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REVIEW ARTICLE

Incidence of hepatotoxicity associated with addition of immune checkpoint blockade to systemic solid tumor therapy: a meta-analysis of phase 3 randomized controlled trials

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Abstract

Hepatotoxicity is a major immune-related adverse event that may become life-threatening. The impact of adding immune checkpoint blockade (ICB) to systemic therapy on the incidence of hepatotoxicity remains unknown. We performed a systematic review and meta-analysis to compare the incidence of hepatotoxicity among patients with cancer who received therapy with and without addition of ICB. PubMed, Embase, Web of Science, and Cochrane Library were searched to select phase 3 randomized controlled trials (RCTs) evaluating the effect of adding ICB to systemic therapy, placebo, or supportive care. The odds ratio (OR) of any grade and grade 3–5 hepatitis, elevations in aspartate aminotransferase (AST), and alanine aminotransferase (ALT) was pooled for meta-analysis. 43 RCTs with 28,905 participants were analyzed. Addition of ICB increased the incidence of hepatitis (any grade: OR, 2.13, 95% confidence interval [CI] 1.52–2.97, grade 3–5: OR, 2.66, 95% CI 1.72–4.11), elevated AST (any grade: OR, 2.16, 95% CI 1.73–2.70, grade 3–5: OR, 2.72, 95% CI 1.86–3.99), and elevated ALT (any grade: OR, 2.01, 95% CI 1.59–2.54, grade 3–5: OR, 2.40, 95% CI 1.62–3.55). Subgroup analysis based on the ICB mechanism revealed no significant heterogeneity among each mechanism for hepatitis (any Grade: $I^2 = 11.1\%$, p for heterogeneity = 0.32, grade 3–5: $I^2 = 0\%$, $p = 0.48$). Adding ICB to systemic therapy increases the incidence of hepatotoxicity regardless of the mechanism of ICB. Hepatotoxicity is common and vigilant monitoring of liver function is required during ICB therapy for patients with cancer.

Keywords Immune checkpoint blockade · Immune checkpoint inhibitor · Hepatotoxicity · Hepatitis · Immune-related adverse event · Immuno-oncology

Abbreviations

AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
CI	Confidence interval
CTLA-4	Cytotoxic T-lymphocyte antigen
ICB	Immune checkpoint blockade
irAE	Immune-related adverse event
OR	Odds ratio
PD-1	Programmed cell death 1
PD-L1	Programmed death-ligand 1
PRISMA	Preferred reporting items for systematic reviews and mata-analysis
RCT	Randomized clinical trial
trAE	Treatment-related adverse event

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Introduction

Recent advances in cancer immunotherapy have resulted in a paradigm shift in oncologic treatment. Immune checkpoint blockade (ICB) has shown promise in treatment of solid tumors. ICB augments systemic antitumor immunity

by blocking the inhibitory checkpoints such as cytotoxic T-lymphocyte antigen (CTLA-4) and programmed cell death 1 (PD-1) or its ligand, programmed death-ligand 1 (PD-L1), resulting in improvement in survival time in patients with many types of cancer. ICB causes immune-related adverse events (irAEs) which may result in treatment interruption, morbidity, and mortality. The commonly affected organs are the gastrointestinal tract, skin, endocrine glands, and liver [1, 2]. Incidence of hepatotoxicity has been reported to be 2–10% in patients receiving ipilimumab, nivolumab, and pembrolizumab monotherapy, and 25–30% in patients treated with nivolumab and ipilimumab combination treatment [3–6].

Severe hepatotoxicity is an irAE requiring suspension of ICB and initiation of immunosuppression with high-dose corticosteroids, mycophenolate mofetil, or azathioprine [6]. Meta-analyses have demonstrated higher incidence of hepatotoxicity with use of ICB than chemotherapy [7, 8]. However, the results of these meta-analyses were heterogeneous because PD-1 inhibitor use was associated with higher incidence of hepatotoxicity in one meta-analysis but not in another meta-analysis [9, 10]. Therefore, it is important to elucidate the accurate impact of ICB on hepatotoxicity among patients with cancer. Furthermore, recent development of the combination treatment using ICB with other systemic therapy for solid tumors requires reevaluation of the incidence of hepatotoxicity [11–13]. When more than one ICB agent is used, or ICB is given in combination with cytotoxic chemotherapy or molecular-targeted agents, incidence of irAEs including hepatotoxicity may increase. A meta-analysis evaluating the incidence of hepatotoxicity by adding PD-1 or PD-L1 inhibitors to systemic chemotherapy concluded that PD-1/PD-L1 inhibitors were associated with increased risk of hepatitis but not with elevated aspartate aminotransferase (AST) or elevated alanine aminotransferase (ALT) [8]. This was probably due to the small number of clinical trials included in analysis. Other than hepatotoxicity, another study showed association between addition of ICB to systemic therapy and the incidence of pneumonitis [14]. However, no other studies reported the add-on effect of ICB therapy on hepatotoxicity.

