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Meta-analysis

Risk of interstitial lung disease with the use of programmed cell death 1 (PD-1) inhibitor compared with programmed cell death ligand 1 (PD-L1) inhibitor in patients with breast cancer: A systematic review and meta-analysis

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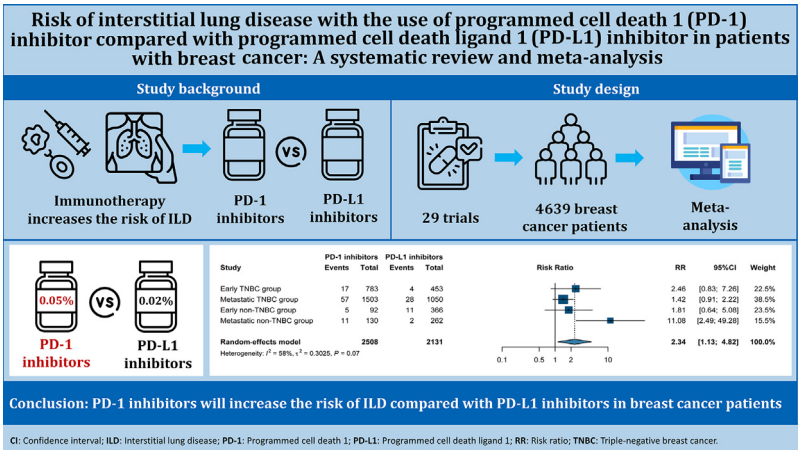
HIGHLIGHTS

- Programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors cause interstitial lung disease (ILD).
- ILD is a rare adverse event; most cases are low-grade but potentially fatal.
- The present meta-analysis included 29 studies with 4639 patients with breast cancer.
- Compared with PD-L1 inhibitors, PD-1 inhibitors will increase the risk of ILD in patients with breast cancer.
- Suitable treatment options for ILD and its early detection and immediate management should be initiated.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors have become integral elements within the current landscape of breast cancer treatment modalities; however, they are associated with interstitial lung disease (ILD), which is rare but potentially fatal. Notably, only a few studies have compared the difference in ILD incidence between PD-1 and PD-L1 inhibitors. Therefore, this study aimed to assess the discrepancies regarding ILD risk between the two immune checkpoint inhibitors. We also reported three cases of ILD after PD-1 inhibitor treatment.

Methods: We comprehensively searched PubMed, EMBASE, and the Cochrane Library to identify clinical trials that investigated PD-1/PD-L1 inhibitor treatment for patients with breast cancer. Pooled overall estimates of incidence and risk ratio (RR) were calculated with a 95% confidence interval (CI), and a mirror group analysis was performed using eligible studies.

Results: This meta-analysis included 29 studies with 4639 patients who received PD-1/PD-L1 inhibitor treatment. A higher ILD incidence was observed among 2508 patients treated with PD-1 inhibitors than among 2131 patients treated with PD-L1 inhibitors (0.05 *vs.* 0.02). The mirror group analysis further revealed a higher ILD event risk in patients treated with PD-1 inhibitors than in those treated with PD-L1 inhibitors (RR = 2.34, 95% CI, 1.13–4.82, $P = 0.02$).

Conclusion: Our findings suggest a greater risk of ILD with PD-1 inhibitors than with PD-L1 inhibitors. These findings are instrumental for clinicians in treatment deliberations, and the adoption of more structured diagnostic approaches and management protocols is necessary to mitigate the risk of ILD.

Introduction

Challenge of programmed cell death 1 and programmed cell death ligand 1 inhibitor treatments for breast cancer

Immunotherapy is a novel option for the management of solid tumors. Immune checkpoint inhibitors, specifically programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors, have shown potential to treat breast cancer. Pembrolizumab, nivolumab, and camrelizumab are PD-1 inhibitors, whereas atezolizumab and durvalumab are PD-L1 inhibitors. According to several studies, the objective response rate (ORR) of PD-1/PD-L1 inhibitor treatment ranges from 12 to 19%.[1–3] PD-1, a negative co-stimulatory receptor, is predominantly expressed on the surface of activated T, B, natural killer T, and dendritic cells and mediates immunosuppression. PD-L1 and programmed cell death ligand 2 (PD-L2) are ligands primarily expressed on the surface of tumor and stromal cells, such as dendritic cells. The PD-1/PD-L1 axis impedes T cell activation, reducing the production of various cytokines by T cells.[4] Furthermore, this type of binding may enhance the development of regulatory T cells, thereby triggering inhibition of the immune response.[5] Blocking the interaction between PD-1 and PD-L1 can enhance T cell responses and mediate anti-tumor activity,[6] empowering the human immune system to combat cancer.[7] However, such inhibition can potentially affect non-malignant tissues, leading to local dysfunction. Consequently, immunotherapy can cause various off-target adverse events (AEs) known as immune-related AEs (irAEs). Therefore, immunotherapy can confer clinical benefits to patients with breast cancer, particularly human epidermal growth factor receptor 2 (HER2)-negative breast cancer and triple-negative breast cancer (TNBC);[8,9] however, it also increases the risk of irAEs. Common irAEs include pneumonitis, hepatitis, colitis, myocarditis, hypothyroidism, and hyperthyroidism (collectively known as organ-specific irAEs) and other general AEs, including fatigue, diarrhea, rash, and musculoskeletal syndromes. Despite the rarity of fatal irAEs reported in many clinical trials, they might significantly affect patients' quality of life and even lead to the discontinuation of immunotherapy.

Interstitial lung disease induced by programmed cell death 1/programmed cell death ligand 1 inhibitor

Interstitial lung disease (ILD) is an organ-specific irAE, which is rare and predominantly presents as a low-grade AE; however, severe ILD cases can be potentially fatal, as indicated in previous reports.[10,11] ILD is a lung parenchymal disorder with pathogenesis, laboratory findings, and clinical manifestations that vary across different specific causes of the disease.[12] The diagnosis of drug-induced ILD is mainly based on a distinct temporal association between causative drug exposure and characteristics syndromes.[13] Identifying ILD events associated with PD-1/PD-L1 inhibitor usage is primarily dependent on radiographic assessments such as computed tomography (CT), which reveals ground-glass opacities and reticular infiltrates.[14] Previous studies have shown that the overall incidence of ILD among patients with advanced cancer treated with PD-1/PD-L1 inhibitor ranged from 2.7 to 5%.[15,16] One meta-analysis suggested that compared with standard chemotherapy, PD-1 inhibitors increased the risk of ILD in patients with cancer patients,[17] however, this meta-analysis did not encompass breast cancer data. Furthermore, several meta-analyses focusing on patients with TNBC indicated that compared with chemotherapy, PD-1/PD-L1 inhibitor increased the overall irAE risk.[18–22] This trend was also found in pneumonitis,[20,21] indicating that PD-1/PD-L1 inhibitor treatment might potentially increase ILD risk in patients with TNBC. Furthermore, a recent meta-analysis suggested that pembrolizumab (a PD-1 inhibitor) may increase the risk of immune-induced pneumonitis to a greater extent than atezolizumab (a PD-L1 inhibitor).[21] However, whether PD-1 and PD-L1 inhibitors have different risk profiles for ILD in patients with breast cancer remains an open question.

Based on previous reports, we wondered whether PD-1 inhibitors would increase the risk of ILD than PD-L1 inhibitors in patients with breast cancer. To the best of our knowledge, only limited systematic reviews or meta-analyses have compared the difference in ILD incidence between PD-1 and PD-L1 inhibitors. PD-1 inhibitors might be associated with a higher risk of ILD events than PD-L1 inhibitors among patients with lung cancer,[23] particularly for non-small cell lung cancer (NSCLC).[24] Relevant meta-analyses are still required to confirm whether similar conclusions can be generalized to patients with breast cancer, especially those suffering from lung metastasis. Because such a clinical trial is challenging and relatively unfeasible to conduct directly, we conducted the present systematic review and meta-analysis to investigate the differences in the incidence of ILD events between PD-1 and PD-L1 inhibitors in patients with breast cancer.

