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REVIEW

Cancer-related fatigue during treatment with neoadjuvant and/or adjuvant immune checkpoint inhibitors: a systematic review and meta-analysis

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Abstract

Purpose Immune checkpoint inhibitors (ICIs) have transformed cancer therapy, yet cancer-related fatigue (CRF) remains a frequent but poorly characterized adverse effect. We evaluated CRF incidence during ICI treatment in neoadjuvant and adjuvant settings.

Methods We conducted a systematic review of prospective cohort studies and phase 2 or higher trials investigating FDA-approved ICIs in adjuvant or neoadjuvant settings, reporting fatigue as an adverse event or via patient-reported outcomes (PROs). Searches conducted across four databases and ClinicalTrials.gov through September 2024 followed PRISMA guidelines using Covidence software. Studies not in English, lacking full text, or insufficient for meta-analysis were excluded. Data on fatigue incidence and quality of life were extracted. Risk of bias was assessed using the Cochrane tool, and certainty of evidence was graded using GRADEPro. Meta-analysis was performed on all included studies.

Results Forty-three studies met inclusion criteria, primarily involving melanoma, breast, lung, renal, and gastroesophageal cancers. Common ICIs included nivolumab, pembrolizumab, ipilimumab, and durvalumab. Fatigue was more frequent with ICIs versus placebo (risk ratio [RR] 1.21, 95% CI 1.08–1.35), and PROs indicated higher fatigue levels (standardized mean difference 0.12, 95% CI 0.01–0.23). No significant difference was observed between ICIs and chemotherapy (RR 0.81, 95% CI 0.36–1.82). Risk of bias was high due to allocation concealment and open-label designs.

Conclusions ICI monotherapy is associated with modestly increased CRF compared with placebo, as reported by clinicians and patients. These findings underscore the need for patient counseling and further research on the severity and trajectory of ICI-related CRF.

Keywords Immunotherapy · Immune checkpoint inhibitor · Cancer-related fatigue · Meta-analysis · Common terminology criteria for adverse events · Patient-reported outcomes · Quality of life

Introduction

Immune checkpoint inhibitors (ICIs) have transformed cancer care since the early 2000 s, improving survival across more than 40 tumor types. Their use now extends beyond metastatic disease to curative-intent treatment, particularly in neoadjuvant and adjuvant settings [1, 2]. However, the adverse effects of ICIs remain less characterized than those of more conventional therapies such as chemotherapy and radiation, particularly in perioperative and survivorship-focused settings.

Cancer-related fatigue (CRF) is among the most common and debilitating treatment-related toxicities, reported in 33–96% of patients [3–5]. Typically assessed through patient-reported outcome (PRO) measures or clinician-rated tools such as the Common Terminology Criteria for Adverse Events (CTCAE), it is among the most common and debilitating adverse effects of cancer therapy [3, 6, 7] and can persist for years after treatments have been completed, when the patient has no evidence of disease [8]. In the perioperative setting, CRF can impact treatment adherence, delay surgery, and affect recovery [9], making it particularly relevant for

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patients receiving curative-intent immunotherapy. Despite its clinical significance, CRF still remains poorly understood. The exact mechanism by which CRF occurs has yet to be elucidated, though prior studies have implicated cytokine dysregulation, anemia, sleep disturbance, and psychological issues [4, 10].

While individual studies have reported on fatigue associated with ICI therapy, data specific to neoadjuvant or adjuvant use are often inconsistent and underreported in the perioperative context [11–16]. Understanding CRF in this setting, however, is important because patients treated with curative intent have long-term expectations for quality-of-life and survivorship trajectories. To address this gap, we conducted a systematic review and meta-analysis comparing the incidence and severity of CRF among patients receiving ICIs versus control groups (placebo, observation, or non-ICI therapies) in neoadjuvant or adjuvant settings, using both CTCAEs and PROs.

Methods

We conducted this study in accordance with the Cochrane methodology [17] and reported it following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18]. The protocol was registered on the Open Science Framework platform (July 31, 2025; https://doi.org/10.17605/OSF.IO/CKHVS) [19].

Eligibility criteria

We included prospective cohort studies and phase two or higher clinical trials. Studies were eligible if they evaluated any of the 13 U.S. Food and Drug Administration (FDA)-approved ICIs in the neoadjuvant and/or adjuvant setting among adults (aged 18 years or older) with cancer. To be included, studies had to report fatigue data. We excluded studies that were not published in English or not available as full-text articles, studies that were ongoing without available results, studies presenting pooled data without trial-specific outcomes, and studies lacking sufficient data for inclusion in the meta-analysis.

Information sources

We searched electronic databases, including Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (via Ovid), Embase (via Ovid), and Web of Science, from inception through September 30, 2024. ClinicalTrials.gov was also searched to identify additional studies.

Search strategy

A senior librarian (KK) led the development and execution of the search strategy. The strategy included the following terms: "immunotherapy," "neoadjuvant," "adjuvant," "surgery," "radiotherapy," "clinical trial," and "neoplasm," as well as the names of all 13 FDA-approved ICIs: atezolizumab, avelumab, cemiplimab, dostarlimab, durvalumab, ipilimumab, nivolumab, pembrolizumab, relatlimab plus nivolumab, retifanlimab-dlwr, tislelizumab, toripalimab-tpzi, and tremelimumab. No language, date, or publication status restrictions were applied; however, the search strategy excluded gray literature including conference abstracts, animal studies, dissertations, notes, letters, and clinical guidelines. The complete search strategies are provided in Supplementary Table 1. All records were imported into Covidence [20], where duplicates were removed using the platform's automated de-duplication tool.

Selection process

Nine investigators (ASK, BP, CPE, DB, LP, MLO, MSYT, RSU, and YJC) participated in the screening process. Screening was conducted using Covidence in a two-stage process. First, titles and abstracts were independently reviewed by pairs of investigators. Studies deemed potentially relevant were retrieved as full text and independently assessed for eligibility. In cases of disagreement, the record was flagged for conflict resolution, and a third reviewer evaluated the study to make a final decision. Once consensus was reached during full-text screening, eligible studies proceeded to the data extraction stage.

Data collection process

During the data extraction, a standardized form was created in Covidence and piloted using four studies. Pairs of investigators (ASK, AT, BP, CPE, DB, HUH, LP, MK, MLO, MSYT, RSU, and YJC) independently extracted data to ensure accuracy and reduce bias. Covidence automatically flagged discrepancies, which were resolved through discussion and consensus between the reviewers. When no consensus was reached, a third investigator (LP, MLO, and RSU) reviewed the data and made the final decision.

