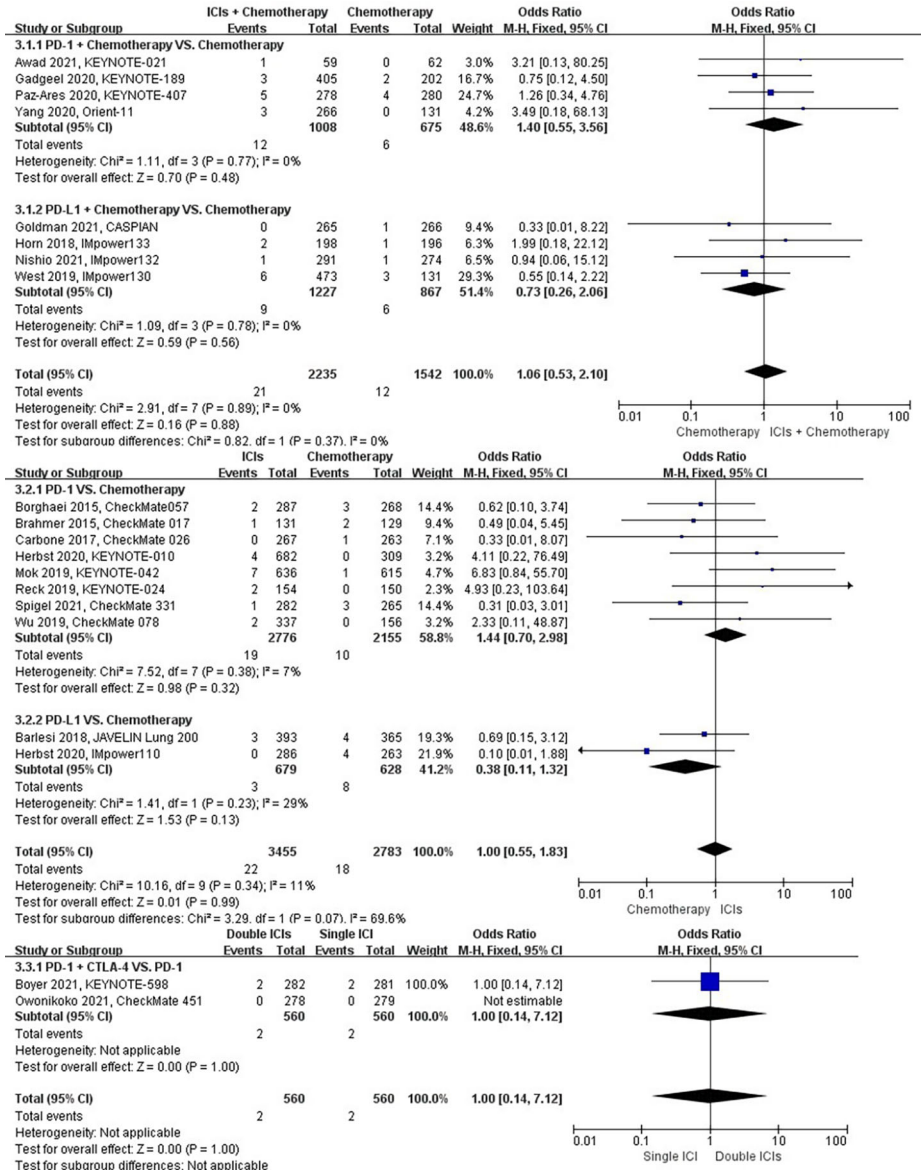

FIGURE 6
The forest plot of different treatment regimens on hemoptysis. Subgroup analyses investigated ICIs plus chemotherapy vs. chemotherapy, ICIs vs. chemotherapy and double ICIs vs. single ICI. CI, confidence interval.

studies (I^2 = 0% and 0%). Double ICIs (P = 0.80; SMD: 1.15; 95% CI: 0.40, 3.32) did not significantly change the incidence of respiratory failure when compared with single ICI with high evidence of heterogeneity among the studies (I^2 = 78%) (Figure 13).

Discussion

As the first FDA-approved ICI on anti-cancer, ipilimumab was used to treat advanced melanoma in 2011 (56). In the next decade, the use of ICIs in cancer treatment rapidly increased, including numerous breakthroughs, expanded treatment landscape for many malignancies, and improved outcomes, specifically NSCLC (57–59). Nivolumab, a PD-1 inhibitor, brought a promising outcome when it was effectively used as a second-line therapy for patients with advanced NSCLC. In the next phase III trials on advanced squamous and non-squamous NSCLC, nivolumab achieved inspiring results of OS and objective response rate (ORR) (37, 39). In recent years, several phase III clinical trials demonstrated a superior improvement in OS and more durable responses with ICIs or ICIs plus chemotherapy than chemotherapy (27, 29, 30, 32, 33, 44, 60, 61). The clinical choice mainly depends on disease burden, PD-L1 expression, and tumor mutation profile of the tumor. In comparison, the growth of ICIs in SCLC could be more satisfactory. ICIs merely had an achievement that PD-L1 inhibitors plus platinum-based chemotherapy conducted as first-line treatment of extensive-stage SCLC (46, 62).

