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Incidence of pancreatitis with the use of immune checkpoint inhibitors (ICI) in advanced cancers: A systematic review and meta-analysis

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ABSTRACT

Background: Systemic immune side effects including pancreatitis have been reported with the use of Immune Checkpoint Inhibitors (ICI) (CTLA-4, PD-1 and PDL-1). However, the true incidence, risk, causes (tumor or drug specific) of pancreatitis and relation to other immune side effects, especially diabetes mellitus (DM) are unknown.

Methods: We performed a systematic review and meta-analysis of all clinical trials using ICI for the incidence of any grade lipase elevation, pancreatitis or DM.

Results: The incidence of asymptomatic lipase elevation after ICI use is 2.7% (211/7702) and grade 2 pancreatitis is 1.9% (150/7702). No pancreatitis related mortality has been reported in these clinical trials. Patients treated with CTLA-4 inhibitors have increased incidence of pancreatitis when compared to patients treated with PD1 inhibitors 3.98% (95% CI: 2.92 to 5.05) vs 0.94% (95% CI: 0.48 to 1.40); P value < 0.05. Patients treated with ICI for melanoma have increased incidence of pancreatitis when compared to non-melanoma cancers. We also noted an additive increase in incidence of pancreatitis with combination of CTLA4 and PD-1 inhibitors (10.60; 95% CI: 7.89 to 13.32) compared with either CTLA-4 or PD-1 inhibitors alone.

Conclusions: Our study provides precise data for the incidence of pancreatitis among patients using ICI based on tumor types and ICI regimens. ICI use for solid tumors is associated with increased incidence of all grades of lipase elevation and pancreatitis, especially for CTLA-4 agents and ICI combination. Although it does not appear to be associated with mortality, ICI related pancreatitis should be recognized early for appropriate treatment and to potentially reduce long term complications.

Introduction

Immune checkpoint inhibitors (ICI) have shown clinical efficacy in the treatment of multiple cancers including advanced melanoma and multiple non-melanoma cancers(1–3).Cytotoxic T – Lymphocyte antigen-4 (CTLA-4), programmed death-1(PD-1) and programmed death ligand −1 (PD-L1) inhibitors are the most widely studied and used among them(4). They have the ability to regulate T cell activation, proliferation and can increase tumor-specific $CD8^+$ T cell activity resulting in antitumor immunity. The FDA has approved use of multiple ICIs including ipililumab (CTLA-4 inhibitor), nivolumab (PD-1 inhibitor) and pembrolizumab (PD-1 inhibitor) for various cancers and they are now increasingly used in cancer treatment [1,3].

Although immune checkpoint inhibitors have demonstrated clinical efficacy against a broad spectrum of cancers, their use

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results in immune related adverse events (iRAE) caused by uncontrolled activation of immune system, which may be different than the side effects of conventional chemotherapy regimens [4]. iRAE most commonly involve the gastrointestinal tract, lungs, endocrine organs and skin, which may result in discontinuation of immunotherapy despite their antitumor efficacy and occasionally resulting in death of patients [4,5]. Different rates of iRAE have been described with the use of different ICI and combinations of ICI [6,7]. Early diagnosis of immune related adverse events and timely interventions including corticosteroids and biologics may help in preventing long term toxicities and complications [8,9].

Gastrointestinal iRAEs including diarrhea, colitis and hepatitis have been well documented and studied [10–12]. Cases of pancreatitis have been reported after ICI use in clinical trials as well as isolated case studies [13,14]. Concerns about the acute and chronic effects of ICI related pancreatitis have resulted in cessation of effective therapy. However, data regarding the severity, risk factors, incidence and association with other pancreas related adverse events including DM and treatment of ICI related pancreatitis are unclear. Therefore, we conducted a systematic review and meta-analysis to study the incidence and relative risk of pancreatitis with the use of various groups of immune checkpoint inhibitors.

Methods

Data source and search strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISM) statement to report this systematic review and meta-analysis [15]. We conducted a comprehensive search of multiple electronic databases through December 31, 2017. The databases included Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, Web of Science, and Scopus. We also searched the bibliographies of these selected articles, systematic reviews and clinical trial registries (www.clinicaltrials.gov) to identify any additional studies. Abstracts and conference proceedings from previous 5 years were included if all relevant data were provided. Two study investigators (JG and DB) independently reviewed the title and abstract of studies identified in the search to exclude studies that did not address the research question of interest on the basis of pre-specified inclusion and exclusion criteria. The full text and supplementary text of the remaining articles was examined to determine whether it contained relevant information. Conflicts in study selection at this stage were resolved by consensus, referring back to the original article, in consultation with a senior investigator (JF).

Study selection criteria

The following predetermined inclusion criteria were used [1]: single arm or randomized trials evaluating PD-1, PDL-1 and CTLA-4 inhibitors in solid tumors [2]: data available on rates of pancreatitis and lipase elevation assessed by Common Terminology Criteria for Adverse events Version 4.0 and if rates of pancreatitis or lipase elevation were not specifically mentioned in the text or the supplementary data, then the trial protocol was studied to see if pancreatitis was sought either clinically or biochemically. If not mentioned explicitly, then the study was not included.

