# Correspondence

# Gastrointestinal toxicities associated with immune checkpoint inhibitors: a disproportionality analysis leveraging VigiBase, the WHO Adverse Drug Reaction Database

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With the improvement of people's living standards, gastrointestinal adverse reactions caused by various adverse factors have attracted more and more people's attention. A recent study has indicated that coronavirus disease 2019 (COVID-19) could also invade the gastrointestinal tract, leading to gastrointestinal adverse reactions (Song et al., 2020). In recent years, immunotherapy has provided certain effects for some patients with advanced malignant tumors. A microencapsulation of immunoglobulin Y (IgY) was reported to provide an effective way to preserve IgY and improve its performance in the gastrointestinal tract (Zhang J et al., 2020). Immune checkpoint inhibitors (ICIs) can significantly improve the survival of some advanced malignant tumors, especially metastatic malignant melanoma and lung cancer (Afzal et al., 2018; Madden and Kasler, 2019). They include anti-cytotoxic T lymphocyte-associated antigen-4 (anti-CTLA-4) antibodies (ipilimumab and tremelimumab), anti-programmed cell death protein 1 (anti-PD-1) antibodies (nivolumab and pembrolizumab), and anti-programmed death-ligand 1 (anti-PD-L1) antibodies (atezolizumab, avelumab, and durvalumab) (Baxi et al., 2018). Previous studies have shown that ICI combination therapy, such as nivolumab plus ipilimumab, has particular efficacy in lung cancer, renal cell carcinoma, and malignant melanoma (Wolchok

et al., 2017; Derosa et al., 2018; Doroshow et al., 2019). However, ICIs may also lead to many immune-related adverse events (irAEs), even causing severe complications in certain cases. The most well-established toxicities from ICI therapy are gastrointestinal irAEs, including enteritis, enterocolitis, microscopic colitis, and gastritis, which have attracted public attention in recent years; reports of such events associated with ICI therapy also have increased (Tandon et al., 2018; de Malet et al., 2019). These gastrointestinal irAEs may generally respond well to corticosteroids and infliximab (Haanen et al., 2017). Although most of these irAEs are low-grade, a lack of detection and timely treatment may incur severe or fatal complications.

Many clinical oncologists and gastroenterologists are unfamiliar with gastrointestinal irAEs caused by ICI treatment, making it impossible to detect and deal with the resulting immunotoxicity in time. In addition, the previous scientific literature lacks comprehensive and detailed reports on gastrointestinal irAEs caused by ICIs, especially on cases of megacolon. In this study, we used the World Health Organization (WHO) global individual case safety report database, known as VigiBase (herein also referred to as Adverse Drug Reaction Database), which is managed by the Uppsala Monitoring Center in Sweden, to fully understand the gastrointestinal irAEs caused by ICI treatment, and their clinical characteristics.

The present study is a disproportionality analysis leveraging VigiBase, which includes reports from more than 130 countries, and represents over 90% of the world's population. It contains more than 19 million

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individual case safety reports (ICSRs) submitted by national pharmacovigilance centers since 1967. These reports are generally notified post-marketing and originate from many kinds of sources, including pharmacists, healthcare professionals, patients, and physicians. Adverse drug reactions (ADRs) in VigiBase are coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

In the present observational, retrospective, and disproportionate analysis, based on the VigiBase database, we report suspicious gastrointestinal irAEs related to ICI therapy from January 1, 2011 to March 6, 2019, and describe the clinical features of cases in detail. The reference group consists of all the adverse reaction reports in VigiBase during the same study period. The main gastrointestinal irAEs are divided into 13 categories, namely enterocolitis, gastrointestinal perforation, megacolon, duodenitis, intestinal obstruction, esophagitis, diarrhea, colon operation, gastritis, inflammatory bowel disease, gastrointestinal hemorrhage, abdominal discomfort, and vomiting (Table 1).

Each adverse reaction report associated with ICI treatment includes patient characteristics (age and sex), management information (country, reporting date, and notifier), drug information (WHO drug name, indication, route of administration, dosage regimen, start and end dates), and ADR information (MedDRA classification terms, onset of ADRs, and final outcomes). The five ICI drugs reported in the study are anti-PD-L1 antibodies (atezolizumab and durvalumab), anti-CTLA-4 antibody (ipilimumab), and anti-PD-1 antibodies (nivolumab and pembrolizumab). A severe adverse event is defined as an event leading to any other medically important conditions that require hospitalization (initial or prolonged), is life-threatening, or causes death. It is worth noting that reports of ADRs were used for the purposes of this study starting from January 1, 2011.