Data items

Information was extracted on study characteristics, including author contact details, trial registration number, recruitment start and end dates, study location(s), study design, number of centers, sample size, follow-up assessments,

and eligibility criteria. Participant characteristics included cancer type and stage, mean or median age, number/percentage of male participants, number/percentage of white (i.e., Caucasian) participants, baseline fatigue status, and definitive treatment received. For each study, we defined the intervention and comparator groups and documented the number of participants and the number of treatment cycles, frequency, and duration of ICI therapy. For studies reporting fatigue as a continuous outcome, we recorded the fatigue assessment instrument used, its scoring range and units, and the mean and standard deviation for each group. For dichotomous fatigue outcomes, we collected the number of events and corresponding fatigue grades, as defined by the CTCAE. Interventions were grouped under the following categories: (1) ICI monotherapy versus no treatment/placebo, (2) ICI monotherapy versus chemotherapy, (3) ICI monotherapy versus non-ICI immunotherapy (specifically interferon alfa), (4) ICI with a PD-1 inhibitor versus ICI with a CTLA-4 inhibitor, (5) low-dose ICI versus high-dose ICI, (6) ICI with early introduction versus ICI with late introduction, (7) ICI plus ICI versus no treatment/placebo, (8) ICI plus ICI versus ICI monotherapy, (9) ICI plus ICI versus ICI plus targeted therapy, (10) ICI plus targeted therapy/non-ICI immunotherapy versus chemotherapy/radiotherapy, 11) ICI plus targeted therapy/non-ICI immunotherapy versus ICI monotherapy, (12) ICI plus chemotherapy versus no treatment/placebo, and (13) ICI plus chemotherapy/radiotherapy versus ICI monotherapy.

Study risk of bias assessment

We performed a risk of bias assessment using the Cochrane Risk of Bias Tool version 1 [21]. The tool assesses seven domains of potential bias: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias (i.e., contamination, early stopping for benefit, inappropriate influence from sponsors, and scientific misconduct/retractions). Each domain was rated as having a "low," "high," or "unclear" risk of bias, based on the information reported in the study. Pairs of reviewers independently assessed each domain for all included trials, with any disagreements resolved through discussion.

Effect measures

We analyzed both dichotomous and continuous fatigue outcomes. For dichotomous outcomes, we calculated risk ratios (RRs) with 95% confidence intervals (CIs). For fatigue data reported using the CTCAE criteria, we derived denominators from the total number of patients included in the safety analysis. Whenever possible, the denominators for treatment discontinuations (total and due to adverse events) were calculated based on the intention-to-treat population or modified intent-to-treat population, as reported in the source paper. Fatigue PROs were included only when provided as continuous variables; data presented exclusively in graphical form were excluded. For continuous outcomes, we used mean differences (MDs) between groups when studies reported fatigue using the same scale. When studies used different fatigue instruments or reported only overall health-related quality of life scores, we calculated standardized mean differences (SMDs) with 95% CIs. When only select fatigue-related items from the European Organization for Research and Treatment of Cancer quality-of-life instrument (EORTC QLQ-C30) [22] were reported, we extracted those items separately. Lower fatigue scores indicated less fatigue unless otherwise specified.

Synthesis methods

We grouped studies according to outcome type (continuous or dichotomous) and treatment setting (neoadjuvant or adjuvant) for synthesis. When at least two studies reported outcomes that could be compared, we performed meta-analyses using a random-effects model to account for between-study variability. Heterogeneity was assessed using the I^2 statistic and the chi-square test, with I^2 values greater than 50% indicating substantial heterogeneity. Where meta-analysis was not feasible owing to variability in outcome reporting, results were synthesized narratively. All analyses were conducted using Stata version 18 (StataCorp, College Station, TX). Subgroup analyses were performed based on cancer type and ICI class (programmed death protein 1 [PD-1]/programmed death ligand 1 [PD-L1] inhibitors, cytotoxic T lymphocyte–associated protein 4 [CTLA-4] inhibitors, and combination regimens) where data were available.

Reporting bias assessment

We assessed potential reporting bias using a funnel plot when at least ten studies were included in the meta-analysis of the proportion of patients reporting fatigue. The funnel plot was visually inspected for asymmetry, and Egger's test was conducted to statistically evaluate the presence of asymmetry.

Certainty assessment

We assessed the confidence in the body of evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, as outlined in the GRADEpro Handbook [23]. The evidence was evaluated across several domains: risk of bias, inconsistency of results, indirectness of evidence, imprecision, and

publication bias. Each outcome was categorized into one of four levels: high, moderate, low, or very low. High certainty indicates that further research is very unlikely to change our confidence in the estimate of effect, whereas very low denotes that any estimate of effect is highly uncertain and that future studies could substantially alter the conclusions. Evidence may be downgraded one or more levels depending on concerns identified in any of the GRADE domains.

Results

Study selection

A total of 1856 publications were initially identified, and 14 duplicates were removed. Of the remaining records, 1582 were excluded during title and abstract screening. A total of 260 full-text articles were retrieved, of which 217 were excluded for reasons including ineligible study design and no report of fatigue (Fig. 1). A list of ongoing studies and excluded studies that did not provide data suitable for meta-analysis ($n = 10$) is provided in Supplementary Table 2. Among these, one study [24] was excluded because fatigue was reported only for the intervention group, without an explicit statement of the number of participants with fatigue in the ICI group. One study, NCT03138512, had two publications that were considered two separate studies because the papers reported different parts of the same study [25, 26]. In total, 43 studies were included in the final analysis [16, 25–66]. For one study [67], we manually replaced the original with an updated version [68] because the original was retracted to allow reanalysis of survival outcomes, with the final results published in [65].

Study characteristics

Supplementary Table 3 shows the characteristics of the included studies. Out of 43 studies, 19 (44%) were phase 2 and 24 (56%) were phase 3. Forty-two (98%) were parallel group studies and one (2%) was a crossover study [47]. Two studies (5%) were nonrandom trials [51, 61]; all others were randomized controlled trials. Most of the studies ($n = 35$, 81%) were multicenter, and single-center studies were conducted in the USA [29, 30, 40, 44, 56], China [63, 65], and the Netherlands [51]. Sample sizes ranged from 23 to 1301. Thirty-five (81%) of the studies were sponsored by pharmaceutical companies.

Fatigue measurements

Fatigue was evaluated using both PROs and the CTCAE (Fig. 2). The CTCAE criteria were used specifically to report the incidence of fatigue in 42 of 43 studies (98%); the numbers and percentages of patients with fatigue and the specific grades (1–2 and/or 3 or higher) were reported. PROs were used in 10 (23%) of the studies to assess fatigue directly or through health-related quality of life with instruments that included a fatigue domain or item. One study did not specifically report using the CTCAE system to discuss fatigue grades [33]. Of the 10 studies that reported PROs, nine studies used the EORTC QLQ-C30 [31, 34–36, 49, 55, 59, 60, 69], and four studies provided EORTC QLQ-C30 fatigue subscore data [31, 35, 36, 60]. One reported PROs via the Functional Assessment of Cancer Therapy–General (FACT-G) questionnaire [48]. One study reported data using the Functional Assessment of Cancer Therapy Kidney Symptom Index—Disease-Related Symptoms (FKSI-DRS) as well as the CTCAE and EORTC QLQ-C30 [34].