Data abstraction and risk of bias assessment

Data on study-, participant-, disease- and treatment-related characteristics were abstracted onto a standardized form, by two authors (JG and DB) independently and discrepancies were resolved by consensus, referring back to the original article, in consultation with a third reviewer (JF).Two study investigators (JG and KPS) independently rated the quality of included studies by using the Cochrane Risk of Bias Tool [16].

Statistical analysis

We used the random-effects model described by DerSimonian and Laird for analysis and some degree of heterogeneity was expected [17]. Inverse variance method was used to calculate pooled incidence of pancreatitis and 95% confidence interval [CI]). We assessed heterogeneity between study-specific estimates using the inconsistency index (I^2), and used cut-offs of <30%, 30%–59%, 60%–75% and >75% to suggest low, moderate, substantial and considerable heterogeneity, respectively. The primary comparison were made between PD-1, CTLA-4 and PD-L1 inhibitors (alone and in combination) and between melanoma and non-melanoma cancers. Further comparison was made based on study design (phase I/II vs phase III).

Results

Search results

Our search strategy included 33 studies including a total of 7702 patients for systematic review and meta-analysis. Our study selection process is illustrated in Fig. 1. We found 16 trials with PD-1 inhibitors (Nivolumab: n = 12, Pembrolizumab: n = 4) and 10 trials with CTLA-4 inhibitors (Ipilimumab: n = 8, Tremelimumab: n = 2), 4 trials with PDL-1(atelozumab: n = 3, avelumab: n = 1 and 3 trials with combination of PD-1 and CTLA-4(Nivolumab + ipilimumab) inhibitors. We found 16 trials for patients with melanoma cancers including 3498 patients and 17 trials (4204 patients) with non-melanoma cancers including lung cancer (7 trials), lymphoma (2 trials), mesothelioma (2 trials), genitourinary cancers (4 trials), Merkel cell (1 trial), and head and neck cancer (1 trial).

Characteristics of eligible studies

Main characteristics of the included studies and incidence of pancreatitis and lipase elevation are summarized in Table 1. There were 6 phase 1 trials, 10 phase 2 trials and 17 phase 3 trials. The number of patients studied across trials ranged between 12 and 726 patients.

Definition of pancreatitis and lipase elevation

Elevations in lipase was graded according to CTCAE version 4 criteria as Grade 1: > ULN to 1.5× ULN; Grade 2: >1.5× ULN to 2× ULN; Grade 3: 2xULN – 5× ULN, Grade 4: >5× ULN was used. Mortality related to pancreatitis is classified as Grade 5 based on this CTCAE version 4. Pancreatitis was defined as: Grade 2-asymptomatic enzyme elevation or radiologic findings only, Grade 3 - severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support), Grade 4 - Life-threatening consequences; urgent intervention indicated, and Grade 5 - death when data was available based on CTCAE 4. For the purposes of this study and due to the paucity of clinical and radiologic data available, we are primarily focusing on the lipase level elevation.