VigiBase is known as a case–non-case analytic database; therefore, it was used for disproportionality analysis to assess whether suspected drug-induced gastrointestinal events were differentially reported between ICIs and other drugs in the full database. Gastrointestinal irAEs among different ICI regimens were also compared by disproportionality analyses, i. e., anti-PD-1 or anti-PD-L1 versus anti-CTLA-4 monotherapy, and monotherapy versus combination ICI therapy (anti-PD-1 or anti-PD-L1 plus anti-CTLA-4 combination therapy). The analyses aimed to identify adverse drug events by relative frequency, which is

**Table 1 Reports of ICI-associated gastrointestinal irAEs versus those included in the full database of VigiBase (from January 1, 2011 to March 6, 2019)**

| Gastrointestinal irAE | ICSRs for ICIs (ICIs reports in total: 61 931) | ICSRs in full database (reports in total: 13 300 773) | Information component (95% CI) |
|---|---|---|---|
| Enterocolitis | 3066 (4.82%) | 23 850 (0.18%) | 4.80 (4.75–4.85) |
| Gastrointestinal perforation | 380 (0.40%) | 12 983 (0.10%) | 2.68 (2.51–2.80) |
| Megacolon | 15 (0.01%) | 535 (0.004%) | 2.46 (1.62–3.05) |
| Duodenitis | 44 (0.06%) | 4358 (0.03%) | 1.19 (0.71–1.54) |
| Intestinal obstruction | 259 (0.35%) | 25 760 (0.19%) | 1.19 (0.99–1.33) |
| Esophagitis | 62 (0.10%) | 7344 (0.06%) | 0.85 (0.43–1.15) |
| Diarrhea | 3246 (5.24%) | 416 055 (3.13%) | 0.74 (0.69–0.79) |
| Colon operation | 22 (0.04%) | 2858 (0.02%) | 0.70 (−0.01–1.21) |
| Gastritis | 166 (0.27%) | 39 951 (0.30%) | −0.16 (−0.42–0.02) |
| Inflammatory bowel disease | 122 (0.20%) | 42 884 (0.32%) | −0.71 (−1.01–0.49) |
| Gastrointestinal hemorrhage | 365 (0.59%) | 131 244 (0.99%) | −0.74 (−0.92–0.62) |
| Abdominal discomfort | 1136 (1.83%) | 520 487 (3.91%) | −1.09 (−1.19–1.02) |
| Vomiting | 2616 (4.22%) | 1 248 590 (9.39%) | −1.15 (−1.22–1.11) |

ICSRs are described as number (percentage). The information component (IC) reflects the strength of association between the specific treatment and the adverse drug event. Positive IC values are thresholds of signal detection within VigiBase. Different ICIs include ipilimumab, nivolumab, pembrolizumab, atezolizumab, durvalumab, and combination therapy (ipilimumab plus nivolumab, ipilimumab plus pembrolizumab, ipilimumab plus atezolizumab, pembrolizumab plus nivolumab, ipilimumab plus pembrolizumab plus nivolumab). All gastrointestinal irAEs were classified by group queries according to the Medical Dictionary for Regulatory Activities (MedDRA, Version 20.1). ICIs: immune checkpoint inhibitors; irAE: immune-related adverse event; ICSRs: individual case safety reports; CI: confidence interval.

different from the overall reporting of events in the full database. The proportion of selected ADRs reported for ICIs was compared to the proportion in the full database.

Disproportionality analysis can be calculated by the information component (IC) or the reported odds ratio (ROR). The earlier can provide a conservative association metric, and reduce the risk of highlighting false associations compared to the ROR, especially for events with very low expected frequencies in the VigiBase database. Values of IC are only used to compare adverse drug events with the full database, but cannot be used for comparisons of different ICI reporting events among ICI therapies. Therefore, the IC value was used to identify meaningful ICIs that induced irAEs, while the ROR was used to compare the reporting events of ADRs in different ICI subgroups.