Based on the extremely rapid growth of ICIs, various irAEs were reported. In general, irAEs are usual due to nonspecific

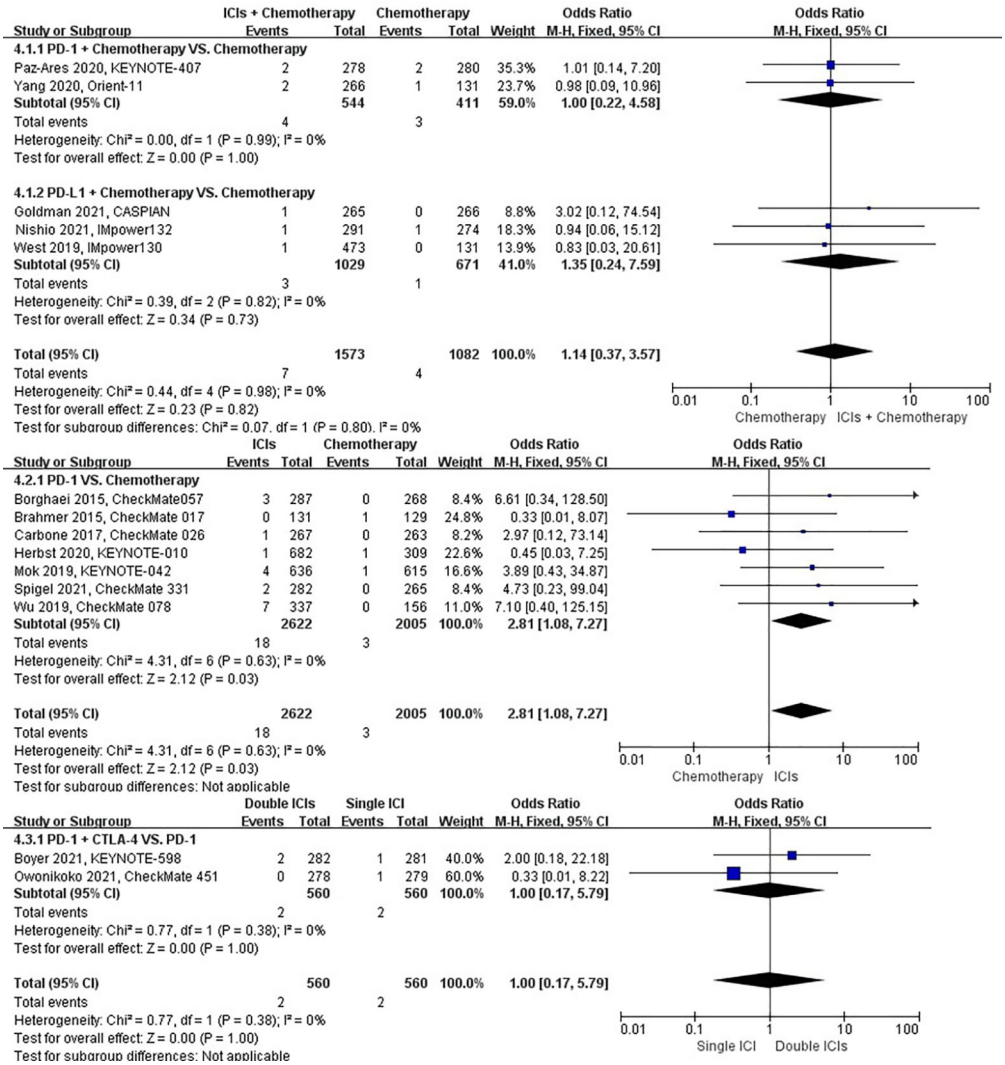

FIGURE 7
The forest plot of different treatment regimens on interstitial lung disease. Subgroup analyses investigated ICIs plus chemotherapy vs. chemotherapy, ICIs vs. chemotherapy and double ICIs vs. single ICI. CI, confidence interval.

immunostimulation, leading to autoimmunity, tissue damage, and organ-specific inflammation (63). They can be divided into cytokine release syndrome and cardiac, pulmonary, dermatologic, endocrine, neurologic, ocular, renal, rheumatologic, gastrointestinal, and hepatic toxicities (64, 65). Dermatologic, endocrine, gastrointestinal, and hepatic toxicities are shared among ICI-treated patients (65, 66). Cardiac and pulmonary toxicities are rare but potentially fatal (20, 67–70). In particular, pulmonary toxicity is rapidly progressive (71). Most of the irAEs caused by pulmonary toxicity occur during 10–12 weeks after ICI therapy, and the early symptoms are mild and nonspecific, such as cough (72). However, some ICI-treated patients may suffer severe ICIs-related respiratory disorders (SAE grade ≥ 3), such as chronic obstructive pulmonary disease, hemoptysis, interstitial lung disease, pleural effusion, pneumonitis, pulmonary embolism, and respiratory failure. Therefore, a broad range of diagnostic processes, including X-ray imaging, angiography, and laboratory analyses, are necessary for ICI-treated patients to distinguish pulmonary embolism, pleural effusion, pneumonitis, pneumothorax, and cancer progression.