Participant characteristics

Supplementary Table 4 shows the characteristics of the participants in the included studies. For all studies, the definitive (curative) treatment was surgery. Only two studies reported baseline fatigue levels [39, 65]. A large range of cancer types were represented; the cancer types most frequently reported were melanoma ($n = 9$, 21%), breast cancer ($n = 7$, 16%), non–small cell lung cancer ($n = 7$, 16%), renal cell carcinoma ($n = 4$, 9%), and gastroesophageal cancer ($n = 4$, 9%). Nine studies (21%) did not specifically report any male participants; out of these nine studies, seven investigated breast cancer and two investigated female reproductive cancers (endometrial, ovarian, fallopian tubes). Out of the breast cancer studies, all but one focused solely on triple-negative breast cancer. In that one breast cancer study [55], one participant (out of 1174) was male (less than 0.1% of participants). Regarding race, 23 studies (53%) did not report the percentage of white participants.

Intervention characteristics

Out of all 43 studies, 17 (40%) studied ICIs in the neoadjuvant, 19 (44%) in the adjuvant setting, and 7 (16%) in both settings. Fourteen studies (33%) studied pembrolizumab; 7 (16%) studied nivolumab monotherapy; 6 (14%) studied nivolumab with ipilimumab; 6 (14%) studied durvalumab; 5 (12%) studied atezolizumab; 3 (7%) studied toripalimab-tpzi (i.e., toripalimab); and 2 (5%) studied ipilimumab monotherapy. Intervention frequency and duration varied widely, ranging from a single dose of ICI up to a frequency of every 4 weeks for a total of 1 year. One study [44] involved administering only one course of neoadjuvant durvalumab (a window of opportunity study of mesothelioma). Supplementary Table 5 shows the interventions and

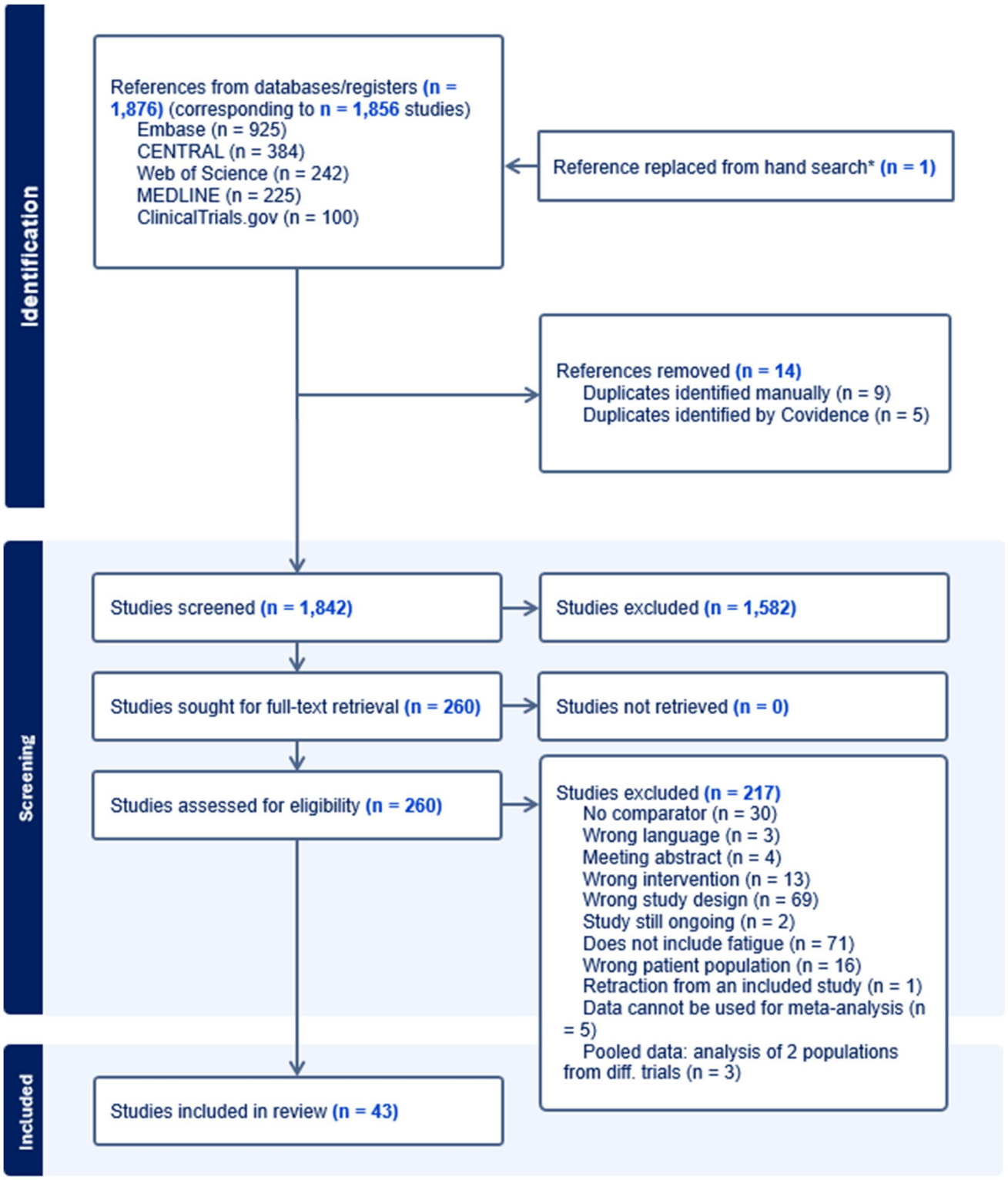
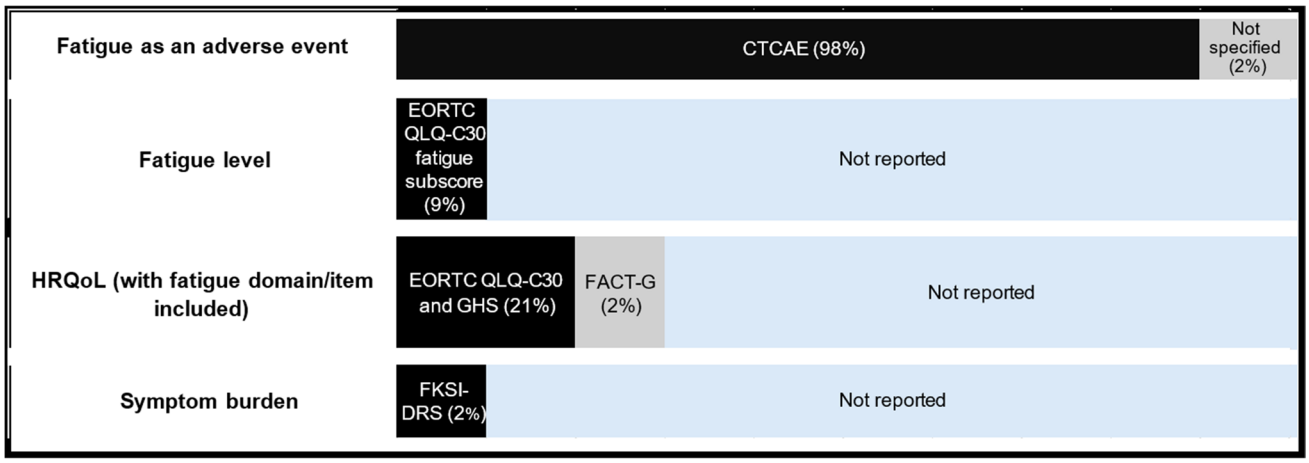