The value of IC, whose calculation is derived from a Bayesian confidence propagation neural network, is used to reflect the strength of the adverse drug event association (Zhao et al., 2001), which is expressed by the logarithm of prior and posterior probabilities of occurrence of ADRs. A positive IC value indicates that adverse drug events are reported more often than all reported events in the full database. The 95% confidence interval (CI) indicates the stability of IC values; the stability is higher when the 95% CI is narrower. Disproportionality for gastrointestinal irAEs induced by ICI subgroups was analyzed by calculating the ROR (95% CI). When the lower value of ROR (95% CI) was larger than one, adverse reactions for the target ICI were notable ADR signals in the adverse drug event. The Bonferroni adjustment method was used to perform the comparisons among different drug treatment regimens, and the ROR CI was adjusted by using $P$=0.01. The clinical characteristics of ADRs were summarized by descriptive statistical methods, while the quantitative variables were compared by using one-way analysis of variance (ANOVA).

According to the VigiBase database, patients who received ICIs reported 61 931 adverse events, whereas patients who were administered any drug reported 13 300 773 adverse events between January 1, 2011 and March 6, 2019. Table 1 shows the IC values for various gastrointestinal adverse events induced by ICI therapy compared to those for the same adverse event in the full database: ICI-associated enterocolitis

(3066 reports for ICIs vs. 23 850 reports for the full database; IC 4.80 (95% CI 4.75–4.85)); ICI-associated gastrointestinal perforation (380 reports for ICIs vs. 12 983 reports for the full database; IC 2.68 (95% CI 2.51–2.80)); ICI-associated duodenitis (44 reports for ICIs vs. 4358 reports for the full database; IC 1.19 (95% CI 0.71–1.54)); ICI-associated intestinal obstruction (259 reports for ICIs vs. 25 760 reports for the full database; IC 1.19 (95% CI 0.99–1.33)). It is worth noting that 15 cases of the rarely reported ICI-associated megacolon were found (535 reports for the full database; IC 2.46 (95% CI 1.62–3.05)). All IC values were positive for the above five gastrointestinal irAEs induced by ICIs, and the values of 95% CI were very narrow, which shows that these adverse events are markedly associated with ICI therapies. Thus, we focus on these five gastrointestinal irAEs to analyze differences between various ICI subgroups, and to explain the clinical characteristics of each gastrointestinal irAE.

As demonstrated in Table 2, the ROR values of the five gastrointestinal irAE were markedly different between ICI therapies, and the ROR values of duodenitis, enterocolitis, and gastrointestinal perforation were the highest in ICI combination treatments (ROR 11.68 (95% CI 7.43–18.34), ROR 93.09 (95% CI 85.85–100.94), and ROR 5.77 (95% CI 3.98–8.37), respectively). We also found that the three gastrointestinal irAEs of duodenitis, enterocolitis, and intestinal obstruction were overreported for patients subjected to ICI combination treatment, versus those who received ICI monotherapy: duodenitis (ROR 8.43 (95% CI 4.70–15.10)), enterocolitis (ROR 3.98 (95% CI 3.64–4.35)), and intestinal obstruction (ROR 1.94 (95% CI 1.37–2.75)). Enterocolitis, gastrointestinal perforation, and megacolon were overreported for patients who received anti-CTLA-4 treatment, versus those subjected to anti-PD-1/PD-L1 treatment (ROR 3.87 (95% CI 3.57–4.20), ROR 5.42 (95% CI 4.37–6.73), and ROR 4.92 (95% CI 1.75–13.82), respectively).

Events of ICI-associated enterocolitis, gastrointestinal perforation, intestinal obstruction, and duodenitis were reported mainly from the Americas (1292/3066 (42.14%), 193/379 (50.92%), 138/259 (53.28%), and 19/44 (43.18%), respectively), while most of the megacolon cases were recorded in Europe (5/15 (33.33%)), as shown in Table 3. There were more male patients than female ones for the five

**Table 2  Major ICI-associated gastrointestinal ADRs compared to the full database of VigiBase (from January 1, 2011 to March 6, 2019)**