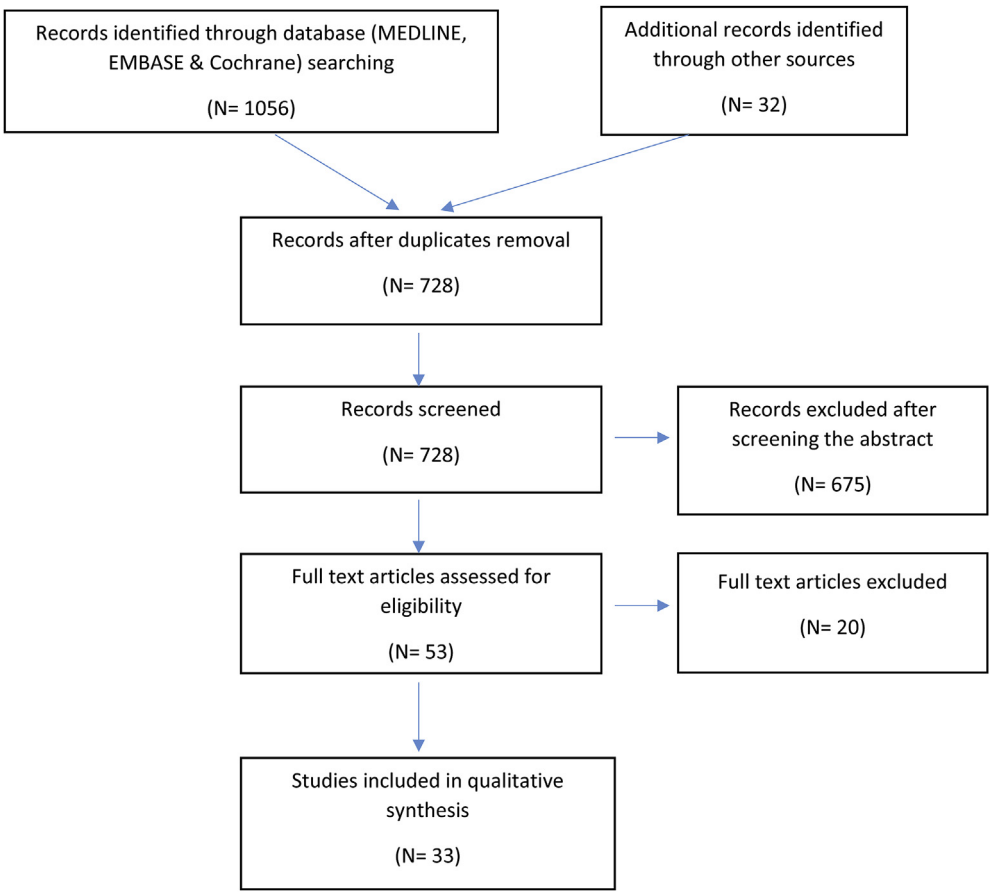


Fig. 1. PRISMA diagram showing the selection of included studies.

Table 1
Characteristics of eligible studies.

Author	Year	Phase	Class	Name	Cancer	N	Any Lipase	Grade 3–5 Lipase/Grade 2 Pancreatitis
Weber [25]	2016	2	PD-1	Nivolumab	Melanoma	92	2/92	1/92
Wolchok [26]	2017	3	PD-1	Nivolumab	Melanoma	313	27/313	14/313
Robert [2]	2015	3	PD-1	Nivolumab	Melanoma	206	2/206	2/206
Weber [27]	2015	3	PD-1	Nivolumab	Melanoma	268	3/268	2/268
Gettinger [28]	2016	1	PD-1	Nivolumab	NSCLC	52	1/52	1/52
Borghaei [29]	2015	3	PD-1	Nivolumab	NSCLC	287	3/287	3/287
Brahmer [30]	2012	1	PD-1	Nivolumab	NSCLC	207	1/207	1/207
Brahmer [31]	2015	3	PD-1	Nivolumab	NSCLC	131	2/131	2/131
Ferris [32]	2016	3	PD-1	Nivolumab	Head	236	4/236	4/236
Motzer [3]	2015	3	PD-1	Nivolumab	Renal	406	3/406	0/406
Younes [33]	2016	2	PD-1	Nivolumab	Lymphoma	80	6/80	4/80
Lesokhin [34]	2016	1	PD-1	Nivolumab	Lymphoma	81	3/81	1/81
Reck [1]	2016	3	PD-1	Pembrolizumab	NSCLC	154	1/154	1/154
Herbst [35]	2016	3	PD-1	Pembrolizumab	NSCLC	682	3/682	2/682
Robert [36]	2014	1	PD-1	Pembrolizumab	Melanoma	173	1/173	1/173
Robert [7]	2015	3	PD-1	Pembrolizumab	Melanoma	555	0/555	0/555
Robert [37]	2013	2	CTLA-4	Ipilimumab	Melanoma	29	2/29	0/29
Eggermont [38]	2016	3	CTLA-4	Ipilimumab	Melanoma	471	26/471	26/471
Ascierto [39]	2017	3	CTLA-4	Ipilimumab	Melanoma	726	1/726	0/726
Wolchok [26]	2017	3	CTLA-4	Ipilimumab	Melanoma	313	18/311	12/311
Robert [7]	2015	3	CTLA-4	Ipilimumab	Melanoma	256	0/256	0/256
Postow [6]	2015	3	CTLA-4	Ipilimumab	Melanoma	46	2/46	1/46
Wilgenhof [40]	2013	2	CTLA-4	Ipilimumab	Melanoma	50	1/50	1/50
Maio [41]	2017	2b	CTLA-4	Tremelimumab	Mesothelioma	380	23/380	14/380
Calabro [42]	2013	2	CTLA-4	Tremelimumab	Mesothelioma	29	1/29	1/29
Balar [43]	2017	2	PD-L1	Atezolizumab	Bladder	119	0	0
Kaufman [44]	2016	2	PD-L1	Avelumab	Merkel	88	3/88	3/88
Fehrenbacher [45]	2016	2	PD-L1	Atezolizumab		142		
Postow [6]	2015	3	CTLA-4,PD-1	Nivolumab + Ipilimumab	Melanoma	94	12/94	8/94
Wolchok [26]	2017	3	CTLA-4,PD-1	Nivolumab + Ipilimumab	Melanoma	313	44/31	34/313
Wolchok [46]	2013	1	CTLA-4,PD-1	Nivolumab + Ipilimumab	Melanoma	86	15/86	11/86