Methods

Data sources and search strategy

A systematic literature search of electronic databases, including PubMed, EMBASE, and the Cochrane Library, from inception to July 2023 was conducted to identify ILD risk associated with PD-1 and PD-L1 inhibitor treatment of breast cancer using a predefined algorithm [Supplementary Table 1]. References included in pertinent systematic reviews were also screened. All studies were independently evaluated by two investigators (Lijuan Guo and Xiaoyi Lin), and any discrepancies were resolved by

consensus. The present study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[25] and has been registered on INPLASY with the registration number INPLASY 202360007. ILD and pneumonitis were both considered ILD events.

Eligibility criteria

All included studies were required to meet the following criteria: (1) phase I/II, II, or III randomized clinical trials (RCTs), single-arm studies, and conference abstracts with published, presented, publicly available relevant data; (2) studies with participants who have breast cancer; (3) participants assigned to PD-1 or PD-L1 inhibitor treatment; (4) studies with sufficient information to measure AEs, including ILD events; and (5) studies published in English. Studies were excluded from this analysis based on the following criteria: (1) conventional phase I clinical trials; (2) studies with patients who received radiotherapy; (3) studies that did not provide patients' baseline characteristics; (4) case reports, reviews, meta-analyses, systematic reviews, and cell or animal studies; and (5) studies that included more than two significantly different breast cancer subtypes that could not be paired as a single breast cancer subtype mirror group. For studies with duplicated data, only one was included.

Data extraction

Data were independently extracted from all eligible studies by two investigators (Lijuan Guo and Xin Lin), and discrepancies were resolved by a third investigator (Xiaoyi Lin). The following variables were collected: name of the study, National Clinical Trials identification number, publication year, cancer type, study phase, study type, PD-1/PD-L1 inhibitor types, comparator groups, number of patients who developed ILD events, number of patients in the intervention group, and the PD-L1 immunohistochemistry assay method [Table 1]. Eligible studies using PD-1 or PD-L1 inhibitors were paired as a mirror group based on comparable breast cancer types and stages [Table 2].

Assessment of methodological quality

The methodological quality of all included trials was evaluated using the tool recommended by the Cochrane Collaboration Handbook based on original studies or updated data obtained from clinicaltrial.gov and supplementary materials.[26] The risk of bias (RoB) among the RCTs was evaluated using the Cochrane Collaboration's RoB tool V.2, ascertaining five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. The RoB2 tool can be accessed from the Cochrane Collaboration. For single-arm trials, we used the Joanna Briggs Institute (JBI) checklists to assess the RoB by calculating the number of "yes" answers within 10 questions, and scores $\leq$49.0% were categorized as high RoB, 50.0–70.0% were moderate risk, and >70.0% were low risk.[27,28] In the presentation of the JBI checklists evaluation, green color indicated "yes" answers, red color indicated "no" answers and yellow color indicated "unclear" answers. All assessments were performed independently by two investigators (Lijuan Guo and Xin Lin), and consensus was reached by a third investigator (Xiaoyi Lin).

Data synthesis and statistical analysis

We computed the risk ratio (RR) and 95% confidence interval (CI) to estimate the risk of ILD events using PD-1 inhibitors compared with PD-L1 inhibitors in all included studies. RR $<$ 1 indicated that PD-1 inhibitors yielded a lower risk of developing ILD events than PD-L1 inhibitors. Conversely, RR $>$ 1 indicated that PD-1 inhibitors yielded a higher risk of developing ILD events than PD-L1 inhibitors. All analyses were performed using the meta-package (version 6.0.0) of the R program (version 4.1.3). Publication bias was assessed using funnel plots and Egger's test. Statistical heterogeneity in the results between studies included in the meta-analysis was examined using Cochrane's Q statistics, and inconsistency was quantified using the I^2 statistic to estimate the percentage of total variation across studies due to heterogeneity. The standard cut-off values for the I^2 value were 25% (low heterogeneity), 50% (moderate heterogeneity), and 75% (high heterogeneity).[29] The assumption of homogeneity was considered invalid for P values < 0.05, and all P values were two-tailed. The RRs were calculated using a random-effects model when substantial heterogeneity was assessed ($I^2 >$ 50%, $P < 0.1$); otherwise, the pooled estimated RRs were calculated using a fixed-effects model ($I^2 < 50\%$, $P > 0.1$). Sensitivity analysis was performed by repeating the analyses and omitting one study each time.

Results

Description of studies

Our search strategy identified 1140 studies for the initial eligibility screening (PubMed, 119; EMBASE, 280; Cochrane Library, 741) [Figure 1]. Finally, 29 studies, including 19 RCTs and 10 non-RCTs, were included in this analysis. Of the 19 RCTs, 17 had relevant references[30–47] whereas two did not (DORA and CheckMate 7A8). Among the 10 non-RCTs, eight had relevant references,[48–56] except for BerGenBio 2021 and Bristol-Myers 2021. Detailed information obtained from clinicaltrial.gov is presented in Table 1. These studies evaluated various cancer types and stages: early TNBC (five studies), advanced or metastatic TNBC (15 studies), early HER2+ breast cancers (three studies), advanced or metastatic HER2+ breast cancers (one study), early HER2-hormone receptor-positive breast cancers (three studies), advanced or metastatic HER2-breast cancers (one study), and advanced or metastatic estrogen receptor-positive breast cancers (one study). All selected studies included 4639 patients diagnosed with different breast cancer subtypes or stages and treated with PD-1/PD-L1 inhibitor. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 were used to grade AEs in all these studies.[57]

Incidence of interstitial lung disease events among patients with breast cancer treated with programmed cell death 1 inhibitors compared with those treated with programmed cell death ligand 1 inhibitors

All 29 studies included in this analysis reported ILD events as AEs. The present study suggested that, compared with chemotherapy alone, adding PD-1/PD-L1 inhibitor would increase the risk of ILD events (RR = 2.17, 95% CI, 1.43–3.28, $P < 0.01$), with low heterogeneity (I^2 = 33%, P = 0.11) [Figure 2]. Further analysis was performed to compare the risk of ILD events between PD-1 and PD-L1 inhibitors. Among 2508 patients treated with PD-1 inhibitors, a pooled ILD event incidence of 0.05 (95% CI, 0.03–0.07) was observed [Figure 3A], whereas a pooled ILD event incidence of 0.02 (95% CI, 0.01–0.03) was observed among 2131 patients treated with PD-L1 inhibitors [Figure 3B].

Given the existing heterogeneity, the incidence of ILD events associated with PD-1 and PD-L1 inhibitors was calculated for two different subgroups (cancer stages and subtypes) using a random-effects model. Regarding PD-1 inhibitors, the non-TNBC group (comprising 222 patients) had a much higher pooled incidence (0.05; 95% CI, 0.03–0.07) than the TNBC group (0.05; 95% CI, 0.03–0.07), comprising 2286 patients. The incidence of ILD events was slightly lower in the early breast cancer stage group than in the metastatic breast cancer stage group (0.04 *vs.* 0.05). Regarding PD-L1 inhibitors, the incidence of ILD events did not differ significantly between the early and metastatic breast cancer stage subgroups (0.02 *vs.* 0.02). A similar result was observed for breast cancer subtypes between the non-TNBC and TNBC groups (0.02 *vs.* 0.02). Forest plots of the results are displayed in Figure 4.

In the mirror group analysis, the pooled risk of ILD events was higher in patients treated with PD-1 inhibitors than in those treated with PD-L1 inhibitors (RR = 2.34, 95% CI, 1.13–4.82, P = 0.02) [Figure 5A]. Furthermore, no significant difference was observed in grade 1–2

Table 1
Characteristics of the included studies that reported ILD events as AEs associated with PD-1/PD-L1 inhibitor treatment in patients with breast cancer.