In recent years, some researchers analyzed certain ICIs-related respiratory disorders in digestic and urologic cancer (73, 74). However, a study on comprehensive ICIs-related respiratory disorders in lung cancer is still warranted. In this study, we extracted 22 RCTs and analyzed the risk of top 10 most frequent ICIs-related respiratory disorders in patients with lung cancer. Overall, the analysis revealed that ICIs raise the risk of interstitial lung disease, pleural effusion, and pneumonitis compared with chemotherapy. Furthermore, ICIs plus chemotherapy brought a higher incidence of pneumonitis than chemotherapy. single ICI could provide a lower probability for patients to suffer pneumonitis than double ICIs. Also, other ICIs-related respiratory disorders, including chronic obstructive pulmonary disease, dyspnea, hemoptysis, pneumothorax, pulmonary embolism, pulmonary hemorrhage, and respiratory failure, were analyzed in this study.

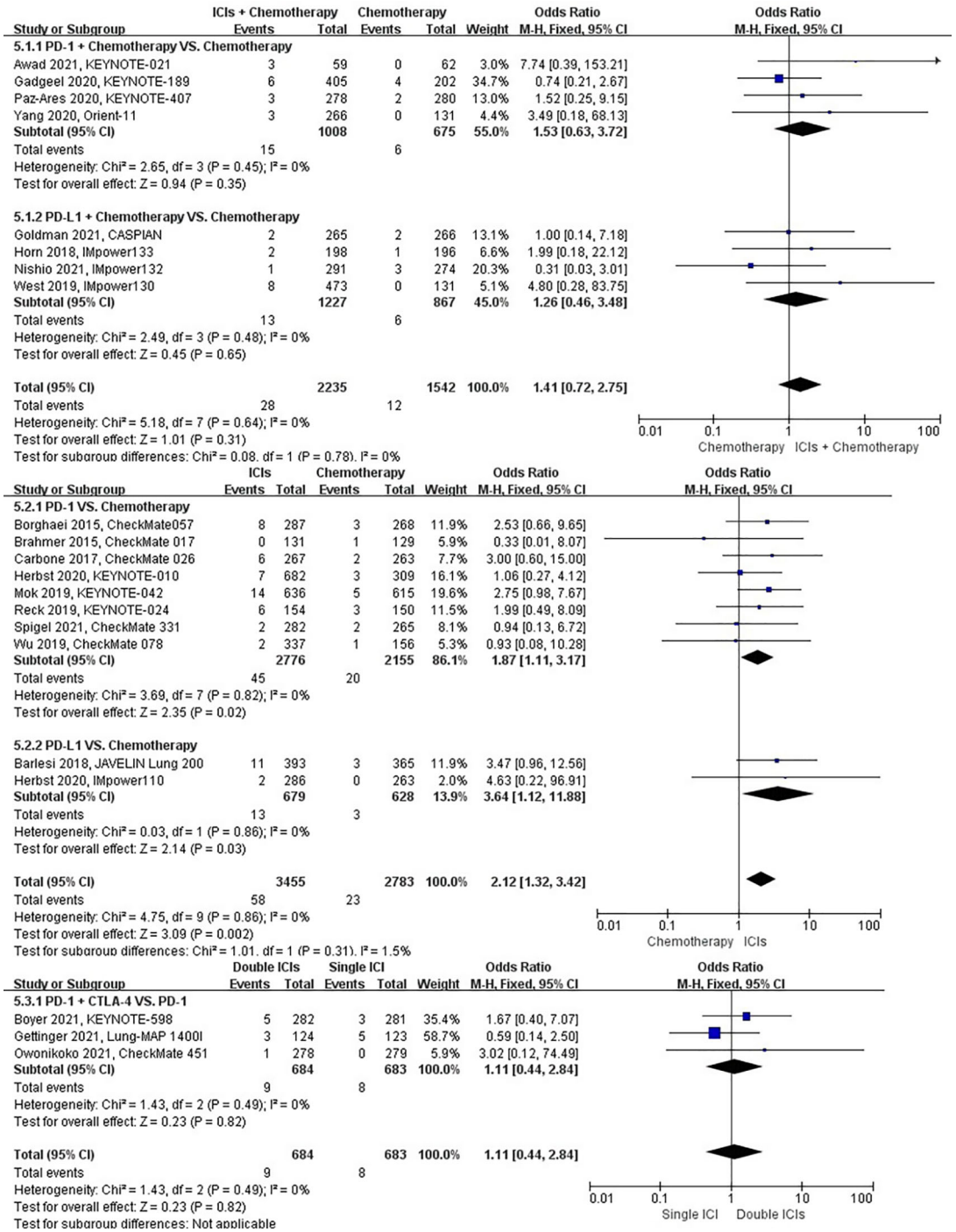

FIGURE 8
The forest plot of different treatment regimens on pleural effusion. Subgroup analyses investigated ICIs plus chemotherapy vs. chemotherapy, ICIs vs. chemotherapy and double ICIs vs. single ICI. CI, confidence interval.

Still, no significant difference was observed among the different treatment regimens.