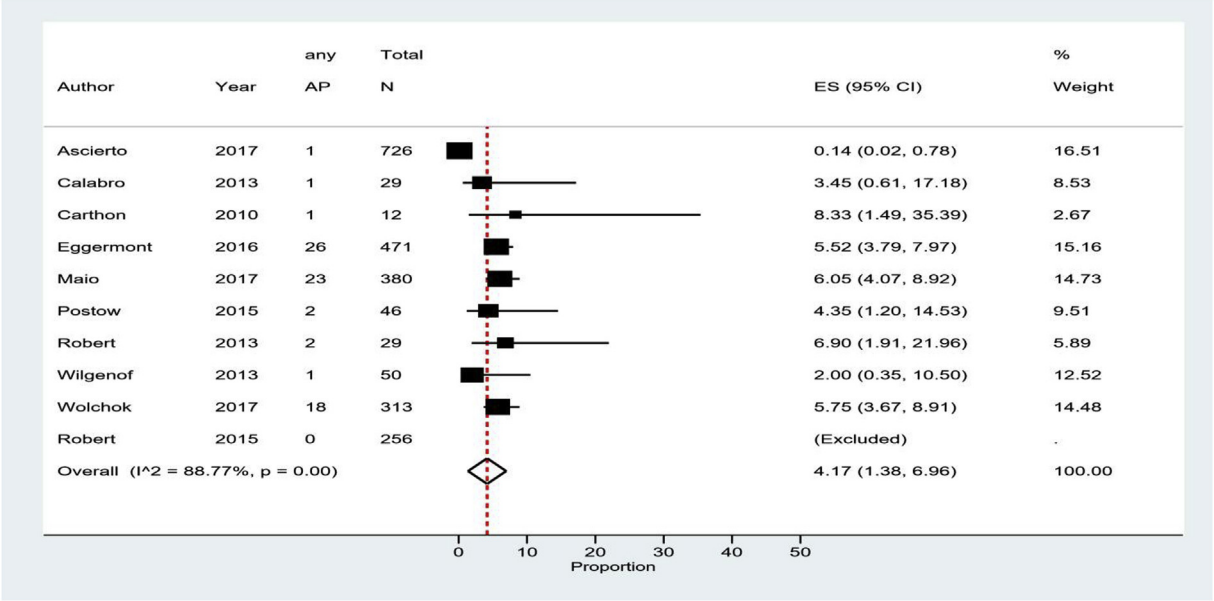
Incidence of lipase elevation and pancreatitis with immune checkpoint inhibitors

Our meta-analysis showed that incidence of all grade lipase elevation with CTLA-4 inhibitors was 4.17% (95% CI: 1.38 to 6.96) and grade 2 pancreatitis was 3.98% (95% CI:2.92 to 5.05) (Fig. 2a and b). Incidence of all grade lipase elevation with PD-1 inhibitors was 1.26% (95% CI: 0.66 to 1.86) and grade 2 pancreatitis was 0.94% (95% CI: 0.48 to 1.40) (Fig. 3a and b).

Our data shows that incidences of all grade lipase elevation (4.17 vs 1.26) and grade 2 pancreatitis (3.98 vs 0.94) were significantly higher with CTLA-4 inhibitors when compared to PD-1 inhibitors (p value < 0.05). We also noted an additive increase in incidence of lipase elevation (Any grade lipase 14.29; 95% CI: 11.20 to 17.38 and Grade 2 pancreatitis 10.60; 95% CI: 7.89 to 13.32) with combination ICI of PD-I and CTLA-4 inhibitors when compared to using either PD-1 or CTLA-4 inhibitors alone in 3 clinical trials (Fig. 4a and b). There was no clear relationship between the occurrence of pancreatitis and treatment duration. There is no reported information on treatment of pancreatitis including steroid use in these trials. There are no reported deaths attributed to immune related pancreatitis in these trials. These data are shown in Table 2.

Incidence of pancreatitis in melanoma vs non melanoma cancers

Patients treated with ICI for melanoma have increased incidence of pancreatitis when compared to non-melanoma cancers. Our study shows that, even after removing the patients with melanoma who were treated with combination ICI, incidence of any grade lipase elevation (2.4% vs 1.6% P value < 0.05) as well as grade 2 pancreatitis (1.8% Vs 1.1% P value < 0.05) were higher in patients with melanoma when compared to non-melanoma cancers.