| Characteristics | Duodenitis | | Enterocolitis | | Gastrointestinal perforation | | Intestinal obstruction | | Megacolon | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *n/n* | ROR (95% CI) | *n/n* | ROR (95% CI) | *n/n* | ROR (95% CI) | *n/n* | ROR (95% CI) | *n/n* | ROR (95% CI) |
| Anti-CTLA-4 vs. full database | 2/4358 | 0.42 (0.11–1.68) | 1239/23850 | 56.67 (53.42–60.11) | 214/12983 | 15.97 (13.96–18.27) | 46/25760 | 1.75 (1.32–2.32) | 9/535 | 15.71 (8.13–30.36) |
| Anti-PD-1/ Anti-PD-L1 vs. full database | 25/4358 | 1.68 (1.14–2.47) | 1143/23850 | 14.52 (13.67–15.41) | 140/12983 | 2.92 (2.46–3.46) | 182/25760 | 2.06 (1.78–2.38) | 5/535 | 3.17 (1.42–7.08) |
| ICI combination vs. full database | 17/4358 | 11.68 (7.43–18.34) | 684/23850 | 93.09 (85.85–100.94) | 26/12983 | 5.77 (3.98–8.37) | 31/25760 | 3.84 (2.78–5.31) | 1/535 | 4.98 (0.70–35.40) |
| Anti-CTLA-4 vs. Anti-PD-1/ Anti-PD-L1 | 2/25 | 0.25 (0.06–1.06) | 1239/1143 | 3.87 (3.57–4.20) | 214/140 | 5.42 (4.37–6.73) | 46/182 | 0.85 (0.62–1.17) | 9/5 | 4.92 (1.75–13.82) |
| ICI combination vs. monotherapy | 17/27 | 8.43 (4.70–15.10) | 684/2382 | 3.98 (3.64–4.35) | 26/354 | 0.98 (0.67–1.44) | 31/228 | 1.94 (1.37–2.75) | 1/14 | 0.83 (0.11–6.25) |

Anti-CTLA-4 refers to any ICSR treated with ipilimumab. Anti-PD-1/PD-L1 refers to any ICSR treated with any of the following four drugs: nivolumab, pembrolizumab, atezolizumab, and durvalumab. ICI combination refers to any ICSR treated with anti-CTLA-4 (ipilimumab) in combination with any one or two of the anti-PD-1/PD-L1, or to any ICSR treated with anti-PD-1 in combination with anti-PD-L1. Comparisons between different drug regimens were performed using the Bonferroni adjustment method. ROR confidence intervals were calculated using $P=0.01$ to adjust. ROR: reported odds ratio; CI: confidence interval; ICI: immune checkpoint inhibitor; ADR: adverse drug reaction; Anti-CTLA-4: anti-cytotoxic T lymphocyte-associated antigen-4; ICSR: individual case safety report; Anti-PD-1: anti-programmed cell death protein 1; Anti-PD-L1: anti-programmed death-ligand 1.

gastrointestinal irAEs except for megacolon (enterocolitis 60.88% vs. 39.12%; gastrointestinal perforation 67.24% vs. 32.76%; intestinal obstruction 60.40% vs. 39.60%; duodenitis 62.79% vs. 37.21%; megacolon 40.00% vs. 60.00%). We also found that reported events of enterocolitis, duodenitis, gastrointestinal perforation, megacolon, and intestinal obstruction, associated with ICI treatment, were observed mainly in patients with lung cancer or malignant melanoma.

As shown in Table 4, reports of enterocolitis (1239 cases, 40.41%) and gastrointestinal perforation (214 cases, 56.32%) were the two most frequent ipilimumab-associated ADRs, while the most of intestinal obstruction cases (86 cases, 33.20%) were nivolumab-associated, and of duodenitis cases (16 cases, 36.36%) were ipilimumab plus nivolumab combination-associated. Megacolon was reported mainly under ipilimumab treatment (9 cases, 60.00%). In addition, there were a small number of reports of anti-PD-L1-associated gastrointestinal irAEs (87 cases of atezolizumab and 43 cases of durvalumab). We conducted a further analysis of follow-up reports on ICI-associated gastrointestinal irAEs. It was found that 1713 cases had the final outcomes reported, including "fatal," "not recovered/not resolved," and "recovered/resolved." Most patients in

the enterocolitis, intestinal obstruction, and duodenitis cases recovered or resolved after appropriate treatment, while most of the gastrointestinal perforation cases (46.61%) had fatal consequences. The number of recovery reports of ICI-associated enterocolitis (71.70%) was higher than that for ICI-associated gastrointestinal perforation, intestinal obstruction, duodenitis, and megacolon combined. Four megacolon cases reported final outcomes: the patient recovered in one case and did not recover in another case, while two cases had fatal consequences.