Study	Year	ClinicalTrials.gov identifier	Cancer type	Study type	Study phase	PD-1/PD-L1 inhibitors	Comparator group	Number of patients who developed ILD events	Number of patients evaluated for safety	Antibody clone
KATE2[30]	2020	NCT02924883	HER2+ EBC	RCT	Phase II	Atezolizumab	Chemotherapy + Placebo	1	133	SP142
IMpassion131[31]	2021	NCT03125902	Metastatic TNBC	RCT	Phase III	Atezolizumab	Chemotherapy + Placebo	1	432	SP142
hIMpassion130[32]	2021	NCT02425891	Metastatic TNBC	RCT	Phase III	Atezolizumab	Chemotherapy + Placebo	18	460	SP142
IMpassion031[33]	2020	NCT03197935	Early TNBC	RCT	Phase III	Atezolizumab	Chemotherapy + Placebo	1	164	SP142
COLET[34]	2021	NCT02322814	Metastatic TNBC	RCT	Phase II	Atezolizumab	Chemotherapy + Placebo	3	62	SP142
IMpassion050[35]	2022	NCT03726879	HER2+ EBC	RCT	Phase III	Atezolizumab	Chemotherapy + Placebo	1	226	NR
GeparNuevo[36]	2019	NCT02685059	Early TNBC	RCT	Phase II	Durvalumab	Chemotherapy + Placebo	1	92	SP263
I-SPY2[37,38]	2020	NCT01042379	HR + HER2- EBC	RCT	Phase II	Durvalumab	Chemotherapy	4	73	NR
			HR + HER2- EBC			Pembrolizumab	Chemotherapy	3	69	
KEYNOTE-355[39]	2020	NCT02819518	Metastatic TNBC	RCT	Phase III	Pembrolizumab	Chemotherapy + Placebo	14	562	22C3
KEYNOTE-522[40]	2020	NCT03036488	Early TNBC	RCT	Phase III	Pembrolizumab	Chemotherapy + Placebo	17	783	22C3
KEYNOTE-119[41]	2021	NCT02555657	Metastatic TNBC	RCT	Phase III	Pembrolizumab	Chemotherapy	2	309	22C3
Tolaney et al., 2020[42]	2020	NCT03051659	HR + HER2- EBC	RCT	Phase II	Pembrolizumab	Eribulin	3	44	22C3
Liu et al., 2020[43]	2020	NCT03394287	Metastatic TNBC	RCT	Phase II	Camrelizumab	Camrelizumab	2	40	22C3
SAFIR02-Breast IMMUNO[44]	2021	NCT02299999	HER2- MBC	RCT	Phase II	Durvalumab	Chemotherapy	1	129	SP142
NeoTRIP[45]	2022	NCT02620280	Early TNBC	RCT	Phase III	Atezolizumab	Chemotherapy	0	138	SP142
Terranova-Barberio et al., 2020[46]	2020	NCT02395627	ER + MBC	RCT	Phase II	Pembrolizumab	NA	1	34	SP263
ALICE[47]	2022	NCT03164993	Metastatic TNBC	RCT	Phase II	Atezolizumab	Chemotherapy + Placebo	5	68	SP142
DORA	2022	NCT03167619	Metastatic TNBC	RCT	Phase II	Durvalumab	Chemotherapy	2	45	NR
CheckMate 7A8	2022	NCT04075604	ER + HER2- EBC	RCT	Phase II	Nivolumab	Different dose level	2	23	NR
Liu et al., 2022[48]	2022	NCT04303741	Metastatic TNBC	Single-arm trial	Phase II	Camrelizumab	NA	8	46	22C3
PANACEA[49]	2019	NCT02129556	HER2+ MBC	Single-arm trial	Phase Ib/II	Pembrolizumab	NA	7	52	22C3
ENHANCE-1[50]	2021	NCT02513472	Metastatic TNBC	Single-arm trial	Phase Ib/II	Pembrolizumab	NA	19	167	22C3
TOPACIO[51]	2019	NCT02657889	Metastatic TNBC	Single-arm trial	Phase II	Pembrolizumab	NA	1	55	NR
MEDIOLA[52]	2020	NCT02734004	Metastatic TNBC	Single-arm trial	Phase I/II	Durvalumab	NA	0	34	SP263
Foldi et al., 2021[53]	2021	NCT02489448	Early TNBC	Single-arm trial	Phase I/II	Durvalumab	NA	1	59	SP263
Neo-PATH[54]	2022	NCT03881878	HER2+ EBC	Single-arm trial	Phase II	Atezolizumab	NA	6	67	SP142
BerGenBio 2021	2021	NCT03184558	Metastatic TNBC	Single-arm trial	Phase II	Pembrolizumab	NA	1	29	NR
KEYNOTE-086[55,56]	2018	NCT02447003	Metastatic TNBC	Non-RCT	Phase II	Pembrolizumab	NA	7	170	22C3
						Pembrolizumab	NA	2	84	
Bristol-Myers 2021	2021	NCT03098550	Metastatic TNBC	Non-RCT	Phase I/II	Nivolumab	NA	1	41	NR

AEs: Adverse events; EBC: Early breast cancer; ER: Estrogen receptor; HER2: Human epidermal growth factor receptor 2; HR: Hormone receptor; ILD: Interstitial lung disease; MBC: Metastatic breast cancer; NA: Not applicable; NR: Not reported; PD-1: Programmed cell death 1; PD-L1: Programmed cell death ligand 1; RCT: Randomized controlled trial; TNBC: Triple-negative breast cancer.

Table 2
The mirror group design categorizing available studies into four groups based on cancer stages and subtypes.

Groups	Inhibitors	Intervention	Study name	Mean age, years (range)	Grade of ILD
Early TNBC group	PD-1 inhibitors	Pembrolizumab	KEYNOTE-522[40]	49 (22–80)	Reported
	PD-L1 inhibitors	Atezolizumab	IMpassion031[33]	51 (22–76)	Unknown
			NeoTRIP[45]	50 (25–79)	Unknown
		Durvalumab	GeparNuevo[36]	50 (23–76)	Reported
			Foldi et al., 2021[53]	NR	Reported
Metastatic TNBC group	PD-1 inhibitors	Pembrolizumab	KEYNOTE-355[39]	53 (44–63)	Reported
			KEYNOTE-119[41]	50 (43–59)	Reported
			ENHANCE-1[50]	56 (32–88)	Reported
			TOPACIO[51]	54(32–90)	Reported
			KEYNOTE-086[55,56]	53.5 (28–85)	Reported
			BerGenBio 2021	59 (32–81)	Reported
		Camrelizumab	Liu et al., 2020[43]	46 (29–64)	Reported
			Liu et al., 2022[48]	47 (30–65)	Reported
		Nivolumab	Bristol-Myers 2021	55 (NR)	Unknown
	PD-L1 inhibitors	Atezolizumab	IMpassion131[31]	54 (22–85)	Unknown
			IMpassion130[32]	55 (20–82)	Reported
			COLET[34]	52 (20–79)	Unknown
			ALICE[47]	59 (31–77)	Reported
		Durvalumab	MEDIOLA[52]	46 (37–52)	Unknown
			DORA	50 (NR)	Unknown
Early non-TNBC group	PD-1 inhibitors	Pembrolizumab	I-SPY2[38]	50 (27–71)	Reported
		Nivolumab	CheckMate 7A8	64 (NR)	Unknown
	PD-L1 inhibitors	Atezolizumab	IMpassion050[35]	50 (NR)	Unknown
			Neo-PATH[54]	52 (33–74)	Reported
		Durvalumab	I-SPY2[37]	46 (28–71)	Reported
Metastatic non-TNBC group	PD-1 inhibitors	Pembrolizumab	Tolaney et al., 2020[42]	58 (30–76)	Reported
			Terranova-Barberio et al., 2020[46]	59 (32–81)	Reported
			PANACEA[49]	53 (28–72)	Reported
	PD-L1 inhibitors	Atezolizumab	KATE2[30]	54 (48–60)	Reported
		Durvalumab	SAFIR02-Breast IMMUNO[44]	56 (27–79)	Unknown

ILD: Interstitial lung disease; NR: Not reported; PD-1: Programmed cell death 1; PD-L1: Programmed cell death ligand 1; TNBC: Triple-negative breast cancer.