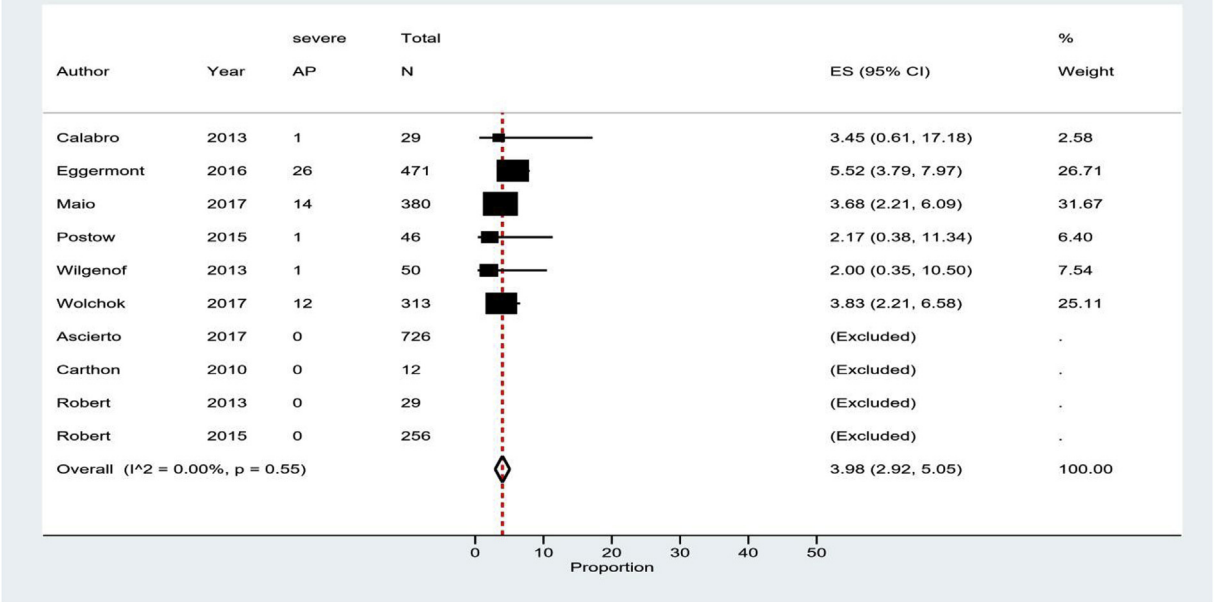
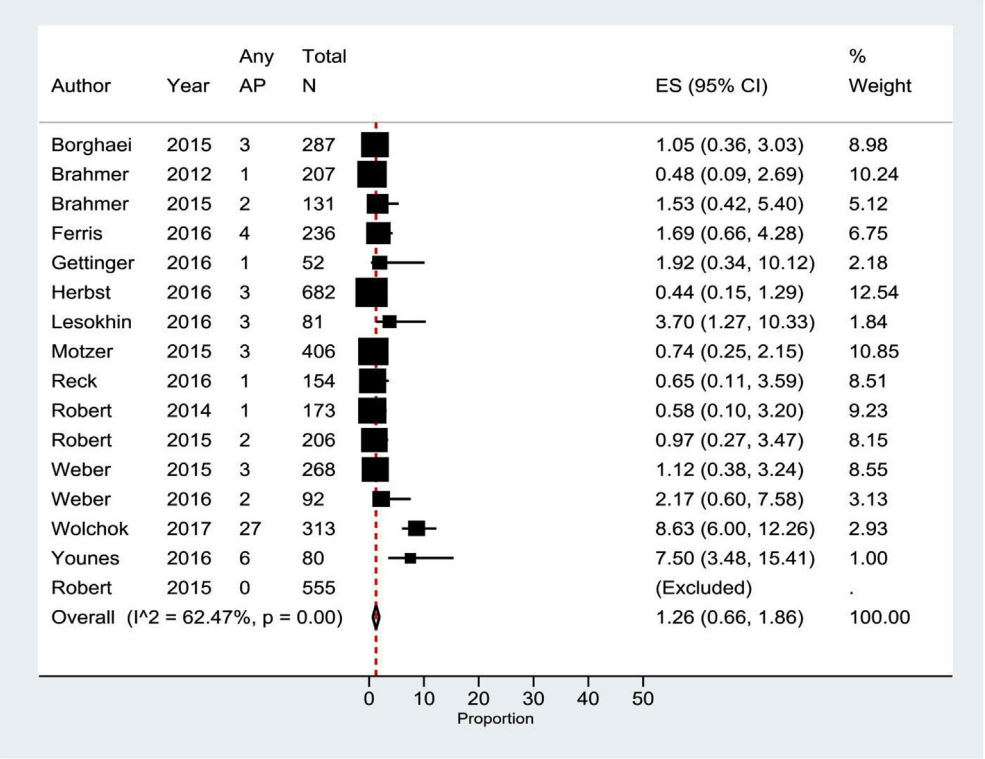


Fig. 2. **A**: Incidence of any grade lipase elevation with CTLA- 4 inhibitors. **B**: Incidence of grade 2 pancreatitis with CTLA- 4 inhibitors.