These previous meta-analyses compared chemotherapeutic regimens with various risks of liver toxicity to ICB therapy. Thus, oncologists require clarity regarding the incidence of hepatotoxicity when ICB is added in an antineoplastic regimen. We conducted a systematic review and meta-analysis to investigate the add-on effect of ICB on the incidence of hepatotoxicity. The partial result of this research was presented at the Annual Meeting of the American Society of Clinical Oncology in June 2021 [15].

Materials and methods

Data search

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Mata-Analysis (PRISMA) criteria. Database including PubMed, Embase, the Cochrane Library, and Web of Science was used to search available literature as of July 7, 2021. The search strategy is described in supplementary table S1. Only the results of phase 3 randomized clinical trials (RCTs) were pooled in this research. The protocol of this research was registered in PROSPERO (https://www.crd.york.ac.uk/prospero/) on December 17, 2020, as CRD42020221414.

Selection criteria

This is a study of the incidence and severity of hepatotoxicity (hepatitis, elevated AST, and ALT) associated with addition of ICB to a treatment regimen containing systemic chemotherapy, another ICB, or supportive care compared with that of chemotherapy, single-agent ICB, or supportive care.

Studies were selected if they met the following criteria: (1) A published study designed as a phase 3 RCT assessing solid tumors. (2) The experimental group of the study was treated with at least one type of ICB with or without other systemic therapy and the control group was treated with systemic chemotherapy, ICB-plus-placebo or ICB monotherapy if the experimental group contained dual-ICB, best supportive care, placebo, or observation. (3) A study with more than two arms where an immune checkpoint inhibitor was included in at least one arm. (4) A trial that the impact of adding ICB can be assessed. (5) The result of the study was written in English. (6) A study revealed the results of at least grade 1–5 or grade 3–5 hepatitis, elevated AST, or elevated ALT.

Studies that did not meet inclusion criteria were excluded. If results of the same clinical trial were reported in several different articles, the article that is most updated, reporting the higher number of adverse events, or describing treatment-related adverse events (trAEs) or irAEs rather than any adverse events, was included in this meta-analysis. In such cases, consensus was reached between authors Y.F. and N.H. regarding inclusion or exclusion of an article.

Data extraction and risk of bias assessment

Data were extracted from eligible studies by two different investigators (Y.F. and N.H.). The following information was obtained from eligible studies: The name of the first author, publication year, study name, type of cancer, cancer status, the treatment setting, name of ICB added to therapy in the control group, classification of ICB, therapeutic regimens used in a control arm, the incidence of grades 1–5 and grade 3–5 hepatotoxicity (hepatitis, elevated AST, and elevated ALT), and the number of patients. Other diseases such as hepatic failure, hepatic injury, and hepatic events were not extracted. The Cochrane Risk of Bias Tool was utilized for evaluation of the risk of bias in each RCT, which was assessed by two reviewers (Y.F. and N.H.) independently [16]. The number of treated patients and the number of patients who developed grade 1–5 and grade 3–5 hepatotoxicity in each treatment arm were recorded from each RCT. We extracted the amount of each hepatic adverse event. If a study included the information of any adverse events, trAEs and irAEs were prioritized for analysis. If a study included both trAEs and irAEs, the group which contained a higher number was chosen for evaluation. When hepatitis was documented as both laboratory abnormalities and diagnoses, only hepatitis categorized as a diagnosis was extracted for analysis. If a study included more than two comparable arms, we chose only one comparable pair which could evaluate the effect of adding ICB and contained the highest number of patients.

Statistical analyses

The odds ratio (OR) for grade 1–5 and grade 3–5 hepatotoxicity was calculated. A meta-analysis for evaluating the contribution of ICB to the hepatotoxicity incidence was performed using random-effects models. Funnel plots were applied to evaluate publication bias. Significance was set for equivalence hypothesis testing using the two-tailed 0.05 level. The two-tailed 0.10 level and $I^2 < 50\%$ were used to set the significance for statistical heterogeneity which was assessed by using Cochran Q statistic and I^2 statistics. We used RevMan 5.4 for calculating these data [17]. We also conducted subgroup analyses based on a type of ICB (PD-1 inhibitor, PD-L1 inhibitor, and CTLA-4 inhibitor), and based on studies comparing ICB plus chemotherapy with chemotherapy alone. An exploratory analysis of the incidence of fatal AEs due to any reasons associated with addition of ICB was performed by using data extracted from articles included in this meta-analysis for hepatotoxicity.

Results

Study selection

After searching the database with title and abstract screening and duplicate removal, 310 articles were potentially eligible for analysis in this research. After detailed evaluation, 43 RCTs with 28,905 participants were included in the final analysis (Supplementary Fig. 1). Incidence of hepatitis, elevation in AST, and elevation in ALT, were analyzed in 34, 29, and 31 RCTs, respectively.