Previous studies have demonstrated that the incidence of ICIs-related interstitial lung disease ranges from 14.5% to 18.6% (75, 76). This study showed that ICIs were more likely to cause interstitial lung disease than chemotherapy. This is similar to other studies showing that ICIs cause interstitial lung disease more frequently than other drugs used to treat NSCLC, such as pemetrexed, erlotinib, gefitinib, docetaxel, gemcitabine, or crizotinib (77–83). However, the mechanisms regulating the occurrence of ICIs-related interstitial lung disease have not been fully elucidated so far. Elevated levels of inflammatory cytokines may be involved in the pathophysiology of irAEs (84, 85). The inflammatory cytokine interleukin 6 (IL-6) induces the differentiation of naive CD4 T

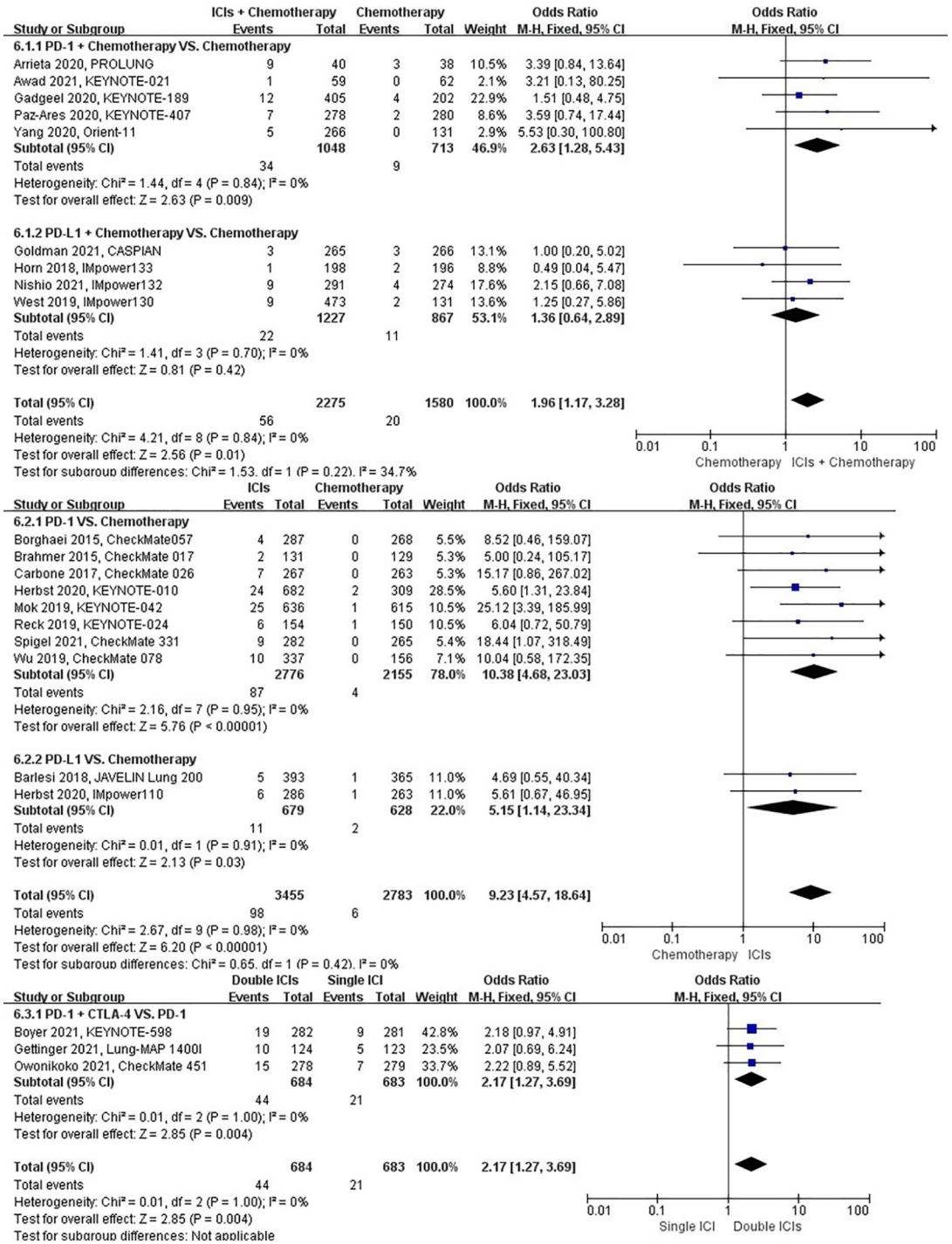

FIGURE 9
The forest plot of different treatment regimens on pneumonitis. Subgroup analyses investigated ICIs plus chemotherapy vs. chemotherapy, ICIs vs. chemotherapy and double ICIs vs. single ICI. CI, confidence interval.

cells into Th17 cells, which may be related to irAE occurrence (86). Th17 cells are critical mediators of various autoimmune diseases by producing IL-17 (87, 88). Likewise, tumor necrosis factor-α (TNF-α) has been associated with irAEs, and anti-TNF-α antibodies were found to improve severe irAEs (89). Patients with poorer performance score and cancer cachexia status have higher levels of inflammatory cytokines, such as IL-6 and TNF-α, and may be more prone to irAE-related diseases, such as ICIs-related interstitial lung disease (90, 91). PD-L1 inhibitors should be less toxic than PD1 inhibitors as they do not prevent the interaction between PD-L2 and PD1 (92). Still, we could not confirm this difference in our study due to data limitations.