Fig. 1 Study disposition (PRISMA flow diagram)



CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organization for Research and Treatment of Cancer; FACT-G: Functional Assessment of Cancer Therapy–General; FKSI-DRS: Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms; GHS: Global Health Score; HRQoL: health-related quality of life; PROs: patient-reported outcomes; QLQ-C30: Quality of Life Questionnaire Core 30

Fig. 2 Survey instruments used for fatigue measurements

concomitant treatments evaluated in the included studies. For this analysis, "ICI monotherapy" refers to studies in which ICI was the only treatment that differed between trial arms. Some studies included identical concomitant treatment, such as chemotherapy, in both the intervention and control groups.

Risk of bias in studies

Supplementary Figure 1 shows the aggregated risk of bias assessment of all included studies. Three studies (7%) were assessed as having a high risk of selection bias, due either to non-randomized study design [51, 61] or because randomization procedure was stratified by disease stage [60]. Allocation concealment was unclear in 10 studies (23%), as the studies did not specifically discuss how allocation concealment was implemented. The risk of performance and outcome detection bias was judged to be high ($n=23$ [53%] and $n=21$ [49%], respectively)—often due to the open-label nature of those studies. The risk of attrition bias was judged to be high in six studies (14%), due to high attrition rates and incomplete outcome data. There was concern for high risk of bias regarding selective outcome reporting ($n=13$, 30%), particularly for studies that did not have complete data by article publication time (e.g., for overall median survival through to the estimated end of study duration). Finally, a high number of studies ($n=30$, 70%) were judged to have unclear risk of other sources of bias because they were funded by pharmaceutical companies that were involved in the formation and development of the study protocols and analysis themselves.

Incidence of fatigue

ICI monotherapy

Participants receiving an ICI were more likely to report fatigue (any grade) compared with participants receiving no treatment, placebo, or the same concomitant treatment as in the intervention group (RR 1.21; 95% CI 1.08–1.35; $I^2=78\%$; 28 studies; 17,098 participants) [16, 25, 27, 28, 31, 32, 34–38, 40–45, 47, 49, 50, 52–55, 57–59, 64]. When results were stratified by type of ICI, ipilimumab (RR 1.33; 95% CI 1.12–1.59; 1 study, $n=945$) [36], nivolumab (RR 1.53; 95% CI 1.01–2.30; $I^2=88\%$; 8 studies, $n=3824$) [25, 28, 31, 40, 42, 43, 53, 58], and pembrolizumab (RR 1.07; 95% CI 1.00–1.13; $I^2=0\%$; 9 studies, $n=7731$) [16, 34, 35, 47, 50, 54, 55, 57, 59] were associated with higher rates of fatigue compared with controls. This statistically significant difference was not observed with atezolizumab, durvalumab, or toripalimab (Fig. 3). Similar results were observed with sensitivity analyses including only studies comparing ICI monotherapy vs placebo (RR 1.17; 95% CI 1.08–1.27, $I^2=0\%$; 8 studies; 7172 participants) [16, 25, 31, 34–36, 43, 47] and ICI monotherapy vs no treatment (RR 2.62; 95% CI 1.25–5.51; $I^2=85\%$; 4 studies; 2542 participants) [28, 32, 37, 44]. The incidence of fatigue grade 1–2 was 5% higher for participants receiving ICIs compared with controls (RR 1.18; 95% CI 1.05–1.33; $I^2=80\%$; 28 studies, $n=17,098$). When removing studies including concomitant chemotherapy in both arms the results were not changed (ICI monotherapy vs placebo: RR 1.16; 95% CI 1.07–1.26; $I^2=0\%$; 8 studies; 7172 participants and ICI monotherapy vs no treatment: RR 2.65; 95% CI 1.26–5.57; $I^2=0\%$; 4 studies; 2542 participants). No statistically significant differences were observed for fatigue