Study characteristics

Among 43 RCTs, 28 studies investigated the efficacy of ICB-containing regimens for patients with advanced cancer in the first-line setting, and 7 studies evaluated it in the second-line setting or beyond. The efficacy of ICB in the neoadjuvant and adjuvant setting was analyzed in 7 studies. No RCTs compared dual immune checkpoint inhibitors plus conventional therapy with conventional therapy alone. Atezolizumab was evaluated in 12 studies, avelumab in 3, durvalumab in 1, ipilimumab in 9, nivolumab in 5, pembrolizumab in 9, and tremelimumab in 4 studies (Table 1).

Meta-analysis of hepatitis

For any-grade hepatitis, 34 RCTs were analyzed with 226 events in the experimental group and 82 events in the control group. Addition of ICB to systemic therapy used in the control group was associated with an increase in the incidence of any-grade hepatitis (OR: 2.13, 95% confidence interval [CI] 1.52–2.97, $p < 0.0001$) (Fig. 1). For grade 3 or more hepatitis, 32 RCTs were analyzed with 115 events in the ICB group and 24 events in the control group. Addition of ICB was associated with an increase in the incidence of severe hepatitis (OR: 2.66, 95% CI 1.72–4.11, $p < 0.0001$) (Fig. 2).

Subgroup analysis according to ICB mechanism revealed an increase in the incidence of any-grade hepatitis with addition of PD-1 inhibitors, PD-L1 inhibitors, and CTLA-4 inhibitors (OR, 3.60, 95% CI 1.70–7.62; OR 1.82, 95% CI 1.12–2.96; OR, 2.32, 95% CI 1.09–4.94, respectively). There was no significant heterogeneity among each subgroup ($I^2 = 11.1\%$, p for heterogeneity = 0.32) (Fig. 1). PD-1 inhibitors and PD-L1 inhibitors were associated with an increase in the incidence of grade 3 or more hepatitis (OR, 4.22, 95% CI 1.76–10.13; OR 2.88, 95% CI 1.39–5.98); however, CTLA-4 inhibitors were not (OR, 1.99, 95% CI 0.85–4.67). There was no significant heterogeneity among each subgroup ($I^2 = 0\%$, p for heterogeneity = 0.48) (Fig. 2).