In this study, a total of 81 pleural effusion events occurred in the ICIs vs. chemotherapy group, among which 58 and 23 patients

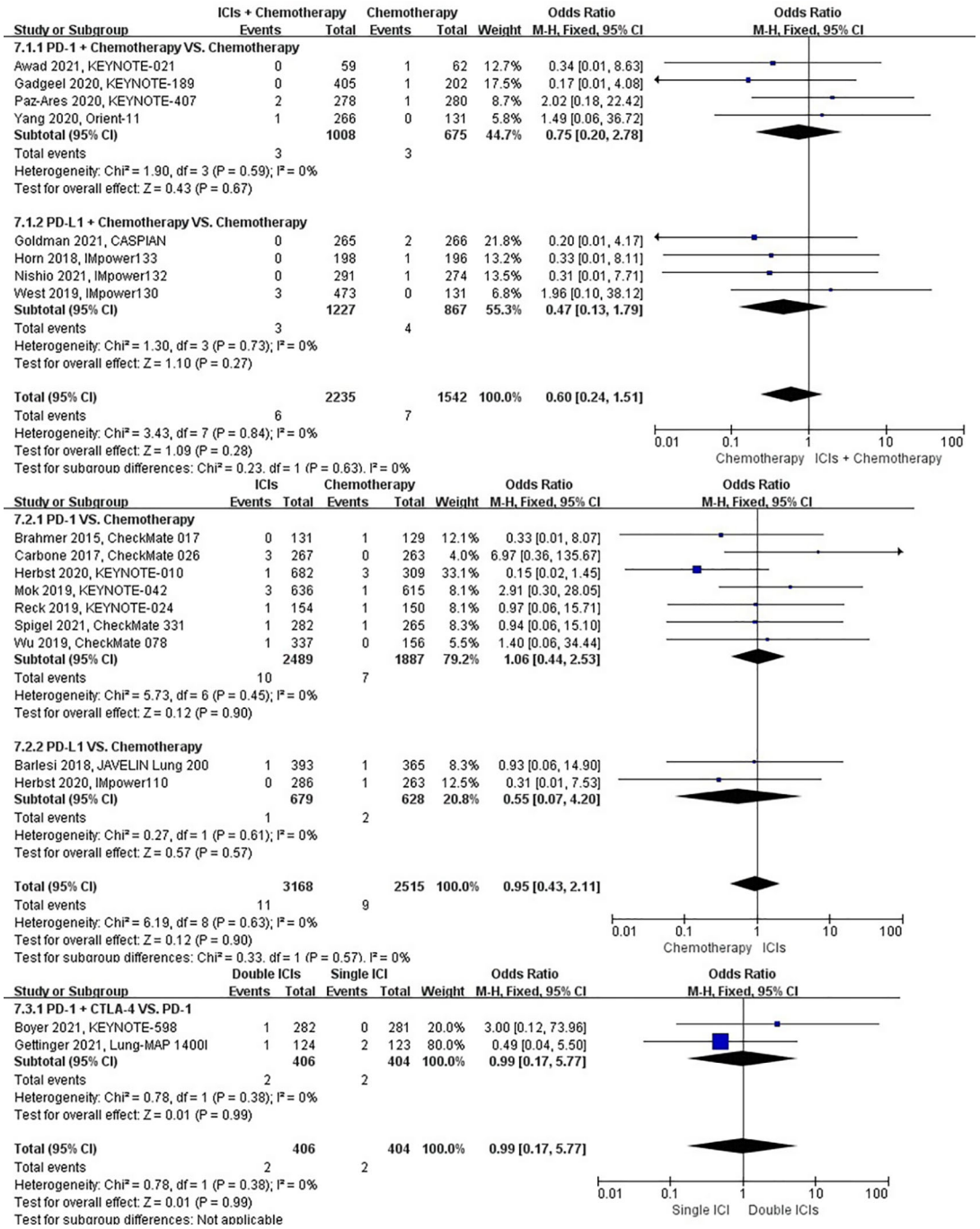

FIGURE 10
The forest plot of different treatment regimens on pneumothorax. Subgroup analyses investigated ICIs plus chemotherapy vs. chemotherapy, ICIs vs. chemotherapy and double ICIs vs. single ICI. CI, confidence interval.

developed pleural effusion after applying ICIs and using chemotherapy, respectively; ICIs significantly increased the risk of pleural effusion compared with chemotherapy ($P < 0.05$). Pleural effusion has been reported as an irAE, but there are few studies on ICIs-related pleural effusion, most of which are case reports (93–95). Two patients were reported to develop recurrent pleural effusions that accumulated rapidly within days after each puncture and required multiple thoracentesis for the first 8 weeks after administration of nivolumab (95). In another study, a patient was not initially diagnosed with pleural dissemination or malignant pleural effusion. However, cytology and radiography or thoracoscopy did not find evidence of malignancy in the pleural effusion and malignant nodules, respectively. Hypoalbuminemia and cardiac insufficiency, which may cause pleural effusion, were also excluded. And the pleural effusion responded well after corticotherapy, suggesting that this may be an irAE (94). Pleural effusion is considered to be related to the pseudo-progression of the disease (95). However, so far, there is no detailed research to explain