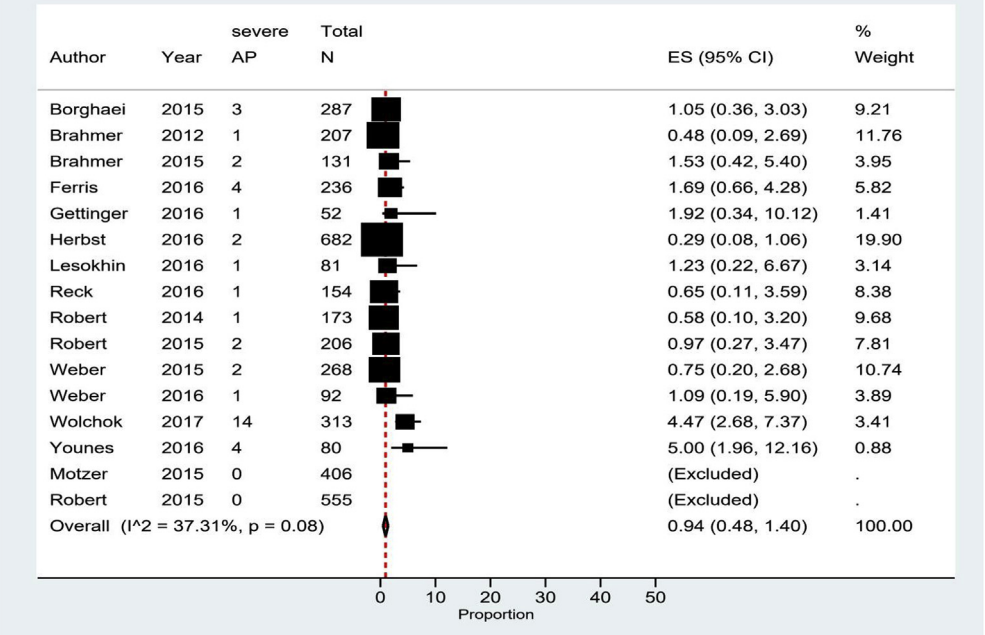


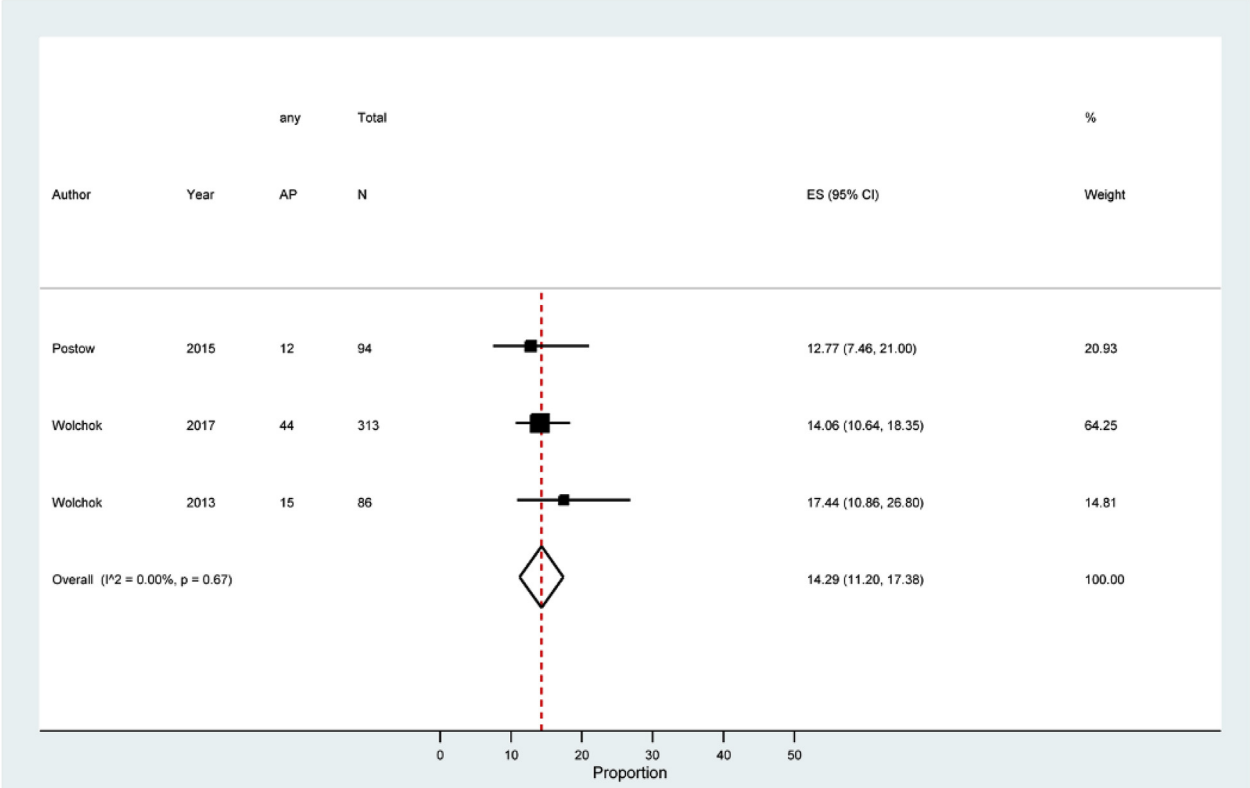
Fig. 3. **A**: Incidence of any grade lipase elevation with PD-1 inhibitors. **B**: Incidence of grade 2 pancreatitis with PD-1 inhibitors.

Relationship between ICI pancreatitis and DM

6 of the 33 studies provided data on the presence or absence of ICI related DM, 14 cases of any grade DM were reported. 6 of these were reported as grade 3–5. However we are not able to make any association between the presence of ICI related pancreatitis and DM from this data-analysis.