Table 1 List of randomized controlled trials analyzed in this meta-analysis

First Author	Year	Study	Cancer	Cancer status	Study setting	ICI added	Control arm	Analyzed hepatotoxicity	Patients		
									ICI	Control	Ref.
Bajorin DF	2021	CheckMate 274	Urothelial	Muscle-invasive	Adjuvant	Nivolumab	Placebo	Hepatitis, AST, ALT	351	348	[27]
Bellmunt J	2021	IMvigor 010	Urothelial	Muscle-invasive	Adjuvant	Atezolizumab	Observation	Hepatitis, AST, ALT	390	397	[28]
Boyer M	2021	KEYNOTE 598	NSCLC	Metastatic	1st line	Ipilimumab	Placebo + pembrolizumab	Hepatitis, AST, ALT	282	281	[29]
Cortes J	2020	KEYNOTE 355	Breast	Advanced	1st line	Pembrolizumab	GEM/PTX/nab-PTX + CBDCA	ALT	562	281	[30]
Di Giacomo AM	2021	NIBIT-M2	Melanoma	Brain metastasis	1st line	Ipilimumab	Fotemustine	AST, ALT	26	27	[31]
Eggermont AMM	2016	EORTC 18,071	Melanoma	Resected Stage III	Adjuvant	Ipilimumab	Placebo	AST, ALT	471	474	[32]
Eggermont AMM	2018	KEYNOTE 054	Melanoma	Resected Stage III	Adjuvant	Pembrolizumab	Placebo	Hepatitis	509	502	[33]
Ferris RL	2020	EAGLE	Head and Neck	Recurrent or metastatic	2nd line	Tremelimumab	Durvalumab	ALT	247	240	[34]
Finn RS	2020	KEYNOTE 240	HCC	Advanced	2nd line	Pembrolizumab	Placebo + BSC	Hepatitis, AST, ALT	279	134	[35]
Galsky MD	2020	IMvigor 130	Urothelial	Metastatic	1st line	Atezolizumab	Placebo + GEM + CDDP/CBDCA	Hepatitis	453	390	[36]
Govindan R	2017	Study 104	NSCLC	Advanced	1st line	Ipilimumab	Placebo + CBDCA + PTX	AST, ALT	388	361	[37]
Gutzmer R	2020	IMspire 150	Melanoma	Advanced	1st line	Atezolizumab	Placebo + Vemurafenib + Cobimetinib	AST, ALT	230	281	[38]
Hodi FS	2010	MDX010-20	Melanoma	Metastatic	2nd or later line	Ipilimumab	gp100	Hepatitis, AST, ALT	380	132	[39]
Hodi FS	2018	CheckMate 067	Melanoma	Advanced	1st line	Ipilimumab	Placebo + Nivolumab	Hepatitis, AST, ALT	313	313	[40]
Horn L	2018	IMpower 133	SCLC	Metastatic	1st line	Atezolizumab	Placebo + CBDCA + VP-16	Hepatitis	198	196	[41]
Janjigian YY	2021	CheckMate 649	GEJ	Advanced	1st line	Nivolumab	CAPOX/FOLFOX	AST, ALT	782	767	[42]
Jotte R	2020	IMpower 131	NSCLC	Advanced	1st line	Atezolizumab	CBDCA + nabPTX	Hepatitis	343	340	[43]
Kang YK	2017	ATTRACTION-2	Gastric	Advanced	3rd or later line	Nivolumab	Placebo	Hepatitis, AST, ALT	330	161	[44]
Kelly RJ	2021	CheckMate 577	GEJ	Resected stage II-III	Adjuvant	Nivolumab	Placebo	AST	532	260	[45]
Kwon ED	2014	CA184-043	Prostate	mCRPC	2nd line	Ipilimumab	Placebo following radiotherapy	Hepatitis, AST, ALT	393	396	[46]
Lee NY	2021	JAVELIN Head and Neck	Head and Neck	Locally-advanced	Definitive CRT	Avelumab	Placebo + CRT	Hepatitis, AST, ALT	348	344	[47]
Miles D	2021	IMpassion 131	Breast	Advanced	1st line	Atezolizumab	Placebo + PTX	Hepatitis, AST, ALT	432	217	[48]
Mittendorf EA	2020	IMpassion 031	Breast	Stage II–III	Adjuvant	Atezolizumab	Placebo + nabPTX—> ADR + CPA	Hepatitis, AST, ALT	164	167	[49]
Moore KN	2021	IMagyn 050	Ovarian	Stage III–IV	1st line	Atezolizumab	Placebo + PTX + CBDCA + Bevacizumab	Hepatitis	644	642	[50]
Nishio M	2020	IMpower 132	NSCLC	Stage IV	1st line	Atezolizumab	CDDP/CBDCA + PEM	Hepatitis	291	274	[51]
Paz-Ares L	2018	KEYNOTE 407	NSCLC	Metastatic	1st line	Pembrolizumab	Placebo + CBDCA + PTX/nabPTX	Hepatitis	278	280	[13]
Paz-Ares L	2019	CASPIAN*	SCLC	Extended	1st line	Durvalumab	CDDP/CBDCA + VP-16	Hepatitis, AST**, ALT**	265	266	[52, 53]
Planchard D	2020	ARCTIC	NSCLC	Metastatic	3rd or later line	Tremelimumab	Durvalumab	Hepatitis, AST, ALT	173	117	[54]
Powles T1	2020	DANUBE	Urothelial	Advanced	1st line	Tremelimumab	Durvalumab	Hepatitis, AST, ALT	340	345	[55]
Powles T2	2020	JAVELIN Bladder 100	Bladder	Advanced	1st line (maintenance)	Avelumab	GEM + CDDP/CBDCA—> BSC	Hepatitis, AST, ALT	350	350	[56]
Powles T	2021	KEYNOTE 361	Urothelial	Advanced	1st line	Pembrolizumab	CDDP/CBDCA + GEM	Hepatitis, AST, ALT	349	342	[57]
Pujade-Lauraine E	2021	JAVELIN Ovarian 200	Ovarian	Advanced	2nd or later line	Avelumab	PLD	Hepatitis, AST, ALT	182	177	[58]

Table 1 (continued)

First Author	Year	Study	Cancer	Cancer status	Study setting	ICI added	Control arm	Analyzed hepatotoxicity	Patients		
									ICI	Control	Ref.
Reck M	2016	CA184-156	SCLC	Extended	1st line	Ipilimumab	CDDP/CBDCA + VP-16	AST, ALT	478	476	[59]
Rizvi NA	2020	MYSTIC	NSCLC	Metastatic	1st line	Tremelimumab	Durvalumab	Hepatitis	372	374	[60]
Robert C	2011	CA184-024	Melanoma	Advanced	1st line	Ipilimumab	Dacarbazine	Hepatitis, AST, ALT	247	251	[61]
Rodriguez-Abreu D	2021	KEYNOTE 189*	NSCLC	Metastatic	1st line	Pembrolizumab	Placebo + CDDP/CDBCA + PEM	Hepatitis, ALT***	405	202	[62, 63]
Rudin CM	2020	KEYNOTE 604	SCLC	Metastatic	1st line	Pembrolizumab	Placebo + VP-16 + CDDP/CBDCA	Hepatitis	223	223	[64]
Schmid P1	2020	IMpassion 130	Breast	Advanced	1st line	Atezolizumab	Placebo + nab-PTX	Hepatitis, AST, ALT	453	437	[65]
Schmid P2	2020	KEYNOTE 522	Breast	Stage II–III	Neoadjuvant	Pembrolizumab	Placebo + CBDCA + PTX—> AC/EC	Hepatitis, AST, ALT	781	389	[66]
Shitara K	2020	KEYNOTE 062	Gastric	Advanced	1st line	Pembrolizumab	Placebo + 5-FU/Capecitabine + CDDP	Hepatitis	250	244	[67]
Socinski MA	2018	IMpower 150	NSCLC	Metastatic	1st line	Atezolizumab	CBDCA + PTX + Bevacizumab	Hepatitis, AST, ALT	393	394	[68]
Sugawara S	2021	TASUKI-52	NSCLC	Advanced	1st line	Nivolumab	Placebo + CBDCA + PTX + Bevacizumab	Hepatitis	273	275	[69]
West H	2019	IMpower 130	NSCLC	Metastatic	1st line	Atezolizumab	CBDCA + nabPTX	Hepatitis, AST, ALT	473	232	[70]