(RR = 0.95, 95% CI, 0.62–1.47, $P = 0.82$) or grade 3–5 (RR = 1.54, 95% CI, 0.65–3.65, $P = 0.33$) ILD events between PD-1 and PD-L1 inhibitors [Figures 5B and C]. However, unlike the group with grade 1–2 ILD events, the group with grade 3–5 ILD events showed a potential trend in which PD-1 inhibitors might present a higher risk of ILD events than PD-L1 inhibitors in patients with breast cancer.

In the ILD incidence groups, meta-analyses indicated high heterogeneity across studies for both PD-1 ($I^2 = 80\%$; $P < 0.01$) and PD-L1 ($I^2 = 73\%$, $P < 0.01$) inhibitors, suggesting that the heterogeneity might be due to the different study designs, including both RCTs and non-RCTs [Figure 3]. Notably, the differences in cancer subtypes or stages among the included studies may partly explain the high heterogeneity within the groups [Table 1]. In the mirror group analysis, we divided the 29 studies into four groups according to comparable cancer subtypes and stages. Heterogeneity was still high in the pooled ILD event analysis ($I^2 = 58\%$; $P = 0.07$); however, the group with grade 1–2 ILD events showed low heterogeneity ($I^2 = 35\%$; $P = 0.20$), whereas the group with grade 3–5 ILD events did not show any heterogeneity ($I^2 = 0\%$; $P = 0.73$) [Figure 5].

Risk of bias in included studies

The Cochrane Collaboration tool was used to evaluate the RoB, showing that 11 studies had an overall low RoB and one had a high RoB [Supplementary Figure 1]. Regarding single-arm studies, the results of the RoB using the JBI checklist showed only good-quality trials (Liu et al., 2022,[48] Foldi et al., 2021,[53] and Neo-PATH[54]), and one trial had a high RoB (BerGenBio 2021) [Supplementary Figure 2]. Among the RCTs, nine were open-label[37,38,41–46] (including DORA and CheckMate 7A8), whereas 10 were double-blinded.[30–36,39,40,47] Sensitivity analyses using random-effects models for the risk of ILD events associated with PD-1 and PD-L1 inhibitors are shown in the Supplementary Material [Supplementary Figures 3 and 4]. There was no evidence of publication bias for ILD events in PD-1 (Egger's test, $P = 0.51$) or PD-L1 (Egger's test, $P = 0.13$) inhibitors groups. Publication bias plots for both groups did not show visual asymmetry; therefore, publication bias was unlikely [Supplementary Figures 5–8].

Discussion

The present study's results indicated that compared with chemotherapy, the use of PD-1/PD-L1 inhibitor increased the risk of ILD events among patients with breast cancer, and more importantly, PD-1 inhibitors were associated with a higher incidence of ILD events than PD-L1 inhibitors. To our knowledge, this study is one of the few meta-analyses comparing the incidence of ILD events between PD-1 and PD-L1 inhibitors in patients with breast cancer.

Immunotherapy with programmed cell death 1/programmed cell death ligand 1 inhibitor increases the risk of interstitial lung disease events in patients with breast cancer

Notably, several studies have reported that the combination of immunotherapy with chemotherapy for solid cancers increases the risk of AEs, including immune-related pneumonitis.[22,23,58] According to the present study's results, compared with chemotherapy alone, the addition of PD-1/PD-L1 inhibitor immunotherapy significantly increased the risk of ILD events in patients with breast cancer. Notably, many possible mechanisms may be involved in the development of immunotherapy-related ILD events; however, cytotoxic and immune mechanisms may be the main reasons for the development of multiple toxic effects, pulmonary inflammation, and fibrosis.[13] The interaction between PD-1 and PD-L1 allows tumor cells to escape attack from cytotoxic T cells, and PD-1/PD-L1 inhibitor that block this interaction can enhance the anti-tumor activity of T cells.[59] However, PD-1/PD-L1 inhibitor might cause an imbalance between immune effectors and T cells simultaneously, abnormal infiltration of lymphocytes, and an increased number of activated T cells, leading to lung injury.[11,60] Compared with standard chemotherapy, PD-1/PD-L1 inhibitor exert an immunological effect on pulmonary tissues and generate significant inflammatory responses.

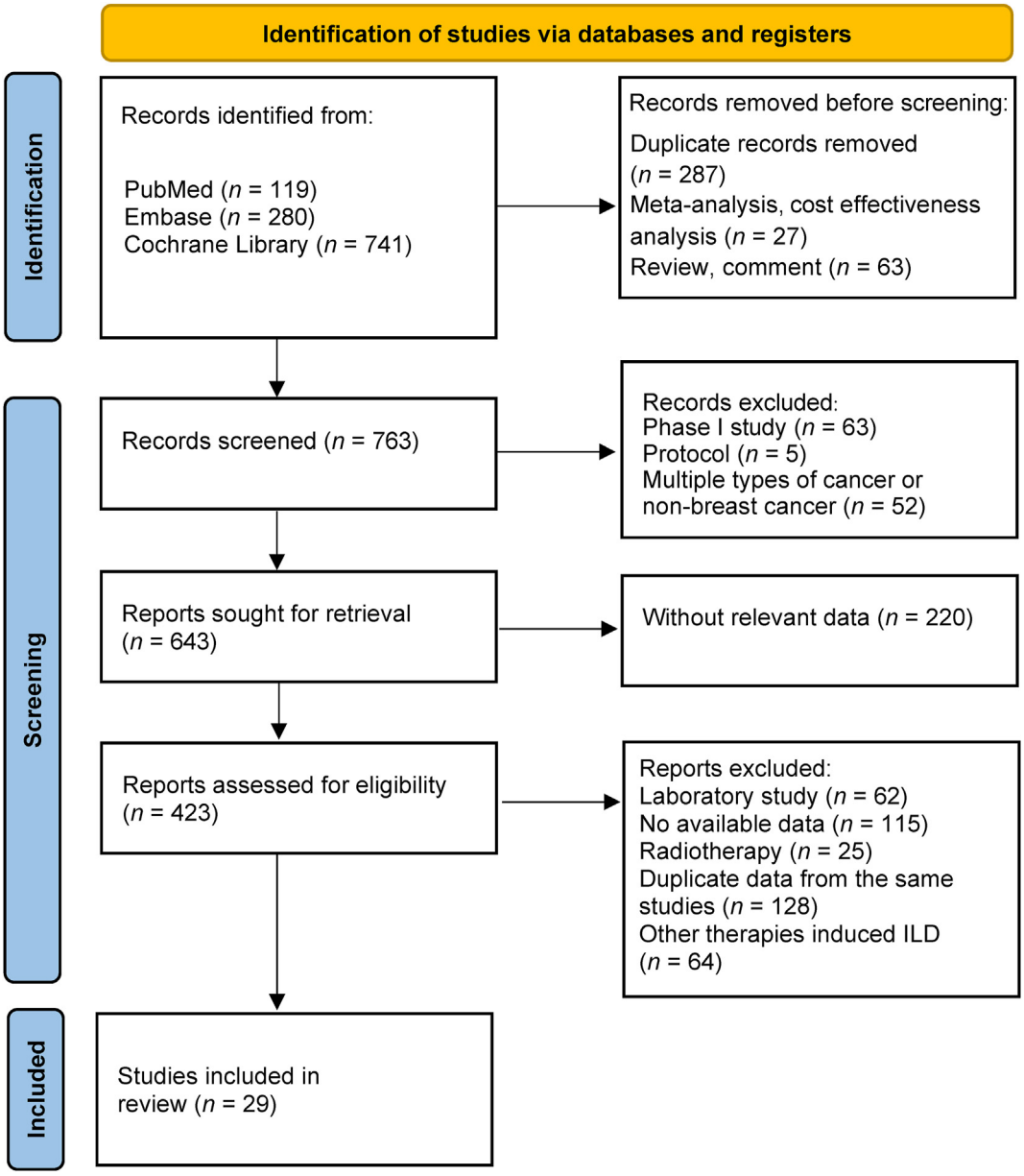

Figure 1. PRISMA flow chart of trials filtering and research selection. ILD: Interstitial lung disease; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