Discussion

Data regarding the incidence and relative risks of pancreatitis related to ICI use are unclear. Our study shows that the incidence of all grade lipase elevation and pancreatitis is significantly higher in the ICI group compared to standard chemotherapy as confirmed by phase III studies. Our data also shows that patients treated with combination treatment and CTLA-4 inhibitors have an increased



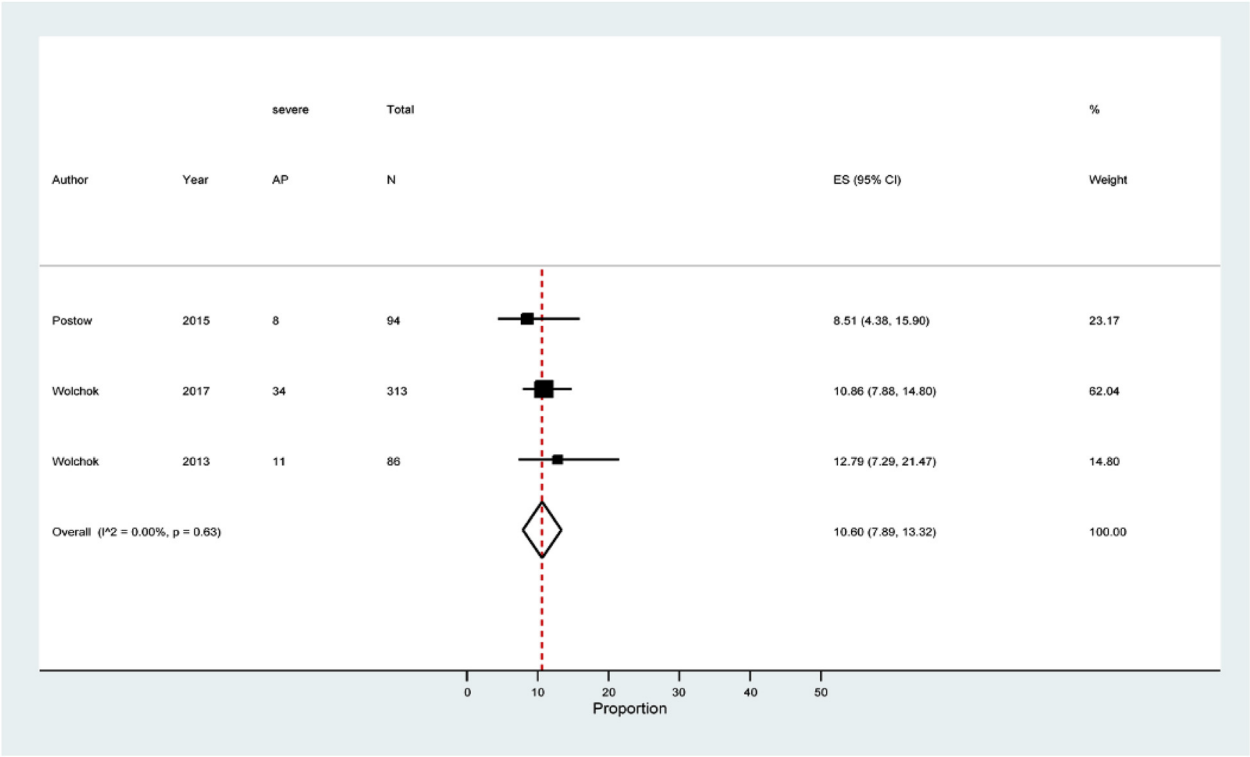


Fig. 4. A: Incidence of any grade lipase elevation with combination of CTLA-4 and PD-1 inhibitors. **B**: Incidence of grade 2 pancreatitis with combination of CTLA-4 and PD-1 inhibitors.

Table 2
Incidence of Pancreatitis for CTLA4 and PD-1: Alone or in combination.

Drug Class	Number of studies	Total Patients	Events Any Lipase	Events Pancreatitis	Incidence Any Lipase	Incidence Pancreatitis
CTLA-4	10	2312	75	55	4.17% (95% CI:1.38 to 6.96)	3.98% (95% CI:2.92 to 5.05)
PD-1	16	3923	62	39	1.26% (95% CI: 0.66 to 1.86)	0.94% (95% CI: 0.48 to 1.40)
CTLA-4+ PD-1	3	493	71	53	14.29% (95% CI: 11.20 to 17.38)	10.60% (95% CI: 7.89 to 13.32)

incidence of pancreatitis when compared to patients treated with PD1 inhibitors. These differences have been noted with other iRAEs related to ICI. However no mortality related to ICI associated pancreatitis was noted in our study, unlike mortality documented for other iRAE related to ICI such as colitis. While our study was unable to make an association between ICI related pancreatitis and other ICI related iRAE, the rate of ICI related DM was noted to be low at 1% [18]. Finally, we noted that patients treated with ICI for melanoma have an increased incidence of pancreatitis when compared to non-melanoma cancers. To our knowledge, this tumor specific preference has not been shown for other ICI related iRAE.