*Data from two different articles were used for analysis. **Data from Goldman et al. were used for analysis. ***Data from Gandhi et al. were used for analysis

5-FU 5-fluorouracil; *AC* adriamycin + cyclophosphamide; *ADR* adriamycin; *AST* aspartate aminotransferase; *ALT* alanine aminotransferase; *BSC* best supportive care; *CAPOX* capecitabine + oxaliplatin; *CBDCA* carboplatin; *CDDP* cisplatin; *CPA* cyclophosphamide; *CRT* chemoradiotherapy; *EC* epirubicin + cyclophosphamide; *FOLFOX* 5-fluorouracil + oxaliplatin; *GEJ* gastroesophageal junction; *GEM* gemcitabine; *HCC* hepatocellular carcinoma; *mCRPC* metastatic castration-resistant prostate cancer; *nabPTX* nab-paclitaxel; *NSCLC* non-small cell lung cancer; *PEM* pemetrexed; *PLD* pegylated liposomal doxorubicin; *PTX* paclitaxel; *SCLC* small cell lung cancer; *VP-16* etoposide

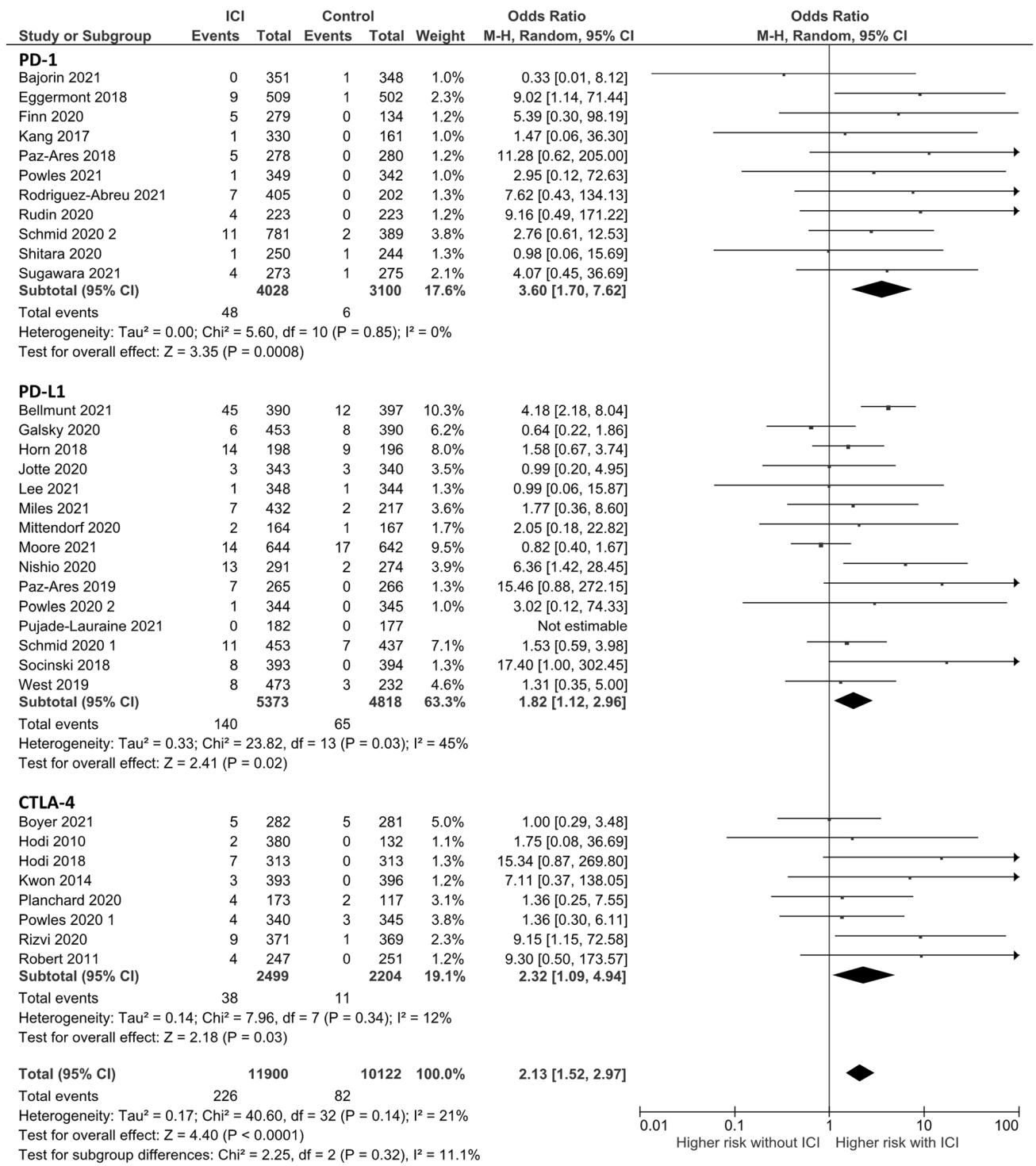

Fig. 1 Forest plot of any-grade hepatitis based on the mechanism of immune checkpoint blockade. ICI, immune checkpoint inhibitor; CI, confidence interval; PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T-lymphocyte antigen

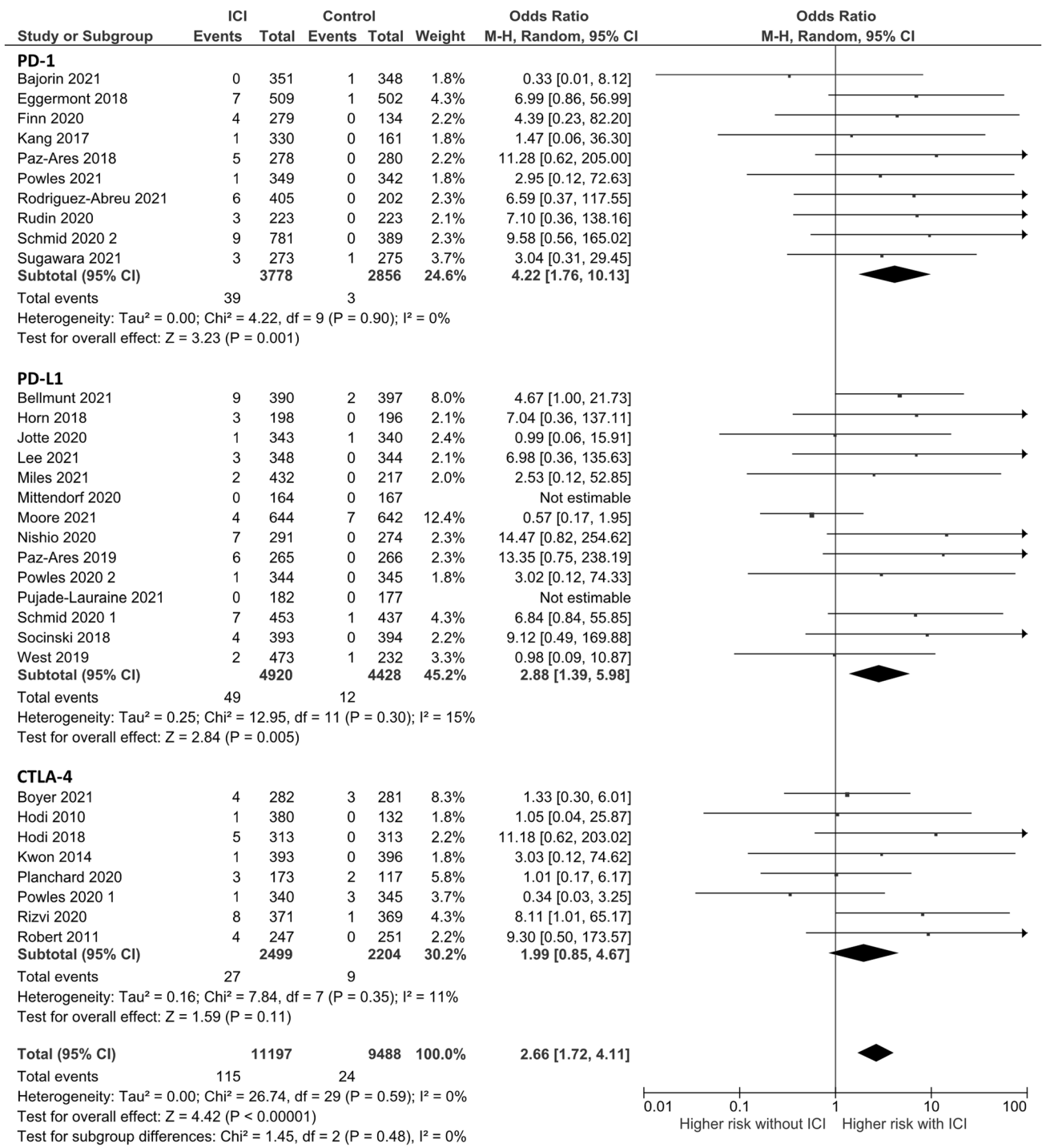

Fig. 2 Forest plot of grade 3–5 hepatitis based on the mechanism of immune checkpoint blockade. ICI, immune checkpoint inhibitor; CI, confidence interval; PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T-lymphocyte antigen