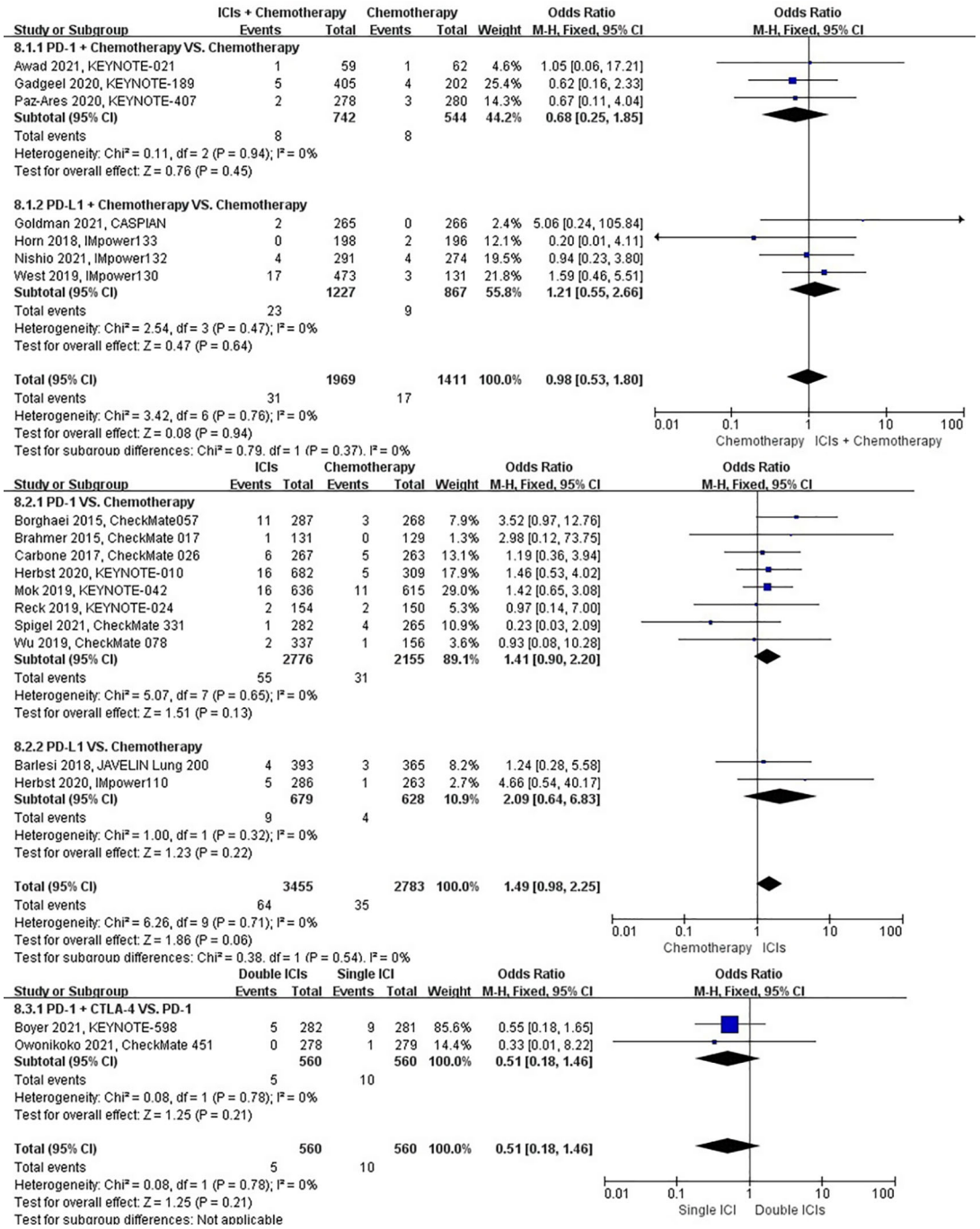

FIGURE 11
The forest plot of different treatment regimens on pulmonary embolism. Subgroup analyses investigated ICIs plus chemotherapy vs. chemotherapy, ICIs vs. chemotherapy and double ICIs vs. single ICI. CI, confidence interval.

this. Moreover, the mechanism still needs to be elucidated, and further research is warranted.

In some RCTs, the incidence of ICIs-related pneumonitis was approximately 1.06% (95% CI: 0.53–2.11) for CTLA-4 inhibitors, 3.02% (95% CI: 2.31–3.93) for PD-1 inhibitors, and 7.09% (95% CI: 5.52–7.16) for PD-1 combined with CTLA-4 inhibitors (28, 30, 37, 39, 96–114). ICIs-related pneumonitis is hypothesized to be a chronic inflammatory state (114). Its symptoms are nonspecific and usually present with cough, dyspnea, shortness of breath, and hypoxia (115, 116). This study demonstrated that the risk of pneumonitis after treatment of PD-1 combined with CTLA-4 was higher than that of PD-1 alone, which is similar to the previous study (116) showing that the risks of pneumonitis (3.47-fold) and severe pneumonitis (3.48-fold) were higher with ipilimumab combined with nivolumab than nivolumab or ipilimumab alone. Therefore, the combination of CTLA-4 and PD-1 may cause a higher incidence of pneumonitis than either drug (110–112). CTLA-4 inhibitors attenuate T cell activation early in the immune response. PD-1 inhibitors can