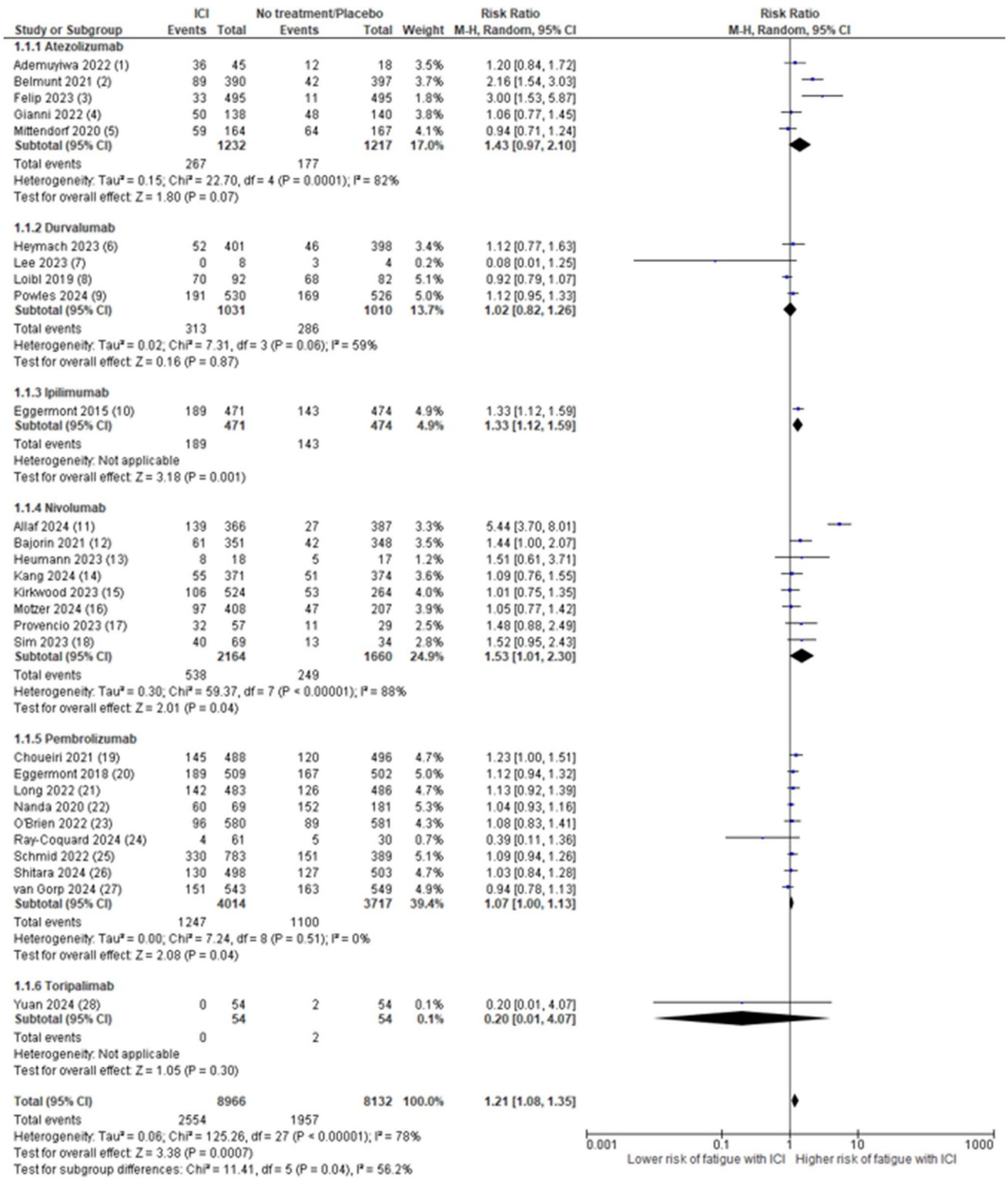


Fig. 3 Forest plot showing fatigue (any grade) results. *M-H* Mantel–Haenszel test, *ICI* immune checkpoint inhibitor

grade 3 or higher for the main analysis or sensitivity analyses (RR 1.29; 0.95–1.75; $I^2=0\%$; 28 studies, $n=17{,}098$) (ICI monotherapy vs placebo: RR 1.26; 95% CI 0.61–2.61; $I^2=0\%$; 8 studies; 7172 participants and ICI monotherapy vs no treatment: RR 2.70; 95% CI 0.68–10.68; $I^2=0\%$; 4 studies; 2542 participants).

There were no statistically significant differences in fatigue (any grade) between ICI monotherapy and chemotherapy (RR 0.81; 95% CI 0.36–1.82; $I^2=78\%$; 2 studies, $n=868$) [53, 69]. However, when ICI monotherapy (3 mg/kg or 10 mg/kg) was compared with non-ICI immunotherapy (interferon alfa-2b), lower fatigue rates (any grade) were observed with ICI monotherapy (RR 0.63; 95% CI 0.54–0.75 for 3 mg/kg ICI, $n=358$ participants; and RR 0.71; 95% CI 0.62–0.81 for 10 mg/kg ICI, $n=391$) [48].

Participants receiving ICI immunotherapy with a PD-1 inhibitor reported higher rates of fatigue (any grade and grade 1–2) compared with participants receiving a CTLA-4 inhibitor (any grade: RR 1.11; 95% CI 1.01–1.21, 2 studies, $n=2198$, $I^2=0\%$; and grade 1–2: RR 1.17; 95% CI 1.02–1.33, 2 studies, $n=2{,}198$, $I^2=37.4\%$) [39, 60]. No statistically significant differences in fatigue were found between participants receiving ipilimumab at a high dose (10 mg/kg) versus those receiving a low dose (3 mg/kg) [48],or between participants receiving ICI on the first day of treatment versus the third day [63].

ICI combined with another ICI

No statistically significant differences in fatigue were observed in the reported rates of fatigue (any grade, grade 1–2, grade 3 or higher) between patients assigned a combination of ICIs (e.g., durvalumab + tremelimumab, nivolumab + ipilimumab, and durvalumab + monalizumab) versus those in the placebo/no-treatment group [25, 26, 44], those receiving ICI monotherapy [25, 30, 33, 44, 51, 56], or those receiving ICI treatment with targeted therapy (2 estimates) [33].

ICI combined with targeted therapy, non-ICI immunotherapy, or chemotherapy and/or radiotherapy

No statistically significant differences were observed in the reported rates of fatigue (any grade, grades 1–2, grade 3 or higher) between patients assigned to the following comparisons: (1) ICI plus targeted therapy (e.g., pembrolizumab + dabrafenib) or ICI plus non-ICI immunotherapy (e.g., nivolumab + urelumab) versus chemotherapy/radiotherapy (3 estimates) [40, 65]; (2) ICI plus targeted therapy/non-ICI immunotherapy versus ICI monotherapy (5 estimates) [33, 40, 46]; (3) ICI plus chemotherapy (i.e., toripalimab + chemotherapy) versus no treatment [62]; or (4) ICI plus chemotherapy or radiotherapy versus ICI monotherapy [29, 53] versus ICI immunotherapy [25, 30, 33, 44, 51, 56].

Patient-reported outcomes

Fatigue levels

ICI monotherapy

ICI monotherapy was associated with higher levels of fatigue compared with placebo (SMD 0.12; 95% CI 0.01–0.23; 3 studies [31, 35, 36] $I^2=30\%$). Ipilimumab (SMD 0.22; 95% CI 0.01, 0.43; 1 study) [36] and pembrolizumab (SMD 0.15; 95% CI 0.01–0.29; 1 study) [35] each showed a small but significant increase in fatigue whereas nivolumab demonstrated no meaningful difference compared with placebo (Fig. 4). No statistically significant differences were observed between ICI therapy with a PD-1 inhibitor and ICI therapy with a CTLA-4 inhibitor [60].

Health-related quality of life

ICI monotherapy

Participants in the ICI groups showed no statistically significant difference in global health status/quality of life compared with participants assigned to controls (with or without chemotherapy as a concomitant treatment for both groups) (SMD −0.06; CI −0.14 to 0.02; $I^2=40\%$; 6 studies; 4203 participants), [31, 34–36, 55, 59], or placebo without concomitant treatment (SMD −0.08; 95% CI −0.21 to 0.05; $I^2=61\%$; 4 studies; 2415 participants) [31, 34–36], except for participants receiving ipilimumab who had lower quality-of-life levels compared with participants in the placebo/no treatment group (MD − 4.98; 95% CI − 9.16 to − 0.8) [36]. No differences were observed between participants receiving ICI monotherapy versus chemotherapy (2 estimates) [69]. Contrastingly, in 1 study comparing ICI monotherapy versus non-ICI immunotherapy (i.e., high-dose interferon alfa-2b), participants receiving ipilimumab (3 or 10 mg/kg) had higher quality-of-life scores at 12 weeks compared with the control group (3 mg/kg: MD 12.80; 95% CI 8.84–16.76; and 10 mg/kg: MD 10.20; 95% CI 6.09–14.31) [48]. No statistically significant differences were observed between ICI therapy with a PD-1 inhibitor and ICI therapy with a CTLA-4 inhibitor [60] or when comparing ICI at a high dose versus a low dose (ipilimumab at 10 mg/kg versus 3 mg/kg) [48].