Meta-analysis of elevations in liver enzymes

For any-grade and grade 3–5 AST elevation, 28 and 29 RCTs were analyzed with 1059 and 234 events in the experimental group, and with 476 and 59 events in the control group. For any-grade and grade 3–5 ALT elevation, 30 and 31 RCTs were assessed with 1292 and 332 events in the experimental group, and with 590 and 102 events in the control group. Addition of ICB to systemic therapy used in the control group was associated with an increase in the incidence in

any-grade and grade 3–5 elevation in AST and ALT (Any-grade AST elevation: OR, 2.16, 95% CI 1.73–2.70, grade 3–5 AST elevation: OR, 2.72, 95% CI 1.86–3.99, any-grade ALT elevation: OR, 2.01, 95% CI 1.59–2.54, grade 3–5 ALT elevation: OR, 2.40, 95% CI 1.62–3.55). Subgroup analysis based on the mechanism of ICB revealed each subtype was associated with an increase in the incidence of these hepatotoxicities (Supplementary Fig. 2–5).

Subgroup analysis of studies comparing ICB plus chemotherapy with chemotherapy alone

The incidence of hepatitis and elevations in AST and ALT among studies that compared ICB and chemotherapy with chemotherapy alone was also analyzed. Addition of ICB to chemotherapy was associated with an increase in the incidence of any-grade hepatitis and grade 3–5 hepatitis (OR, 1.87, 95% CI 1.22–2.85; OR, 3.05, 95% CI 1.63–5.70), any-grade and grade 3–5 elevation in AST (OR, 2.03, 95% CI 1.43–2.90; OR, 2.92, 95% CI 1.47–5.82), and any-grade and grade 3–5 elevation in ALT (OR, 1.82, 95% CI 1.34–2.47; OR, 2.21, 95% CI 1.24–3.95) (Supplementary Fig. 6–11).

Subgroup analysis of trials comparing ICB with placebo or supportive care

Among 43 trials, 8 RCTs compared ICB monotherapy with placebo or supportive care In this setting, ICB monotherapy was associated with an increase in the incidence of any-grade hepatitis and grade 3–5 hepatitis (OR, 4.04, 95% CI 2.29–7.12; OR, 3.39, 95% CI 1.34–8.58), any-grade and grade 3–5 elevation in AST (OR, 2.40, 95% CI 1.79–3.22; OR, 2.97, 95% CI 1.49–6.06), and any-grade and grade 3–5 elevation in ALT (OR, 3.00, 95% CI 1.93–4.65; OR, 3.92, 95% CI 1.58–9.75).

Exploratory analysis of fatal adverse events based on the mechanism of immune checkpoint blockade

The incidence of fatal AEs of any causes by adding ICB to systemic therapy was analyzed. Information of fatal AEs was available in 43 RCTs included in the meta-analysis for hepatotoxicity. Addition of ICB to systemic therapy was associated with an increase in the incidence of fatal AEs (OR, 1.64, 95% CI 1.27–2.13). Each mechanism of ICB showed tendency to increase the incidence of fatal AEs and there was no significant heterogeneity among these subgroup ($I^2 = 0\%$, p for heterogeneity = 0.55) (Supplementary Fig. 12).

Risk of bias and publication bias assessment

The publication bias was evaluated using funnel plots shown in supplementary Fig. 13. Each funnel plot was relatively symmetrical and no obvious publication bias was observed. The summary of risk of bias for each trial is shown in supplementary Fig. 14. All studies included in this meta-analysis were RCTs and the overall risk of bias was low. Lack of blinding was seen in 16 RCTs.

Discussion

This systematic review and meta-analysis demonstrated that addition of ICB to systemic therapy such as chemotherapy or another ICB or to placebo or supportive care was associated with greater hepatotoxicity than regimens including chemotherapy alone, single-agent ICB, or supportive care. Hepatotoxicity is common during ICB-containing therapy, and therefore, vigilant monitoring of liver function tests is required while patients with advanced cancer receive ICB therapy. This is the most comprehensive analysis of the add-on effect of ICB on the incidence and severity of hepatic adverse events.