A study showed that PD-1 inhibitors yielded a higher risk of ILD events than PD-L1 inhibitors among patients with NSCLC.[23,24] In the present study, similar conclusions were drawn regarding breast cancer. The present study did not suggest a statistical difference in ILD risk according to grades. Notably, the results showed a potential tendency for PD-1 inhibitors to increase the risk of grade 3–5 ILD events among patients with breast cancer, which might be consistent with the results of a previous meta-analysis reporting that PD-1 inhibitors were significantly associated with a higher incidence of grade 3–4 ILD events among patients with NSCLC,[24] indicating that these two cancer types might share similar characteristics in terms of the effect of PD-1 inhibitors on ILD development. We speculate that our negative results may be because patients with NSCLC are more likely to develop drug-related toxic effects in their lungs and are more prone to advance into developing ILD events. Furthermore, patients with lung cancer are more likely to have a smoking history (tobacco can damage the underlying lung parenchyma) and lung conditions, such as pulmonary disease, which is less common in patients with breast cancer. Furthermore, some studies have suggested that the existing tumor burden in lung might be a significant reason.[24] Further studies with more relevant data on patients with breast cancer are warranted. A previous study reported that seven patients with NSCLC died of ILD events, and all of them were treated with PD-1 inhibitors.[24] Another study reported four pneumonitis-related deaths among patients with NSCLC.[61] In the present study, only two trials reported patient deaths due to ILD events,[39,40] and the patients were treated with PD-1 inhibitors (pembrolizumab). PD-1 inhibitors might also be associated with a higher risk of ILD event-related death than PD-L1 inhibitors, possibly due to timely diagnosis and therapy, which reduced the risk of death directly caused by ILD. Owing to a lack of relevant data, the present study could not compare the risk of death between PD-1 and PD-L1 inhibitors; therefore, further studies should compare the risk of death due to ILD events between both immune checkpoint inhibitors. In the subgroup analysis of the breast cancer subtype, we found that the non-TNBC group might have a higher incidence of ILD events than the TNBC group that received PD-1 inhibitor treatment; however, the potential mechanism remains unknown. In the present meta-analysis, the median age of

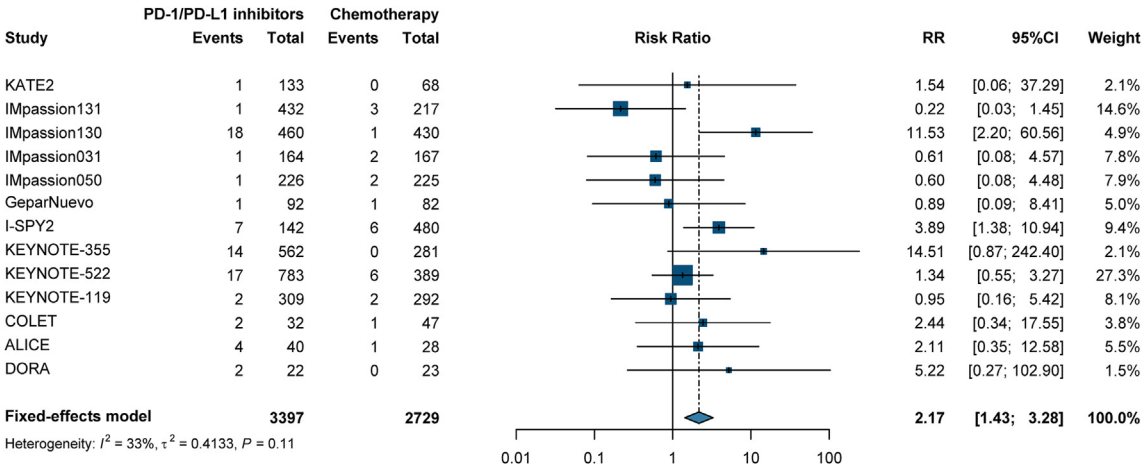

Figure 2. Forest plot of pooled analysis comparing the risk of ILD events between PD-1/PD-L1 inhibitor and chemotherapy. CI: Confidence interval; ILD: Interstitial lung disease; PD-1: Programmed cell death 1; PD-L1: Programmed cell death ligand 1; RR: Risk ratio.

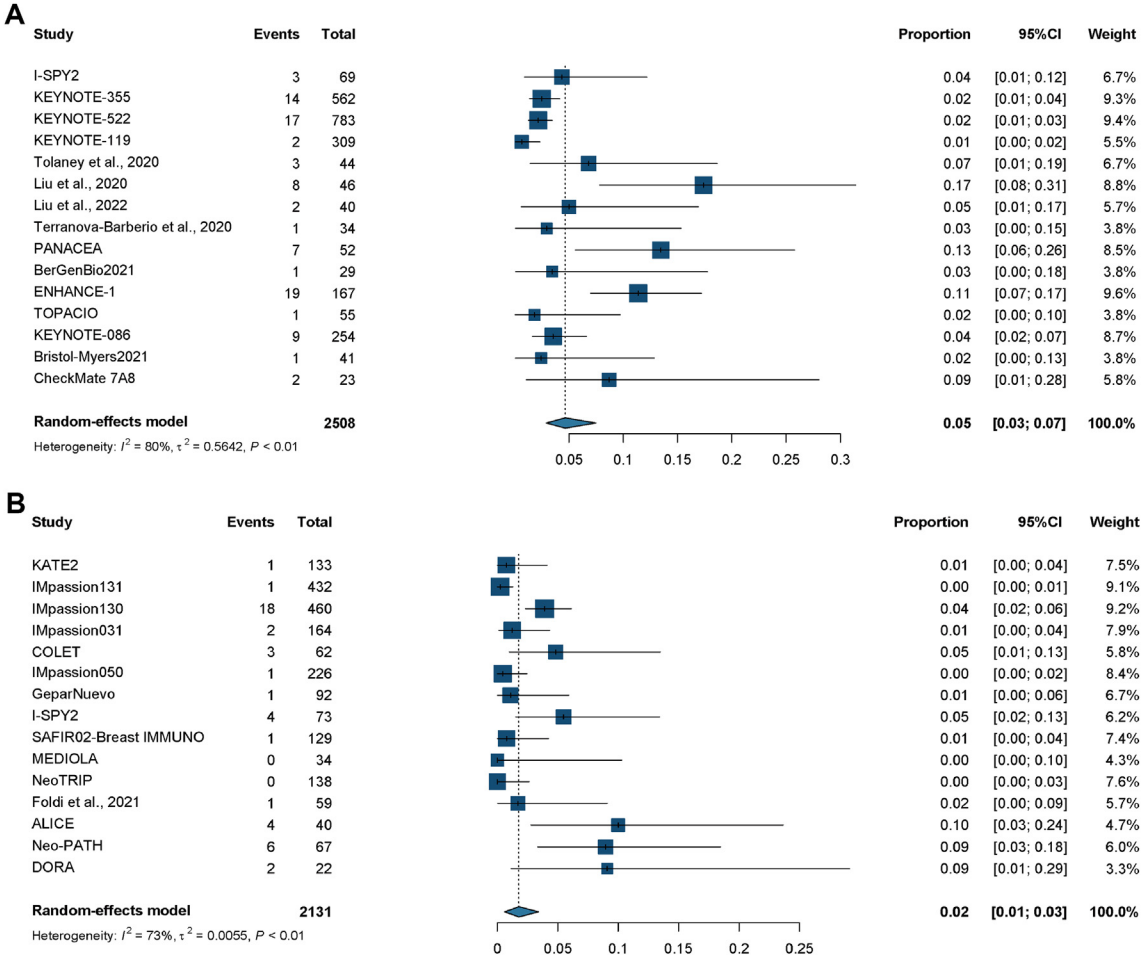

Figure 3. Forest plots of the pooled incidence of ILD events among patients with breast cancer treated with PD-1 and PD-L1 inhibitors. (A) The pooled ILD event incidence associated with PD-1 inhibitors. (B) The pooled ILD event incidence associated with PD-L1 inhibitors. CI: Confidence interval; ILD: Interstitial lung disease; PD-1: Programmed cell death 1; PD-L1: Programmed cell death ligand 1.

patients in the non-TNBC group seemed higher than that in the TNBC group, suggesting that age was an underlying risk factor for ILD events.