Additionally, we analyzed time to onset for ICI-associated gastrointestinal irAEs. We found that the time to onset of enterocolitis associated with anti-CTLA-4 and ICI combination treatment was earlier compared to that associated with anti-PD-1/PD-L1 monotherapy (anti-CTLA-4 (55.44±3.25) d, anti-PD-1/PD-L1 (119.50±5.15) d, and combination therapy (58.49±4.64) d), and the time to onset of enterocolitis was not significantly different between anti-CTLA-4 and ICI combination treatments (Fig. 1a). As shown in Fig. 1b, the time to onset of gastrointestinal perforation was not significantly different between anti-CTLA-4 and anti-PD-1/PD-L1 monotherapy (anti-CTLA-4 (58.08±6.45) d and anti-PD-1/PD-L1 (61.67±8.44) d, $P=0.7998$). Furthermore, the time to

**Table 3  Basic information of ICI-associated gastrointestinal ADR cases reported to VigiBase (from January 1, 2011 to March 6, 2019)**

| Basic information | Enterocolitis (*n*=3066) | Gastrointestinal perforation (*n*=379) | Intestinal obstruction (*n*=259) | Duodenitis (*n*=44) | Megacolon (*n*=15) |
|---|---|---|---|---|---|
| Year | | | | | |
| 2011 | 23 (0.75%) | 8 (2.11%) | 4 (1.54%) | 0 | 0 |
| 2012 | 84 (2.74%) | 28 (7.39%) | 9 (3.47%) | 0 | 3 (20.00%) |
| 2013 | 103 (3.36%) | 20 (5.28%) | 2 (0.77%) | 0 | 2 (13.33%) |
| 2014 | 233 (7.60%) | 49 (12.93%) | 10 (3.86%) | 2 (4.55%) | 0 |
| 2015 | 369 (12.04%) | 79 (20.84%) | 28 (10.81%) | 5 (11.36%) | 3 (20.00%) |
| 2016 | 425 (13.86%) | 45 (11.87%) | 30 (11.58%) | 7 (15.91%) | 1 (6.67%) |
| 2017 | 754 (24.59%) | 55 (14.51%) | 62 (23.94%) | 10 (22.73%) | 6 (40.00%) |
| 2018 | 934 (30.46%) | 88 (23.22%) | 98 (37.84%) | 15 (34.09%) | 0 |
| 2019 | 141 (4.60%) | 7 (1.85%) | 16 (6.18%) | 5 (11.36%) | 0 |
| Gender | | | | | |
| Female | 1080/2761 (39.12%) | 115/351 (32.76%) | 99/250 (39.60%) | 16/43 (37.21%) | 9/15 (60.00%) |
| Male | 1681/2761 (60.88%) | 236/351 (67.24%) | 151/250 (60.40%) | 27/43 (62.79%) | 6/15 (40.00%) |
| Age (year) | | | | | |
| 0–17 | 3/2173 (0.14%) | 0 | 0 | 0 | 0 |
| 18–44 | 218/2173 (10.03%) | 16/290 (5.52%) | 14/205 (6.83%) | 5/36 (13.89%) | 1/13 (7.69%) |
| 45–65 | 870/2173 (40.04%) | 117/290 (40.34%) | 109/205 (53.17%) | 16/36 (44.44%) | 6/13 (46.15%) |
| >65 | 1082/2173 (49.79%) | 157/290 (54.14%) | 82/205 (40.00%) | 15/36 (41.67%) | 6/13 (46.15%) |
| Region | | | | | |
| Africa | 3/3066 (0.10%) | 0 | 1/259 (0.39%) | 0 | 0 |
| Americas | 1292/3066 (42.14%) | 193/379 (50.92%) | 138/259 (53.28%) | 19/44 (43.18%) | 4/15 (26.67%) |
| Asia | 403/3066 (13.14%) | 65/379 (17.15%) | 61/259 (23.55%) | 9/44 (20.45%) | 4/15 (26.67%) |
| Europe | 1198/3066 (39.07%) | 109/379 (28.76%) | 51/259 (19.69%) | 15/44 (34.09%) | 5/15 (33.33%) |
| Oceania | 170/3066 (5.54%) | 12/379 (3.17%) | 8/259 (3.09%) | 1/44 (2.27%) | 2/15 (13.33%) |
| Notifier[a] | | | | | |
| Notifier1 | 2391/2912 (82.11%) | 289/366 (78.96%) | 205/248 (82.66%) | 40/42 (95.24%) | 9/14 (64.29%) |
| Notifier2 | 521/2912 (17.89%) | 77/366 (21.04%) | 43/248 (17.34%) | 2/42 (4.76%) | 5/14 (35.71%) |
| Indication[b] | | | | | |
| Malignant melanoma | 1533/2350 (65.23%) | 168/277 (60.65%) | 67/180 (37.22%) | 14/34 (41.18%) | 8/10 (80.00%) |
| Lung cancer | 608/2350 (25.87%) | 78/277 (28.16%) | 53/180 (29.44%) | 11/34 (32.35%) | 2/10 (20.00%) |
| Kidney cancer | 83/2350 (3.53%) | 4/277 (1.44%) | 9/180 (5.00%) | 4/34 (11.76%) | 0 |
| Bladder cancer | 44/2350 (1.87%) | 10/277 (3.61%) | 29/180 (16.11%) | 1/34 (2.94%) | 0 |
| Gastric cancer | 12/2350 (0.51%) | 8/277 (2.89%) | 8/180 (4.44%) | 0 | 0 |
| Prostate cancer | 20/2350 (0.85%) | 3/277 (1.08%) | 2/180 (1.11%) | 0 | 0 |
| Colon cancer | 13/2350 (0.55%) | 1/277 (0.36%) | 8/180 (4.44%) | 2/34 (5.88%) | 0 |