Hepatotoxicity has been variably defined in RCTs evaluating ICB but most RCTs define hepatitis as an immune-related adverse event and identify elevations in transaminase levels as a treatment-related adverse event. To comprehend the overall hepatotoxicity and eliminate potential observer bias that hepatotoxicity tends to be reported more in the ICB treatment group, this meta-analysis analyzes both hepatitis and elevated transaminase levels.

Subgroup analysis according to ICB mechanism revealed an increase in the incidence of hepatitis and transaminase elevation accompanied addition of each ICB subtype to a treatment regimen. In this analysis, CTLA-4 inhibitors were the only ICB subtype not associated with an increase in the incidence of severe hepatitis but heterogeneity was not observed among subgroups. Data regarding the difference in hepatotoxicity among each class of ICB are limited. Previous studies showed the incidence of immune-mediated hepatotoxicity is relatively low in PD-1 inhibitor use (0.7–2.1%), and intermediate in PD-L1 inhibitor use and standard-dose CTLA-4 inhibitor use (0.9–12%) [18]. Histopathologic findings in ICB-related hepatotoxicity may vary between PD-1/PD-L1 and CTLA-4 inhibitors, which could explain the different incidence of hepatotoxicity in each mechanism of ICB [19–22]. However, a relationship between differing histopathologic appearance and clinical incidence of hepatotoxicity associated with ICB subtypes has not yet been established. Our meta-analysis did not directly compare ICBs of differing mechanisms. Future research may better elucidate the risk of hepatotoxicity associated with various ICB mechanisms.

Clinical factors conferring an increased risk for ICB-related hepatotoxicity have not yet been established yet. A retrospective review of patients with autoimmune disease

and melanoma treated with a CTLA-4 inhibitor demonstrated an association with irAEs, however, immune-mediated hepatitis was not observed in the study cohort [23]. Prior incidence of irAE from ICB is also associated with an increase in the risk of other irAEs, but the incidence of hepatitis in this setting remains unclear [24]. A retrospective study of patients with malignancy treated with ICB suggested prior use of ICB and female sex were associated with increased risk of grade 3–5 immune-mediated hepatitis [25]. Our study showed that the addition of ICB to systemic therapy increased the risk of hepatotoxicity, however, our data are not sufficient to address risk factors for this condition. Further research to identify clinical risk factors for hepatotoxicity is needed.

Additionally, our exploratory analysis showed addition of ICB was associated with an increased incidence of fatal toxicity. Causes of fatal toxicity in this analysis were not limited to hepatotoxicity but including any grade 5 AEs. One meta-analysis showed the incidence of fatal toxicity due to ICB use occurred early after therapy initiation [26]. Therefore, careful monitoring for AEs especially soon after initiation of ICB-containing regimens is required.

Our study has several limitations. First, though this meta-analysis includes more than 40 RCTs, a number of malignancies including colorectal cancer, renal cell carcinoma, and hematologic malignancies were not analyzed in this research. This is because trials of these cancer types contained a different agent in the experimental and control group and did not meet inclusion criteria in this meta-analysis. Caution should be exercised when applying the results of the study to treatment of these malignancy types. Second, the unclear definition of hepatitis may lead to under or overestimation of the incidence of hepatitis in each trial. The majority of RCTs in this meta-analysis reported hepatitis under the category of irAE or AE of special interest, suggesting potential observer bias regarding the incidence of hepatitis. However, more than half of the clinical trials in this meta-analysis are double-blind placebo-controlled trials, mitigating the potential for bias. Furthermore, the incidence of hepatitis is consistent with that of transaminase elevation, which was categorized as treatment-related adverse effect. Third, though our meta-analysis suggests that addition of ICB to an anti-neoplastic regimen may increase the incidence of hepatotoxicity, a network meta-analysis would be necessary to compare the impact of each mechanism of ICB on this adverse effect.

Conclusion

The addition of ICB to a systemic treatment regimen was associated with an increase in the incidence of hepatitis, severe hepatitis, and elevation in transaminase levels among patients with solid tumors regardless of the mechanism of ICB. Hepatotoxicity is common during ICB therapy, and therefore, clinicians should maintain vigilance for hepatotoxicity while patients with advanced cancer are treated with an ICB-containing therapy.

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Declarations

Conflict of interest None of the authors have a conflict of interest to report for the submitted work. M.D.G. reports stock from Rappta Therapeutics; a consulting/advisory role for BioMotiv, Janssen, Dendreon, Merck, GlaxoSmithKline, Lilly, Astellas Pharma, Genentech, Bristol-Myers Squibb, Novartis, Pfizer, EMD Serono, AstraZeneca, Seattle Genetics, Incyte, Aileron Therapeutics, Dracen, Inovio Pharmaceuticals, NuMab, Dragonfly Therapeutics, Basilea, Urogen, Infinity Pharmaceuticals, and Gilead; and institutional research funding from Janssen Oncology, Dendreon, Novartis, Bristol-Myers Squibb, Merck, AstraZeneca, and Genentech/Roche.

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