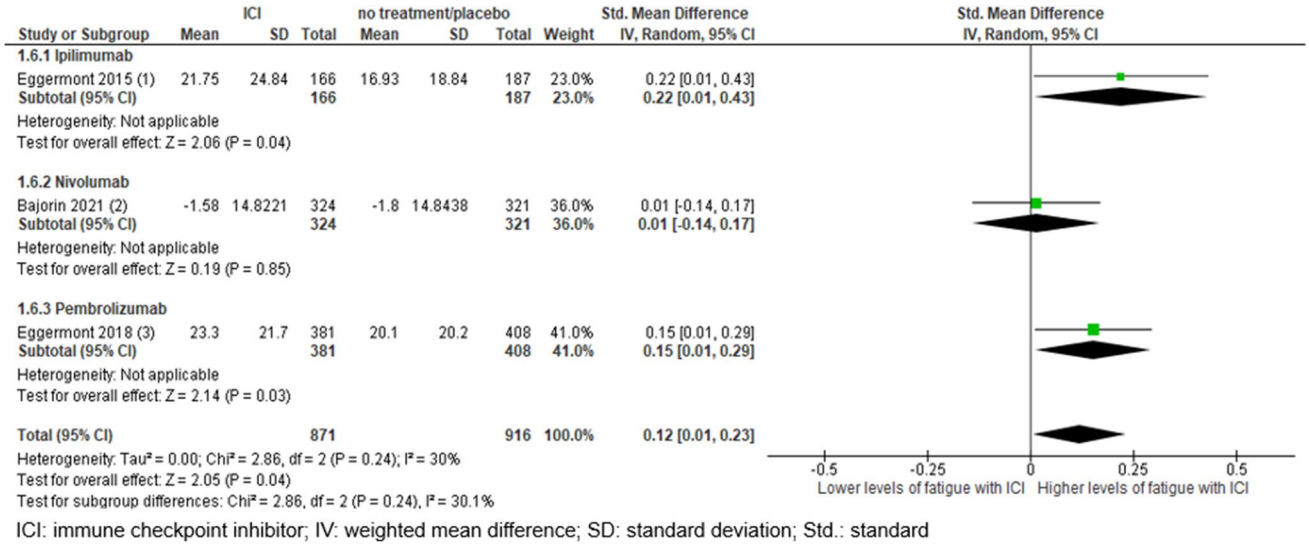


Fig. 4 Forest plot showing fatigue levels

Total treatment discontinuations

ICI monotherapy

When ICI monotherapy versus placebo or no treatment was pooled, the overall effect indicated a significantly higher risk of discontinuation compared with controls (RR 1.22; 95% CI 1.08–1.39, 26 studies, 16,423 participants, $I^2 = 89\%$) [16, 25, 27, 28, 31, 32, 34–38, 40, 42–45, 47, 49, 50, 52, 54, 55, 57–59, 64]. Similar results were observed with sensitivity analyses including only studies comparing ICI monotherapy vs placebo (RR 5.78; 95% CI 3.93–8.51, $I^2 = 76\%$; 8 studies; 7214 participants) [16, 25, 31, 34–36, 43, 47] but not when analyzing ICI monotherapy vs no treatment (RR 2.10; 95% CI 0.85–5.23; $I^2 = 98\%$; 4 studies; 2646 participants) [28, 32, 37, 44]. Nivolumab was associated with a higher risk of discontinuation (RR 1.47; 95% CI 1.02–2.35, 7 studies, 3830 participants, $I^2 = 96\%$) [25, 28, 31, 40, 42, 43, 58], as was pembrolizumab, which also showed a statistically significant increase in discontinuation risk (RR 1.31; 95% CI 1.13–1.53, 9 studies, 7797 participants, $I^2 = 79\%$) [16, 34, 35, 47, 50, 54, 55, 57, 59]. In contrast, durvalumab demonstrated a significantly lower risk of treatment discontinuation compared with controls (RR 0.80; 95% CI 0.68–0.93, 3 studies, 1243 participants, $I^2 = 0\%$) [44, 45, 52]. Atezolizumab and toripalimab did not demonstrate statistically significant differences between treatment arms [27, 32, 37, 38, 49, 64]. Similarly, no statistically significant differences were found when pembrolizumab was compared with chemotherapy [69], ipilimumab (3 or 10 mg/kg) was compared with a high dose of interferon alfa-2b, high-dose ipilimumab (10 mg/kg) was compared with a low dose (3 mg/kg) [48], or ICI introduction on the first day of treatment was compared with introduction on the third day (late introduction) [63].

PD-1 monotherapy was associated with a 45% reduction in the risk of discontinuation compared with CTLA-4 monotherapy (RR 0.55; 95% CI 0.51–0.59, 2 studies, 2,198 participants, $I^2 = 88\%$) [39, 60]. Nivolumab and pembrolizumab demonstrated a significantly reduced discontinuation risk relative to ipilimumab (RR 0.54; 95% CI 0.47–0.61, and RR 0.56; 95% CI 0.51–0.62, respectively) [39, 60].

ICI combined with another ICI

No statistically significant differences in treatment discontinuations were found when the ICI plus ICI group was compared with the placebo/no-treatment group [25, 26, 44]. However, ICI plus ICI (combination therapy) was associated with a significantly higher risk of total treatment discontinuation compared with ICI monotherapy (RR 1.98; 95% CI 1.58–2.50, 5 studies, 735 participants, $I^2 = 0\%$) [13, 25, 30, 44, 56]. In the nivolumab plus ipilimumab subgroup, treatment discontinuation was significantly more frequent than with nivolumab alone (RR 1.98; 95% CI 1.57–2.50, 3 studies, 669 participants, $I^2 = 0\%$) [25, 30, 56]. When ICI plus ICI was compared with targeted therapy, no statistically significant differences were observed [33].

ICI combined with targeted therapy, non-ICI immunotherapy, or chemotherapy and/or radiotherapy

No statistically significant differences in total discontinuation rates were observed between ICIs combined with targeted therapy and chemo/radiotherapy (2 studies, 3 estimates) [40, 65] or versus ICI monotherapy (1 study) [40].

However, participants receiving pembrolizumab + dabrafenib + trametinib concurrently (instead of sequentially) were less likely to discontinue treatment compared to participants receiving pembrolizumab alone (RR 0.45; 95% CI 0.20, 0.70; 1 study; 40 participants) [46]. No differences were observed between participants receiving toripalimab plus chemotherapy plus radiotherapy versus chemotherapy plus radiotherapy [62] or those receiving an ICI plus chemotherapy versus the ICI monotherapy group [29, 61].

Treatment discontinuations due to adverse events

ICI monotherapy

Participants in the ICI monotherapy group were more likely to discontinue treatment due to adverse events compared with the placebo/no-treatment group (RR 4.84; 95% CI 3.34–6.99, 21 studies, 14,546 participants, $I^2 = 84\%$) [16, 25, 28, 31, 32, 34–37, 40, 42–44, 47, 49, 54, 55, 57–59, 64]. When removing studies including concomitant chemotherapy in both arms the results were not changed (ICI monotherapy vs placebo: RR 6.01; 95% CI 3.78–9.54; $I^2 = 79\%$; 7 studies; 6053 participants) [25, 31, 34–36, 43, 47]. Atezolizumab showed a markedly elevated discontinuation risk (RR 12.55; 95% CI 6.92–22.78, 3 studies, 2132 participants, $I^2 = 0\%$) [32, 37, 49], as did ipilimumab (RR 12.28; 95% CI 7.92–19.02, 1 study, 951 participants) [36], nivolumab (RR 4.50; 95% CI 2.16–9.36, 7 studies, 3830 participants, $I^2 = 80\%$) [25, 28, 31, 40, 42, 43, 58] and pembrolizumab (RR 3.90; 95% CI 2.55–5.88, 8 studies, 7512, $I^2 = 81\%$) [16, 34, 35, 47, 54, 55, 57, 59] compared with controls (Supplementary Figure 2). This difference was also observed when ipilimumab at 3 mg/kg (RR 2.08; 95% CI 1.69–2.57, 1 study, 1159 participants) and 10 mg/kg (RR 3.22; 95% CI 2.66–3.91, 1 study, 1147 participants) were compared with high-dose interferon alfa-2b [48].