The reasons why PD-1 inhibitors result in a higher risk of ILD events than PD-L1 inhibitors remain uncertain; however, some hypotheses have been proposed. One of the most widely accepted hypotheses is that the likely mechanism is associated with PD-L2, which not only interacts with PD-1 but also with repulsive guidance molecule b (RGMb). PD-1 inhibitors can reduce the interaction between PD-1 and PD-L2, increasing the

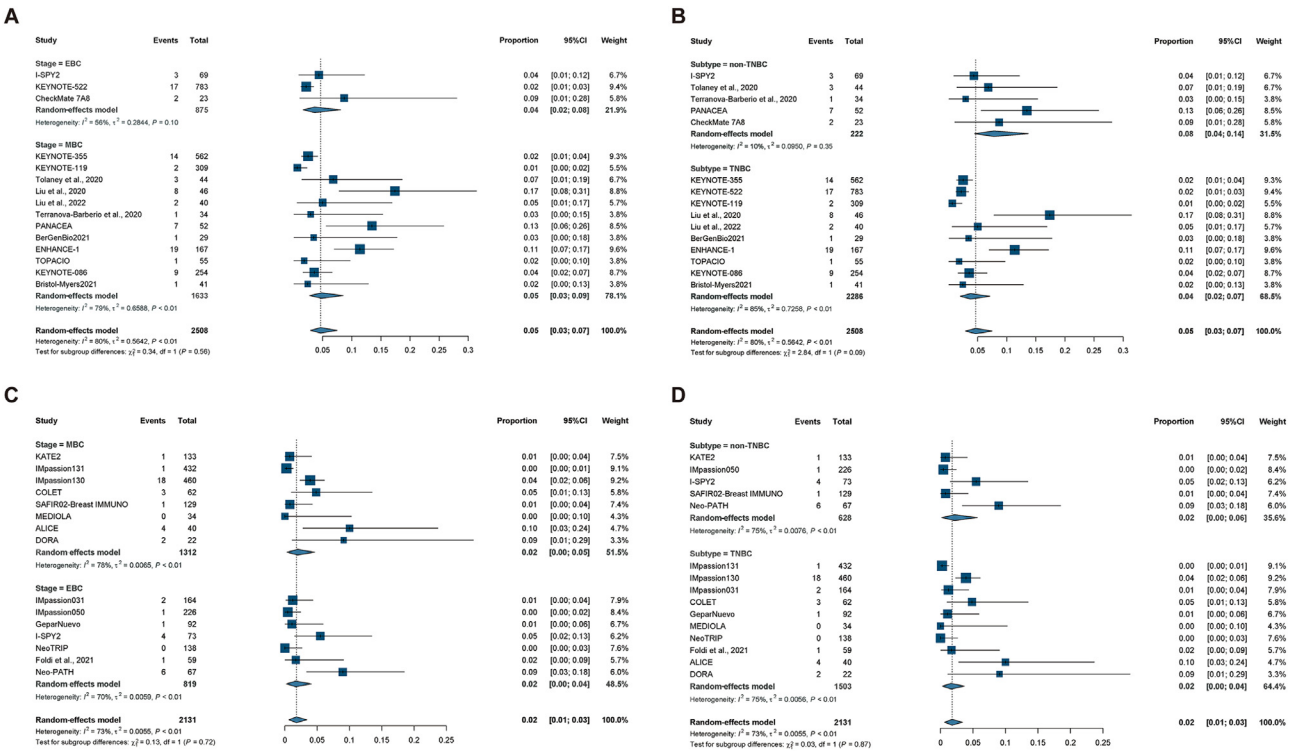

Figure 4. Forest plots of subgroup analyses estimating the pooled ILD event incidence associated with PD-1 and PD-L1 inhibitors. (A) Pooled ILD event incidence associated with PD-1 inhibitors in breast cancer stage subgroup. (B) Pooled ILD event incidence associated with PD-1 inhibitors in breast cancer subtype subgroup. (C) Pooled ILD event incidence associated with PD-L1 inhibitors in breast cancer stage subgroup. (D) Pooled ILD event incidence associated with PD-L1 inhibitors in breast cancer subtype subgroup. CI: Confidence interval; df: Degree of freedom; EBC: Early breast cancer; ILD: Interstitial lung disease; MBC: Metastatic breast cancer; PD-1: Programmed cell death 1; PD-L1: Programmed cell death ligand 1; TNBC: Triple-negative breast cancer.