Data are expressed as number (percentage). [a] Notifier1 refers to physician, pharmacist, or other healthcare professional; Notifier2 refers to lawyer or consumer. [b] Indication refers to the primary tumors treated by ICIs. ICI: immune checkpoint inhibitor; ADR: adverse drug reaction.

onset of intestinal obstruction, as shown in Fig. 1c, was not significantly different between anti-CTLA-4 and anti-PD-1/PD-L1 monotherapy (anti-CTLA-4 (45.40±9.89) d and anti-PD-1/PD-L1 (91.60±14.45) d, $P$=0.1760).

Early clinical outcomes with ICI therapies have indicated that ICIs can improve patient survival;

therefore, such therapies have been widely used to treat many malignant tumors, such as malignant melanoma (Wolchok et al., 2017; Afzal et al., 2018), renal cell carcinoma (Derosa et al., 2018), lung cancer (Doroshow et al., 2019; Madden and Kasler, 2019), and urothelial cancer (Rodriguez-Vida et al., 2018). Meanwhile, ICIs can also disturb the maintenance of patient

**Table 4  Comparison of ICI regimen for ICI-associated digestive system ADRs reported to VigiBase (from January 1, 2011 to March 6, 2019)**

| ICI regimen/outcome | Enterocolitis (*n*=3066) | Gastrointestinal perforation (*n*=380) | Intestinal obstruction (*n*=259) | Duodenitis (*n*=44) | Megacolon (*n*=15) |
|---|---|---|---|---|---|
| Drug group | | | | | |
| Ipilimumab | 1239 (40.41%) | 214 (56.32%) | 46 (17.76%) | 2 (4.55%) | 9 (60.00%) |
| Nivolumab | 660 (21.53%) | 67 (17.63%) | 86 (33.20%) | 11 (25.00%) | 5 (33.33%) |
| Pembrolizumab | 406 (13.24%) | 60 (15.79%) | 58 (22.39%) | 12 (27.27%) | 0 |
| Atezolizumab | 46 (1.50%) | 10 (2.63%) | 30 (11.58%) | 1 (2.27%) | 0 |
| Durvalumab | 31 (1.01%) | 3 (0.79%) | 8 (3.09%) | 1 (2.27%) | 0 |
| Ipilimumab plus nivolumab | 656 (21.40%) | 25 (6.58) | 29 (11.20%) | 16 (36.36%) | 1 (6.67%) |
| Ipilimumab plus pembrolizumab | 19 (0.62%) | 1 (0.26%) | 1 (0.39%) | 1 (2.27%) | 0 |
| Ipilimumab plus atezolizumab | 1 (0.03%) | 0 | 0 | 0 | 0 |
| Pembrolizumab plus nivolumab | 1 (0.03%) | 0 | 0 | 0 | 0 |
| Ipilimumab plus pembrolizumab plus nivolumab | 7 (0.23%) | 0 | 1 (0.39%) | 0 | 0 |
| Drug doses | | | | | |
| Monotherapy with ipilimumab | | | | | |
| 3 mg/kg | 392/742 (52.83%) | 61/136 (44.85%) | 7/26 (26.92%) | 0 | 2/7 (28.57%) |
| 10 mg/kg | 120/742 (16.17%) | 22/136 (16.18%) | 9/26 (34.62%) | 1/1 (100.00%) | 1/7 (14.29%) |
| <500 mg | 156/742 (21.02%) | 43/136 (31.62%) | 3/26 (11.54%) | 0 | 4/7 (57.14%) |