PD-1 monotherapy was associated with a 72% lower risk of treatment discontinuation due to adverse events compared with CTLA-4 monotherapy (RR 0.28; 95% CI 0.17–0.46, 2 studies, 2198 participants, $I^2 = 88\%$) [39, 60]. Nivolumab and pembrolizumab showed a markedly reduced risk of discontinuation relative to ipilimumab (RR 0.22; 95% CI 0.16–0.29, and RR 0.36, 95% CI 0.30–0.43, respectively) [39, 60]. Similarly, a high dose of ipilimumab (10 mg/kg) was associated with a 1.55 times higher risk of discontinuation due to adverse events compared with a low dose (3 mg/kg) (95% CI 1.34–1.79) [48]. When toripalimab introduction on the first day of treatment was compared with introduction on the 3rd day (late introduction), no statistically significant differences were found [63].

ICI combined with another ICI

No statistically significant differences were found when the ICI plus ICI group was compared with the placebo/no-treatment group. ICI plus ICI therapy was associated with a significantly higher risk of treatment discontinuation due to adverse events compared with ICI monotherapy (RR 2.44; 95% CI 1.80–3.30, 5 studies, 735 participants, $I^2 = 0\%$) [25, 30, 33, 44, 56]. The nivolumab plus ipilimumab combination showed an apparent increase in discontinuation risk relative to nivolumab alone (RR 2.43; 95% CI 1.79–3.29, 3 studies, 669 participants, $I^2 = 0\%$) [25, 30, 56]. When ICI plus ICI was compared with targeted therapy, no statistically significant differences were observed [33].

ICI combined with targeted therapy, non-ICI immunotherapy, or chemotherapy and/or radiotherapy

No statistically significant differences in discontinuation rates due to adverse events were observed in comparisons of ICI therapy combined with targeted therapy versus chemo-radiotherapy (2 studies, 3 estimates) [40, 65] or versus ICI monotherapy (1 study) [40].

Reporting biases

Supplementary Figure 3 shows the funnel plot for the primary outcome, fatigue (any level), for comparing ICI monotherapy with no treatment/placebo. Most estimates were clustered near the pooled relative risk. Although the estimates for a few studies were slightly displaced, particularly some durvalumab and toripalimab comparisons at lower precision, there was no clear visual evidence of marked asymmetry. This symmetry was confirmed with Egger's test, which showed no evidence of small-study effects (intercept 0.95, standard error 0.80, $p = 0.24$).

Certainty of evidence

Table 1 shows a summary of findings and certainty of the evidence for studies whose primary comparison was ICI monotherapy versus placebo/no treatment. The certainty of the evidence ranged between high and low. The certainty of evidence for PROs was downgraded because more than half of the studies were judged to be at high risk of bias for blinding of participants and/or outcome assessors, which may influence fatigue reporting. We also downgraded evidence with substantial inconsistency that could not be fully explained by clinical or methodological differences.

Table 1 Certainty of evidence for the primary comparison of ICI monotherapy versus no treatment/placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (Studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no treatment/placebo	Risk with ICI monotherapy				
Fatigue (any grade) assessed with: CTCAE	241 per 1000	291 per 1000 (260 to 325)	RR 1.21 (1.08 to 1.35)	17,098 (28 RCTs)	⨁⨁◯◯ Low[a,b]	ICI monotherapy may result in a slight increase in fatigue (any grade)
Fatigue (grade 1–2) assessed with: CTCAE	233 per 1000	275 per 1000 (245 to 310)	RR 1.18 (1.05 to 1.33)	17,098 (28 RCTs)	⨁⨁◯◯ Low[a,b]	ICI monotherapy may result in a slight increase in fatigue (grade 1–2)
Fatigue (grade 3 or higher) assessed with: CTCAE	9 per 1000	11 per 1000 (8 to 16)	RR 1.29 (0.95 to 1.75)	17,078 (28 RCTs)	⨁⨁◯◯ Low[a,c]	ICI monotherapy may result in little to no difference in fatigue (grade 3 or higher)
Treatment discontinuation (total)	336 per 1000	409 per 1000 (362 to 466)	RR 1.22 (1.08 to 1.39)	16,423 (26 RCTs)	⨁⨁⨁◯ Moderate[b]	ICI monotherapy probably results in a slight increase in treatment discontinuation (total)
Treatment discontinuation (due to AEs)	39 per 1000	191 per 1000 (132 to 276)	RR 4.84 (3.34 to 6.99)	14,546 (21 RCTs)	⨁⨁⨁◯ Moderate[b]	ICI monotherapy probably results in a large increase in treatment discontinuation (due to AEs)
Fatigue level assessed with: EORTC QLQ-C30—fatigue subscore Scale from: 0 to 100	-	SMD 0.12 higher (0.01 higher to 0.23 higher)	-	1787 (3 RCTs)	⨁⨁⨁⨁ High	ICI monotherapy results in an increase in fatigue level
HRQoL	-	SMD 0.06 lower (0.14 lower to 0.02 higher)	-	4203 (6 RCTs)	⨁⨁⨁◯ Moderate[d]	ICI monotherapy probably results in little to no difference in HRQoL
Symptom burden—pembrolizumab assessed with: FKSI-DRS Scale from: 0 to 36	The mean symptom burden—pembrolizumab was 32.51 points	MD 0.66 points lower (1.35 lower to 0.03 higher)	-	628 (1 RCT)	⨁⨁⨁◯ Moderate[d]	ICI monotherapy probably does not reduce symptom burden

GRADE Working Group grades of evidence—High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

AE adverse event, *CTCAE* common terminology criteria for adverse events, *EORTC QLQ-C30* European organization for research and treatment of cancer quality of life questionnaire core 30, *FKSI-DRS* functional assessment of cancer therapy kidney symptom index–disease-related symptoms, *GRADE* grading of recommendations assessment, development and evaluation, *HRQoL* health-related quality of life, *MD* mean difference, *RR* risk ratio, *SMD* standardized mean difference

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

[a]Half or more of the studies were judged at high risk of bias for blinding of participants and/or outcome assessors, which may influence reporting of fatigue

[b]$I^2 \geq 50\%$ with clear variability in the size of effect

[c]Confidence intervals around the pooled effect include both important harm and no effect. Optimal information size was not met