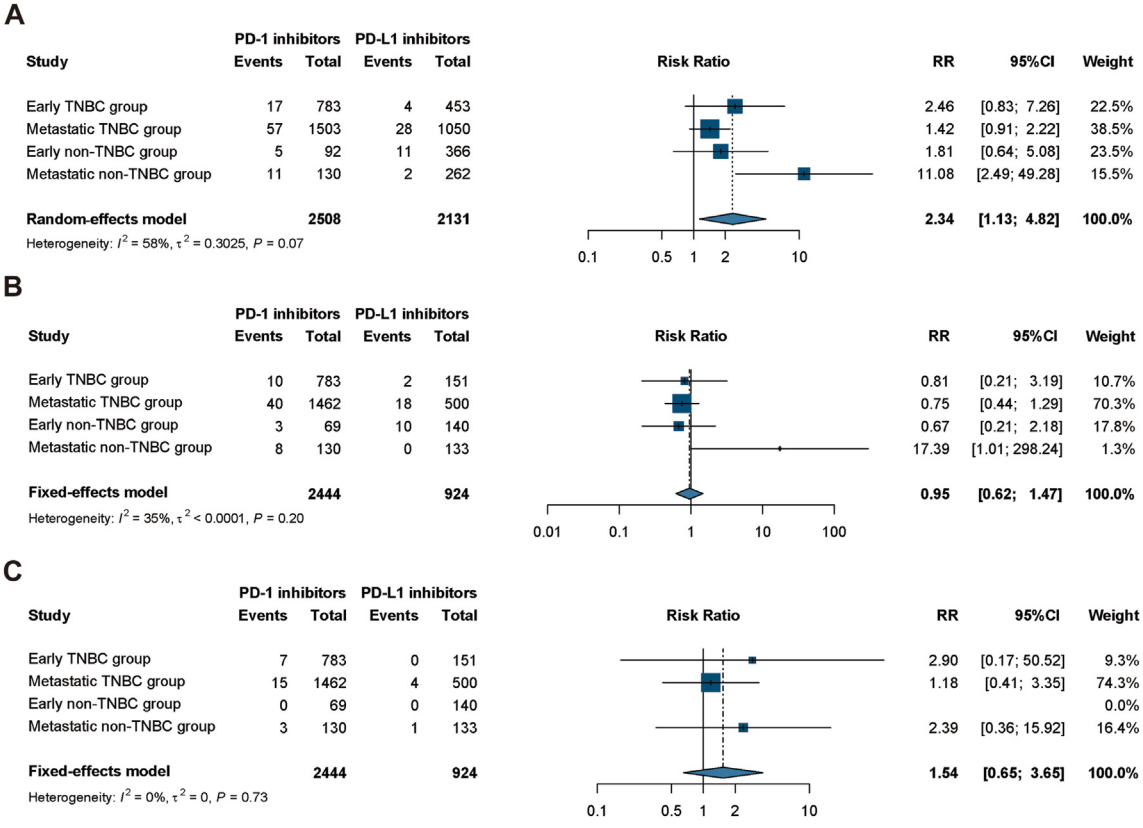

Figure 5. Forest plots of the mirror group analysis comparing the risk of ILD events between PD-1 and PD-L1 inhibitors in patients with breast cancer. (A) The pooled risk of overall ILD events between PD-1 and PD-L1 inhibitors. (B) The pooled risk of grade 1–2 ILD events between PD-1 and PD-L1 inhibitors. (C) The pooled risk of grade 3–5 ILD events between PD-1 and PD-L1 inhibitors. CI: Confidence interval; ILD: Interstitial lung disease; PD-1: Programmed cell death 1; PD-L1: Programmed cell death ligand 1; RR: Risk ratio; TNBC: Triple-negative breast cancer.

interaction between RGMb and PD-L2, resulting in T cell clonal expansion and mediation of ILD.[62,63] In contrast, PD-L1 inhibitors do not influence the interaction between PD-L2 and PD-1, which might explain the difference in ILD risk between PD-1 and PD-L1 inhibitors. In subgroup analysis, PD-1 inhibitors were associated with a higher incidence of ILD events in patients without TNBC. However, because the number of non-TNBC patients treated with PD-1 inhibitors was much smaller than the number of patients with TNBC, future studies should acknowledge these differences and perform updated analyses. Furthermore, patients with metastatic breast cancer treated with PD-1 inhibitors are prone to developing a higher incidence of ILD events, which may be attributed to patients with metastatic or advanced breast cancer being prone to having a worse general condition and even lung metastases. A slight difference was observed in the PD-L1 inhibitor subgroups, which might be because the drug-related lung toxicity of PD-L1 inhibitors is lower than that of PD-1 inhibitors.

Case description of interstitial lung disease in patients with triple-negative breast cancer

At our institution, three patients with TNBC developed ILD events after pembrolizumab treatment. According to the NCI CTCAE v5.0,[57] Patient 1 was diagnosed with grade 2 ILD, Patient 2 had grade 3 ILD, and Patient 3 had grade 4 ILD initially but eventually died of ILD (grade 5). The patients' characteristics are presented in Table 3.

For Patient 1 (a 40-year-old female), CT imaging showed a spectrum of findings typically observed in cases of interstitial pneumonitis [Figure 6A]. She was treated with intravenous methylprednisolone pulse therapy at an initial dosage of 500 mg/day for 5 days, followed by oral prednisone at a dosage of 40 mg/day, and the ILD resolved after 4 weeks. After treatment, her chest CT condition improved compared to the previous record [Figure 6B]. Regarding Patient 2, a 57-year-old female diagnosed with grade 3 ILD, CT findings revealed multiple sheet-like increased density shadows in both lungs; the right lung was more significant, and a lesion of the dorsal segment of the lower lobe was observed [Figure 6C]. After prednisone treatment at an initial dosage of 50 mg/day and gradual reduction of the dosage with scheduled follow-up, the patient showed a good response, and her CT images suggested that the lesions were absorbed more than before [Figure 6D], with ILD reverting to grade 2, and she continued steroid therapy under close follow-up. However, for Patient 3 (a 72-year-old female), the symptoms rapidly progressed 6 weeks after the diagnosis, and CT imaging showed multiple patchy cord-like increased density shadows in both lungs; the right lung had mainly solid density, whereas the left lung had mainly ground-glass density [Figure 6E]. Even under a high-intensity treatment regimen, methylprednisolone was administered at a dosage of 500 mg/day and combined with gamma globulin at a dosage of 20 g/day to suppress autoimmunity. Subsequently, with high levels of positive end-expiratory pressure mechanically ventilated for 2 min/day, CT re-examination revealed that the extent of the pneumonitis lesions had increased [Figure 6F], and the patient eventually died of ILD. Notably, Patient 1 was the only patient with lung metastases; however, her prognosis was the best among the three patients. The difference in the prognoses of the three patients might be due to the time of detection and immediate intervention; the earlier the detection and intervention, the better the patient prognosis. These cases demonstrate that ILD is a rare but potentially life-threatening irAE; however, early diagnosis, systematic treatment, timely re-examination, and close follow-up could result in a better prognosis.

Interstitial lung disease in patients with breast cancer: risk factors, diagnosis, and management

Drug-induced ILD is a large series of irAEs that can range from mild (grade 1) to severe (grade 3); some rare cases are life-threatening (grade 4) and even fatal (grade 5) according to the NCI CTCAE criteria.[57] The Pneumotox website (www.pneumotox.com) reports that >600 types of drugs can cause pulmonary injury and lead to ILD or parenchymal lung disease (data updated in July 2023). Owing to different types of drugs and doses, even when using the same drugs as in the cases in the present study, the risk of ILD and the clinical and radiological features differ from patient to patient. The diagnosis of ILD depends mainly on the exclusion of other lung diseases, and CT imaging and bronchoscopy are important approaches for clinicians.[64] The development of a standard criterion for ILD detection and prevention is challenging. However, previous studies have identified several factors that might help screen high-risk patients, including smoking, pre-existing lung disease, previous ILD history, cancer, age, male sex, Asian ethnicity, cancer treatment history (radiotherapy or chemotherapy), underlying pulmonary neoplasms, comorbidities, alcohol consumption, and diabetes.[64–66] In such cases, risk-prediction models and corresponding scales for ILD in patients with breast cancer are warranted for early detection and prevention.

According to our institution's experience and expert opinions about ILD,[66] the following recommendations might be referable. First, before immunotherapy decision-making, the physician should carefully evaluate the status of patients, including the baseline level of respiratory function, to choose the most suitable treatment (for example, a patient with breast cancer at a high risk of developing ILD should be treated with PD-L1 inhibitors instead of PD-1 inhibitors, according to the present study). Second, if patients show suspicious syndromes of ILD (shortness of breath, cough, fever, chest pain, and others), physical and vital sign examinations, CT imaging, blood tests, and respiratory function tests should be performed for further diagnosis. The most important part is identifying the grade of ILD (grades 1–5) and using suitable treatment and follow-up approaches. In most cases, drugs that induce ILD should be discontinued, and steroids should be administered to patients. Notably, specific treatments are determined by the grade of ILD severity. For example, patients with grade 3 ILD should be hospitalized and undergo oxygen therapy, whereas pulse therapy should be considered for patients with grade 4 ILD. In summary, the treatment of ILD mainly involves discontinuing suspicious drugs and using immunosuppressive therapy such as steroid therapy. Non-invasive or invasive mechanical ventilation is sometimes needed in severe cases, and the treatment approach should be guided and adjusted according to the grade of ILD severity.[66]

This study had several limitations. First, this was a literature-based meta-analysis, not based on individual patient data, and it is inevitably subject to publication bias. Second, owing to the lack of head-to-head studies, both RCTs and non-RCTs were included in our meta-analysis, and some studies were open-label, leading to the non-identical characteristics of these trials and the heterogeneity of our study. The heterogeneity in this study may have been due to the different methodologies used in the included studies; for instance, some studies were RCTs, whereas others were single-arm studies. Moreover, the baseline characteristics of all patients were not completely similar, especially the expression status of PD-L1 and breast cancer subtypes. Among all the studies included, the most commonly used PD-L1 inhibitor antibody clone types were 22C3 (31.0%) and SP142 (31.0%), which are also the most commonly used methods in immunohistochemistry for PD-L1 expression;[67] however, SP263 (17.2%) was also used in some studies [Table 1]. Different methods of PD-L1 status testing could have induced heterogeneity in this study and should be addressed in future studies. Furthermore, PD-1 inhibitors also yield a higher risk of ILD than PD-L1 inhibitors in patients with lung cancer, and patients with breast cancer who have pulmonary metastases might have a worse lung condition owing to the damage from lung cancer lesions and radiation injury of lung function according to chest radiotherapy.[68] In some cases, the limited focus of the lung would be removed by the surgeon.[69] In such cases in the present study, pulmonary metastases might be a confounder; however, relevant data for further analysis were limited; therefore, a more comprehensive study should be conducted in the future. Third, our research did not include unpublished studies that are still ongoing, and some studies, such as conference abstracts, were not available for full-text

Table 3
Main information on three patients with TNBC who developed ILD events after pembrolizumab treatment at our institution.