| 500–1000 mg | 47/742 (6.33%) | 7/136 (5.15%) | 4/26 (15.38%) | 0 | 0 |
| >1000 mg | 27/742 (3.64%) | 3/136 (2.21%) | 3/26 (11.54%) | 0 | 0 |
| Monotherapy with nivolumab | | | | | |
| 1–2 mg/kg | 13/408 (3.19%) | 5/53 (9.43%) | 5/69 (7.25%) | 0 | 0 |
| ≥3 mg/kg | 246/408 (60.29%) | 26/53 (49.06%) | 38/69 (55.07%) | 4/8 (50.00%) | 0 |
| ≤240 mg | 112/408 (27.45%) | 19/53 (35.85%) | 21/69 (30.43%) | 4/8 (50.00%) | 3/3 (100.00%) |
| 240–480 mg | 37/408 (9.07%) | 3/53 (5.66%) | 5/69 (7.25%) | 0 | 0 |
| Monotherapy with pembrolizumab | | | | | |
| 2 mg/kg | 61/247 (24.70%) | 4/45 (8.89%) | 7/44 (15.91%) | 1/9 (11.11%) | 0 |
| ≤200 mg | 186/247 (75.30%) | 41/45 (91.11%) | 37/44 (84.09%) | 8/9 (88.89%) | 0 |
| Combination therapy | | | | | |
| Ipilimumab (3 mg/kg) plus nivolumab (1–2 mg/kg) | 150/367 (40.87%) | 6/9 (66.67%) | 8/17 (47.06%) | 2/7 (28.57%) | 0 |
| Ipilimumab (3 mg/kg) plus nivolumab (≥3 mg/kg) | 86/367 (23.43%) | 2/9 (22.22%) | 5/17 (29.41%) | 2/7 (28.57%) | 0 |
| Ipilimumab (≤500 mg) plus nivolumab (≤240 mg) | 124/367 (33.78%) | 1/9 (11.11%) | 3/17 (17.65%) | 2/7 (28.57%) | 0 |
| Ipilimumab (≤500 mg) plus nivolumab (>240 mg) | 7/367 (1.91%) | 0 | 1/17 (5.88%) | 1/7 (14.29%) | 0 |
| Outcome | | | | | |
| Recovered/resolved | 960/1339 (71.70%) | 82/221 (37.10%) | 73/134 (54.48%) | 8/15 (53.33%) | 1/4 (25.00%) |
| Not recovered/not resolved | 252/1339 (18.82%) | 36/221 (16.29%) | 35/134 (26.12%) | 7/15 (46.67%) | 1/4 (25.00%) |
| Fatal | 127/1339 (9.48%) | 103/221 (46.61%) | 26/134 (19.40%) | 0 | 2/4 (50.00%) |

Data are expressed as number (percentage). Drug doses are expressed in VigiBase in two forms: mg/kg and total dose. Drug doses are grouped according to dosage and administration recommended in the drug prescription information. Recommended dosage for nivolumab: 3 mg/kg every 2 weeks, 240 mg every 2 weeks, or 480 mg every 4 weeks for different cancers. Recommended dosage for pembrolizumab: 200 mg every 3 weeks, 2 mg/kg every 3 weeks for different cancers. Recommended dosage for ipilimumab: 3 mg/kg every 3 weeks or 10 mg/kg every 3 weeks for different cancers. Recommended dosage for combined ICI therapy: 3 mg/kg nivolumab followed by 1 mg/kg Ipilimumab on the same day every 3 weeks for 4 doses, and then 240 mg nivolumab every 2 weeks or 480 mg every 4 weeks. ICI: immune checkpoint inhibitor; ADR: adverse drug reaction.