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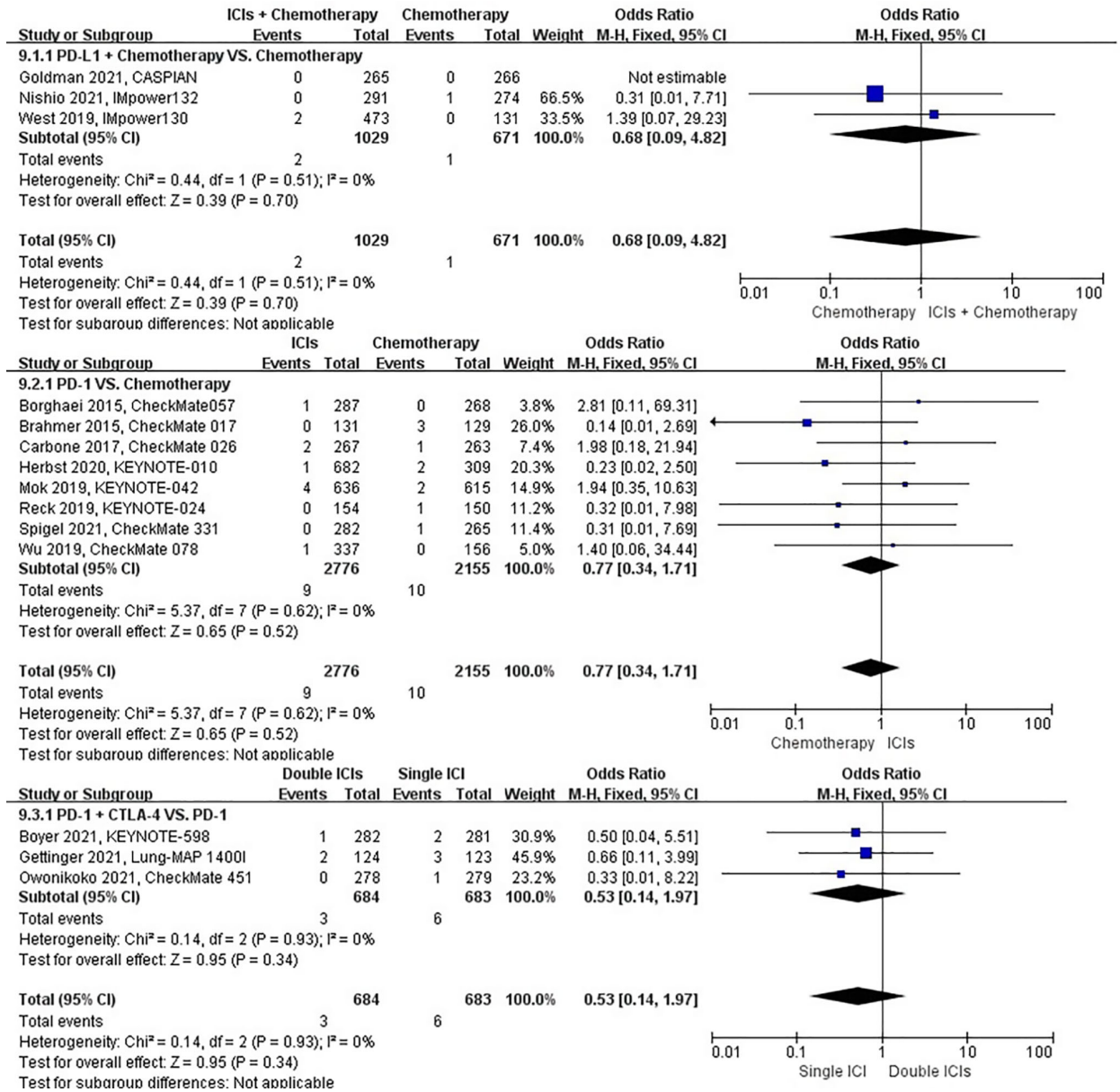

FIGURE 12
The forest plot of different treatment regimens on pulmonary hemorrhage. Subgroup analyses investigated ICIs plus chemotherapy vs. chemotherapy, ICIs vs. chemotherapy and double ICIs vs. single ICI. CI, confidence interval.

inhibit T cells later in peripheral tissue immune response. Therefore, we assumed that the combined application of PD-1 and CTLA-4 may be more prone to lung toxicity than either treatment alone; however, further studies are needed to reveal this molecular mechanism. In this study, we also found that ICIs with or without chemotherapy increased the risk of pneumonitis compared with chemotherapy alone. Interestingly, studies have demonstrated that patients with NSCLC treated with PD-L1 inhibitors have a higher incidence of pneumonitis than those with other cancer types. In a study that compared data from patients with lung cancer and other solid tumors, pneumonitis was more common in patients with lung cancer (26.4% vs. 10.3%) (117). Therefore, tumor damage to lung tissue may make the lungs more prone to side effects after treatment. With the increasing use of ICIs in more neoplastic diseases, the total burden of pneumonitis and mortality will undoubtedly increase.

This study has several limitations. First, NSCLC and SCLC were both investigated in the analysis. A retrospective study demonstrated that squamous cell cancer was a risk factor for ICIs-related pneumonitis (17). As a confounding factor, SCLC might increase heterogeneity to a certain degree. Second, there needed to be more datasets to build single-drug subgroups for certain drug analysis, such as avelumab and sintilimab. Third, the study did not involve LAG3, PD-L2, and other ICIs.

