INTRODUCTION

Review question / Objective: This meta-analysis and systematic review aimed to assess the difference in ILD risk between PD-1 and PD-L1 inhibitors in breast cancer patients.

Rationale: Interstitial lung disease (ILD) is one of the organ specific irAEs in PD-1/PD-L1 inhibitors in breast cancer patients.
L1 inhibitos treatment, which is rare and most of the ILD cases are low grade adverse events, but severe ILD cases are potentially fatal. Previous studies showed that the overall incidence of ILD using PD-1/PD-L1 inhibitors ranged from 2.7% to 5% in advanced cancer patients, and compared with routine chemotherapy, PD-1 inhibitors would increase the risk of ILD in cancer patients, and melanoma might have a lower incidence of ILD compared with non-small cell lung cancer (NSCLC) and renal cell carcinoma, but whether similar conclusions could be generalized to breast cancer patients especially those suffer from lung metastasis, still remains unknown.

**Condition being studied:** ILD is defined as a lung parenchyma disorder, and the pathogenesis, laboratory findings and clinical manifestations are various from different specific causes of the diseases. The diagnosis of drug-induced interstitial lung disease (DILD) mainly depends on a certain temporal association between causative drugs exposure and characteristics syndromes. Identifying ILD events related to PD-1 inhibitors/PD-L1 inhibitors is mainly depended on a radiographic assessment such as computed tomography (CT) with ground-glass opacities and reticular infiltrates.

**METHODS**

**Search strategy:** A systematic literature search of the electronic database PubMed, EMBASE, and Cochrane Library was conducted to identify the ILD events risk related to the treatment of PD-1 inhibitors and PD-L1 inhibitors in breast cancer, covering the period from the inception of the database until December 2022, using a predefined algorithm (Table s1 in supplementary material).

**Participant or population:** Breast cancer patients.

**Intervention:** PD-1 inhibitors.

**Comparator:** PD-L1 inhibitors.

**Study designs to be included:** Phase II or III randomized clinical trials (RCTs), phase I/II trials (included the part of phase II) were also eligible for this study.

**Eligibility criteria:** All included literature should be required to meet the following items: (1) phase II or III randomized clinical trials (RCTs) with published, presented, publicly available data. Owing to few clinical trials were available, phase I/II trials were also eligible for this study; (2) studied with participants who have breast cancer; (3) participants assigned to treatment with PD-1 inhibitors or PD-L1 inhibitors; (4) studies have sufficient information to measure the AEs including ILD events; (5) studies were published in English.

**Information sources:** Electronic database PubMed, EMBASE, and Cochrane Library.

**Main outcome(s):** ILD events.

**Additional outcome(s):** NA.

**Data management:** The methodological quality of all included trials was evaluated using the tool recommended by the Cochrane Collaboration handbook based on the original study or its updated data which was searched from the clinicaltrial.gov and the supplementary materials.

**Quality assessment / Risk of bias analysis:** The risk of bias was evaluated with elements from the Cochrane Collaboration's Risk of Bias (RoB) tool V.2 for determining the risk of bias of RCTs, ascertaining five different domains that including randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and the selection of the reported result. For single-arm trials, we used the Joanna Briggs Institute (JBI) checklists to assessed the risk of bias, by calculating the number of “yes” answers within 10 questions, scores up to 49.0% were categorized as high risk, scores between 50.0% and 70.0% were moderate, and above 70.0% were low risk of bias.
Strategy of data synthesis: We computed the risk ratio (RR) and 95% confidence intervals (CI) to estimate the ILD events risk of PD-1 inhibitors versus PD-L1 inhibitors for all the included studies. RR value1 indicates that the PD-1 inhibitors would increase the risk of developing ILD events, compared with PD-L1 inhibitors. All the analyses were done using the meta package (version 6.0-0) of the R program (version 4.1.3).

Subgroup analysis: The incidence of ILD events of PD-1 inhibitors and PD-L1 inhibitors was calculated for two different subgroups (cancer stage and cancer subtype) using a random effects model.

Sensitivity analysis: Sensitivity analysis was conducted by repeating the analyses with omitting one study each time.

Language restriction: English.

Country(ies) involved: China.

Keywords: Programmed Cell Death 1 Inhibitor; Programmed Cell Death Ligand 1 Inhibitor; Interstitial lung disease; Breast cancer; Immune-related adverse events.

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