Pancreatitis associated with ICI use are under-recognized. Many early clinical trials haven't reported clinical pancreatitis or asymptomatic lipase elevation, as they were often not included in the trial protocols. This is the first meta-analysis that reports the incidence of pancreatitis and lipase elevation in patients treated with immune checkpoint inhibitors. It is the first most comprehensive effort at defining the incidence of pancreatitis across multiple classes of ICIs and comparing the rates of pancreatitis across them. Previous isolated case reports have reported pancreatitis after immune checkpoint inhibitor use [13,14]. However due to the nature of the reporting of clinical trials we were unable to make an association between ICI related pancreatitis and other ICI related iRAE especially diabetes mellitus.

Recognition of ICI treatment related pancreatitis has several important clinical implications. Firstly, consideration for pancreatitis in patients complaining of new onset abdominal pain while either on or after ICI treatment should be considered. Secondly, severe symptomatic pancreatitis is associated with significant morbidity and can result in discontinuation of ICI. Early identification of pancreatitis can result in close monitoring and prompt treatment of symptoms with analgesics and steroids. Thirdly, treatment options including steroid therapy have been reported efficacious for this entity. However due to the nature of our study we were unable to evaluate steroid treatment or response for this entity. Further, the option exists to manage these patients by discontinuation of their ICI. This is often in the setting of patients who have been responding effectively to their ICI treatment. So, increasingly recommendations include continuing treatment through the pancreatitis, if symptomatically manageable. This is supported by our data showing no mortality associated with ICI related pancreatitis, in contrast to a 2% mortality reported for acute interstitial pancreatitis, which can be as high as 20% in patients with pancreatic necrosis. Finally, the prompt recognition and treatment of ICI related pancreatitis, including asymptomatic cases, may decrease the likelihood of the development of chronic pancreatitis with both endocrine and exocrine dysfunction.

The reasons for ICI pancreatitis are multifactorial and are hypothesis generating. CTLA-4 inhibition affecting the immune response at a proximal step compared to PD-1 affecting the cascade more distally may be one of the reasons for more incidence of iRAE with CTLA-4 inhibitors [19]. Genetic deletion and pharmacologic inhibition of CTLA-4 and PD-1 have shown to result in an autoimmune immune pancreatitis phenotype in mouse models mediated by suppression of TReg function and raising effector T cell response. Mice lacking CTLA-4 gene die from lymphoproliferation whereas mice with PD-1 deletion have more limited organ specific autoimmune phenotype [20]. In autoimmune models, PD-L1 has an essential role in protecting mice from T-cell mediated diabetes [21].Previous studies also suggest that patients treated with CTLA-4 inhibitors have different side effect profile compared to PD-1 inhibitors [22,23]. Colitis and hypophysitis seem to occur more common with CTLA-4 blockade whereas pneumonitis and thyroiditis is more frequent with PD-1 blockade [22,24]. These trends are concerning about overall toxicity of CTLA-4 inhibitors compared to PD-1 inhibitors and need to be closely evaluated in future clinical trials of immune checkpoint inhibitors. The finding in our study of an increased rate of ICI related pancreatitis in patients being treatment for melanoma compared with those without melanoma is also thought provoking, as this has not been seen with other ICI related iRAE.

The animal models of CTLA4 and PD-L1 genetic deletion showing a phenotype similar to autoimmune pancreatitis raises the specter that ICI related pancreatitis may represent a model of drug induced autoimmune pancreatitis (AIP). Clinically, ICI related pancreatitis is more similar to AIP than to typical acute pancreatitis, presenting with less severe abdominal pain, lower or no mortality, and the responsivity to steroid therapy. In addition, the extra pancreatic manifestations of AIP, as seen part of a systemic IgG4 process, are very similar to the multisystemic nature of ICI related iRAE. However there is no data available from this or other studies about the diagnostic value of IgG4 or other immunoglobulins levels in ICI related pancreatitis.

The strengths of this study include the large numbers of studies included including 19 phase 3 randomized clinical controlled trials. The major limitation of this study is the reliance on levels of lipase as an indicator of pancreatitis, without specific clinical symptom or radiologic evidence to make a diagnosis of clinical pancreatitis. Asymptomatic elevation of lipase without concerns or progression to clinical pancreatitis might have occurred. Some of the studies in this analysis were also open label resulting in higher chances of bias in reporting pancreatitis. Various trials have used different treatment schedules but the rate of pancreatitis were included for the full cohort as individual data for each treatment schedule was not available. Additional limitations of this study include the inability to associate the ICI related pancreatitis with other ICI related iRAEs especially diabetes, and the absence of treatment or outcomes data.

Pancreatitis is an important iRAE (albeit without mortality) and is a major concern for physicians who are not familiar with treating pancreatitis. Either symptomatic or asymptomatic it can result in cessation or holding effective treatment. Our study defines the risks and presentation and zero mortality. Future prospective clinical trials and multicenter cancer registries should carefully evaluate asymptomatic biochemical and symptomatic pancreatitis. Data regarding restarting ICI after developing iRAE are unclear at this point. Future studies are needed to elucidate mechanisms of immune related adverse events including pancreatitis for development of precise and better treatment options without compromising efficacy of checkpoint blockade inhibitors.

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Conflicts of interest

None.

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None.

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