In conclusion, this study showed that ICI-based treatment, such as ICIs alone, ICIs plus chemotherapy, and double ICIs, can raise the incidences of some respiratory disorders in patients with lung

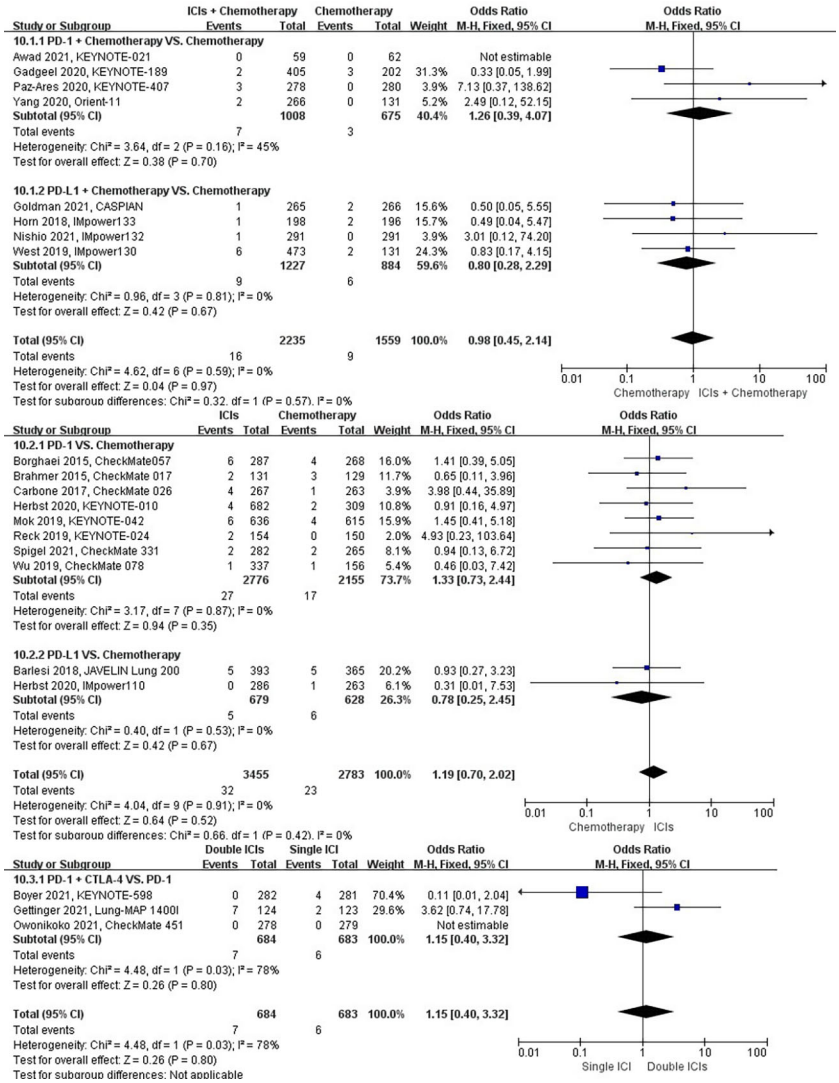

FIGURE 13
The forest plot of different treatment regimens on respiratory failure. Subgroup analyses investigated ICIs plus chemotherapy vs. chemotherapy, ICIs vs. chemotherapy and double ICIs vs. single ICI. CI, confidence interval.

cancer. It suggests that ICIs should be conducted based on a comprehensive consideration to prevent ICIs-related respiratory disorders. To a certain degree, this study might be provided to the clinician as a reference for ICI practice. Of course, more prospective and well-designed clinical trials, and larger sample size real-world studies on various ICIs are still needed to further evaluate therapeutic effects and ICIs-related adverse events.

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

SW conducted the analysis, SL, JJ and LP collected and performed a preliminary analysis of references, HL designed the manuscript, SL and HL wrote the manuscript, LP, SW and LS revised the manuscript. All authors contributed to the article and approved the submitted version.

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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 potential conflicts of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2023.1115305/full#supplementary-material

SUPPLEMENTARY FIGURE 1
The funnel plot for accessing publication bias: chronic obstructive pulmonary diseases.

SUPPLEMENTARY FIGURE 2
The funnel plot for accessing publication bias: dyspnea.

SUPPLEMENTARY FIGURE 3
The funnel plot for accessing publication bias: hemoptysis.

SUPPLEMENTARY FIGURE 4
The funnel plot for accessing publication bias: interstitial lung disease.

SUPPLEMENTARY FIGURE 5
The funnel plot for accessing publication bias: pleural effusion.

SUPPLEMENTARY FIGURE 6
The funnel plot for accessing publication bias: pneumonitis.

SUPPLEMENTARY FIGURE 7
The funnel plot for accessing publication bias: pneumothorax.

SUPPLEMENTARY FIGURE 8
The funnel plot for accessing publication bias: pulmonary embolism.

SUPPLEMENTARY FIGURE 9
The funnel plot for accessing publication bias: pulmonary hemorrhage.

SUPPLEMENTARY FIGURE 10
The funnel plot for accessing publication bias: respiratory failure.

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