Patients	Gender	Age, years	Potential risk factors	Past medical history	Symptoms	Diagnostic approaches	ILD grade
Patient 1	Female	40	Lung metastases; radiotherapy history	TNBC; cT2N0M1 (Lung metastases)	Fever (38.5 °C); dyspnea; shortness of breath	Radiology imaging [Figure 3A]; PaO_2 92 mmHg	Grade 2
Patient 2	Female	57	Radiotherapy history	TNBC; cT2N1M0	Cough; dyspnea; shortness of breath; asthenia	Radiology imaging [Figure 3C]; PaO_2 64 mmHg;	Grade 3
Patient 3	Female	72	Radiotherapy history; COPD history; type 2 diabetes	TNBC; T2N2M0	Fever (38.4 °C); chest pain; ARDS	Radiology imaging [Figure 3E]; PaO_2 32 mmHg; $PaO_2/FIO_2 \leq 200$	Grades 4 to 5

ARDS: Acute respiratory distress syndrome; COPD: Chronic obstructive pulmonary disease; FIO_2: Fraction of inspiration O_2; ILD: Interstitial lung disease; PaO2: Partial pressure of oxygen in arterial blood; TNBC: Triple-negative breast cancer.

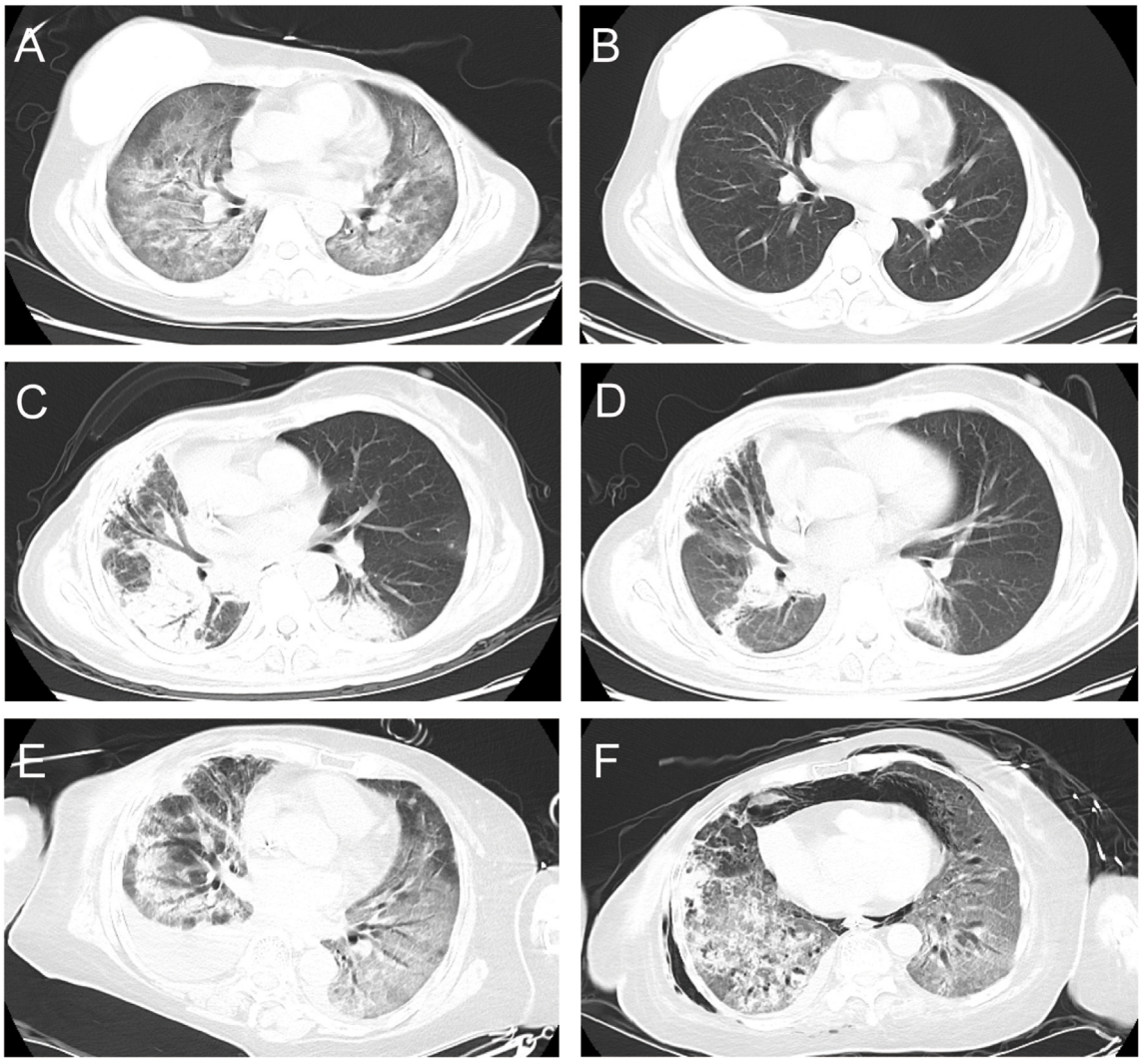

Figure 6. Images of chest CT performed on Patient 1 (A and B), Patient 2 (C and D), and Patient 3 (E and F) with ILD events associated with the use of PD-1 inhibitor. CT: Computed tomography; ILD: Interstitial lung disease; PD-1: Programmed cell death 1.

analysis, which may have led to publication bias in this meta-analysis. Therefore, updated analyses should be conducted in the future. Further related data should be collected, and further analysis must be performed. Future head-to-head studies are important for a more comprehensive comparison of the risk of ILD events between PD-1 and PD-L1 inhibitors.

Conclusion

This meta-analysis suggests that PD-1 inhibitors yield a higher risk of ILD events than PD-L1 inhibitors in patients with breast cancer; ILD is rare but may be serious or even life-threatening. Detection and management of ILD should be initiated immediately, and clinicians should pay more attention to the risk of ILD induced by PD-1 inhibitors.

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Author Contributions

Lijuan Guo, Conceptualization; Xiaoyi Lin, Conceptualization; Xin Lin, Conceptualization; Lijuan Guo, Methodology; Xiaoyi Lin, Software; Lijuan Guo, Validation; Xiaoyi Lin, Validation; Xin Lin, Validation; Lijuan Guo, Formal analysis; Yi Zhang, Resources; Jiali Lin, Resources; Xiangqing Chen, Resources; Yulei Wang, Data curation; Lijuan Guo, Writing – original draft Preparation; Guochun Zhang, Writing - review & editing; Yifang Zhang, Writing - review & editing; Miao Chen, Cases data; Miao Chen, Supervision; Guochun Zhang, Funding acquisition; Yifang Zhang, Funding acquisition.

Ethics statement

This study was performed in compliance with the *Declaration of Helsinki*. Informed consent was obtained from the patients included in the study.

Data availability statement

All data analyzed in this study are included in this article.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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A Graphical abstract was designed using resources from Flaticon.com.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cpt.2023.08.002.

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