[d]Confidence interval includes both a small worsening and a small improvement and crosses the threshold for no effect, leaving uncertainty about the true direction of effect

Discussion

Our systematic review found that ICI monotherapy was associated with increased fatigue compared to placebo or no treatment, as measured by both CTCAEs and PROs. Fatigue rates were similar between ICI monotherapy and chemotherapy, though evidence for ICI combination therapy remains limited and inconclusive. Nivolumab and pembrolizumab monotherapy were linked to higher overall treatment discontinuation risk compared to controls, while durvalumab showed lower risk. Discontinuation due to adverse events was more frequent with ICIs than placebo. To our knowledge, this is the first comprehensive systematic review and meta-analysis to quantify ICI-related fatigue in curative-intent treatment settings, including neoadjuvant and adjuvant use. By incorporating PROs and adhering to Cochrane methodology and PRISMA reporting guidelines, this review provides a rigorous assessment of fatigue in this understudied context. This distinction is clinically important because baseline functional status, perioperative recovery, and expectations for returning to normal function differ substantially from those in metastatic populations. By synthesizing both CTCAE-graded adverse event data and PRO measures, our study captures complementary perspectives on CRF in ICI-treated patients, including clinician-documented incidence and patient-experienced symptom burden.

A previous meta-analysis of seven ICIs found fatigue to be more common with ICI monotherapy versus placebo, consistent with both our CTCAE and PROs findings [70]. In that meta-analysis, fatigue was less likely to occur in patients receiving ICI therapy compared with chemotherapy alone. In contrast, our study found no significant difference in fatigue between ICI monotherapy and chemotherapy, though this comparison was limited by high heterogeneity [53, 69]. Higher fatigue rates with ipilimumab, nivolumab, and pembrolizumab may reflect their earlier FDA approval and greater representation among the 43 included studies. Combination ICI therapy showed slightly higher discontinuation risk than ICI monotherapy, aligning with expectations of increased toxicity [71, 72]. Interestingly, one study found lower discontinuation with pembrolizumab plus dabrafenib and trametinib compared to pembrolizumab alone [46]. All toripalimab studies were conducted in China, limiting global generalizability [62–64]. Increased discontinuation in ICI groups versus placebo was noted, likely due to multiple adverse events rather than fatigue alone.

Regarding PROs, one study comparing ICI monotherapy with high-dose interferon alfa-2b reported higher quality-of-life scores at 12 weeks for ipilimumab recipients. However, the FACT-G instrument used assessed multiple domains beyond fatigue. Thus, these results are likely to reflect broader well-being rather than reduced fatigue alone. Of note, interferon is now largely being replaced by newer treatments such as ICIs or targeted therapies [73]. Anti-CTLA-4 and ipilimumab monotherapy indications are currently scarce and have been replaced by dual-ICI or anti-PD1 monotherapy or other combination strategies [74–76].

In evaluating the certainty of evidence, many studies were judged to have a high risk of bias, largely due to the absence of blinding for both patients and clinicians. Consequently, the certainty of evidence was downgraded. Moreover, substantial heterogeneity across studies further complicates the interpretation of the overall findings. Despite these limitations, this review has several strengths, including comprehensive searches across four databases and ClinicalTrials.gov, duplicate screening and data extraction by independent reviewers, and the use of GRADE to assess certainty of evidence, all of which enhance the transparency and robustness of the conclusions.

Previous reports suggested ICI use may improve CRF in metastatic settings [77]. Our analysis focused on earlier-stage patients receiving ICIs in adjuvant or neoadjuvant settings with curative intent. In this context, even small increases in fatigue may be clinically meaningful, as they can influence perioperative recovery, treatment adherence, and long-term survivorship outcomes.

Limitations include potential COVID-19-related impacts on withdrawal rates and data completeness, though these likely affected both arms similarly. Long-term effects of ICIs on fatigue remain unknown; CRF from conventional therapy can persist for years, and whether ICI-induced CRF follows similar patterns is unclear [3, 72, 78].

PROs remain the gold standard for assessing CRF because they capture a patient's subjective experience [78]. The context in which a PRO is implemented is contingent on the research question being asked [79]. If fatigue severity is the outcome of interest, then a unidimensional scale such as the National Comprehensive Cancer Network Fatigue Intensity Scale could be used [72, 78]. If the question is about interference with activities of daily living or specific CRF domains (e.g., physical, cognitive, and emotional), then the Multidimensional Fatigue Symptom Inventory could be used [80]. In our review, fatigue was analyzed primarily through the EORTC QLQ-C30 [31, 34–36, 49, 55, 59, 60, 69], which is appropriate for symptom solicitation [81]. However, when CRF is already known to exist, the use of instruments specifically targeting fatigue and related symptoms (e.g., pain, sleep, depression) may be more valuable [82].

Future research should integrate objective measures with PROs for more robust assessment [83]. Objective measures such as handgrip strength or finger-tapping assessments [84–86], as well as tools like the "Timed Up and Go" test, may offer mechanistic insights [87], though emotional and cognitive fatigue remain difficult to quantify objectively. An ongoing prospective clinical trial (NCT04990726) integrates longitudinal PROs with serial biospecimen collection in patients receiving neoadjuvant or adjuvant ICI therapy,

exemplifying an approach that may advance understanding of symptom trajectories and underlying biological mechanisms of ICI-related fatigue [88]. However, even with the inclusion of more objective measures, PROs will remain essential because CRF is an inherently subjective experience.

Clinically, these findings underscore the importance of proactive patient counseling regarding the likelihood of fatigue in neoadjuvant and adjuvant curative-intent immunotherapy settings. Because CRF can be profoundly debilitating, preparing patients to expect an increase in fatigue may help them cope more effectively with this symptom. Early recognition and validation of fatigue, systematic evaluation for co-occurring symptoms, and timely incorporation of supportive interventions may mitigate the impact of ICI-related fatigue on perioperative recovery and long-term quality of life. Currently, the most effective interventions for CRF include exercise, cognitive behavioral therapy, and mindfulness-based approaches [89, 90]. Initiating these strategies early in the treatment course may be particularly beneficial, especially given the observed increase in fatigue following the addition of ICI therapy. Furthermore, incorporating baseline and longitudinal patient-reported outcome measures into future neoadjuvant and adjuvant ICI trials should be prioritized to better inform survivorship care planning.

In conclusion, immunotherapy used in the neoadjuvant and adjuvant settings is associated with CRF. However, the added level of fatigue is mild to moderate. In many studies, there were in fact no statistically significant differences in the incidence of fatigue between ICIs and other types of active cancer treatments (e.g., conventional chemotherapy or radiotherapy). Further investigation into ICIs' effect on fatigue is necessary, as this knowledge is critical for counseling patients at the time of cancer treatment selection and initiation as well as future CRF prevention and treatment interventions.

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Data availability Data used for meta-analysis were extracted from published studies. All extracted data are available upon request from the authors.

Declarations

Competing interests The authors declare no competing interests.

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