immune homeostasis, as they suppress coinhibitory molecules between T-cells and other immune cells, which mediate the tumor killing process (Sangro et al., 2020). In addition, ICIs have side effects and toxicities in the process of tumor therapy, commonly referred to as irAEs. Therapies involving ICIs, such
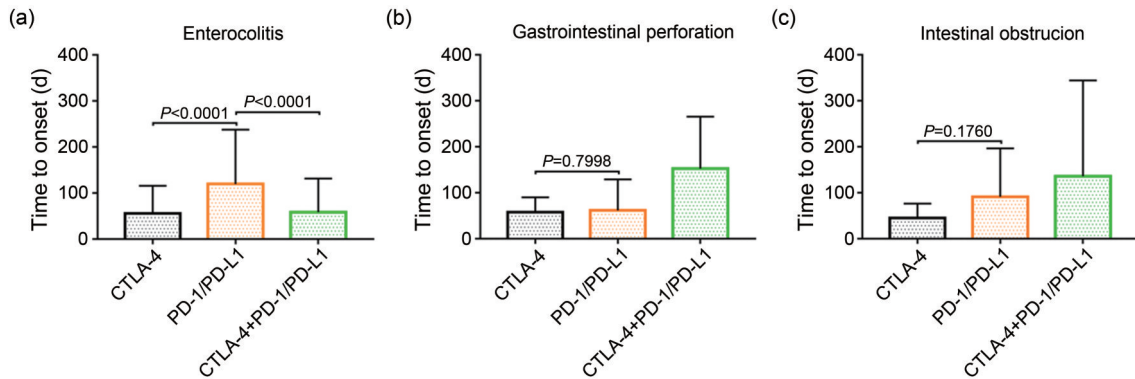
**Fig. 1 Time to onset of ICI-associated gastrointestinal irAEs reported to VigiBase (from January 1, 2011 to March 6, 2019). (a) ICI-associated enterocolitis (*n*=1145); (b) ICI-associated gastrointestinal perforation (*n*=113); (c) ICI-associated intestinal obstruction (*n*=86). Date are expressed as mean±standard deviation. ICI: immune checkpoint inhibitor; irAE: immune-related adverse event; CTLA-4: cytotoxic T lymphocyte-associated antigen-4; PD-1: programmed cell death protein 1; PD-L1: programmed death-ligand 1.**

as anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibodies, have been proved to effectively treat metastatic malignant melanoma and lung cancer (Afzal et al., 2018; Madden and Kasler, 2019). However, they cause gastrointestinal irAEs, including enteritis, enterocolitis, microscopic colitis, and gastritis (Tandon et al., 2018; de Malet et al., 2019). Additionally, certain severe or fatal irAEs were indicated in a previous study, including gastrointestinal perforation and intestinal obstruction associated with ICI therapy (Abu-Sbeih and Wang, 2020).

Thus far, the present study includes the largest and most extensive database of the clinical characteristics of ICI-associated gastrointestinal irAEs, acquired by the analysis of individual case safety reports from the WHO pharmacovigilance database. Consistently with previous studies, our results indicate that ICI-associated enterocolitis, duodenitis, gastrointestinal perforation, and intestinal obstruction are dramatically increased, and the associated risk posed by ICI combination treatment may be higher than that by ICI monotherapy. In addition, 15 cases of the rarely reported ICI-associated megacolon are included herein, which is infrequent in the clinical setting.

Previous research has shown that gastrointestinal irAEs are closely related to anti-CTLA-4 or anti-PD-1/PD-L1 therapy (Xu et al., 2018). It was observed in the present study that, compared to anti-PD-1/PD-L1 therapy, patients receiving anti-CTLA-4 therapy may have a higher risk of developing enterocolitis (ROR 3.87 (95% CI 3.57–4.20)), gastrointestinal perforation (ROR 5.42 (95% CI 4.37–6.73)), and megacolon

(ROR 4.92 (95% CI 1.75–13.82)). The combined ICI therapy of anti-CTLA-4 and anti-PD-1/PD-L1 has been suggested as highly efficient in treating malignant tumors (Yuan et al., 2019). Combined ICI therapy, however, may result in more severe immune-related ADRs (Gu et al., 2019). Our study indicates that, in agreement with previous research, patients receiving combined ICI therapy may have a higher risk of developing gastrointestinal irAEs compared to ICI monotherapy, including duodenitis (ROR 8.43 (95% CI 4.70–15.10)), enterocolitis (ROR 3.98 (95% CI 3.64–4.35)), and intestinal obstruction (ROR 1.94 (95% CI 1.37–2.75)).

In the current study, it is demonstrated that most of the gastrointestinal irAEs occurred in patients with melanoma and lung cancer, with more cases in males than females, except for megacolon. Most of the gastrointestinal irAEs occurred within six weeks, and immune-related enterocolitis in ICI combination therapy manifested earlier than those in anti-PD-1/PD-L1 treatment, which was consistent with previous research (Wang et al., 2018). Additionally, it is indicated that anti-CTLA-4 therapy had a dramatically earlier time to onset of enterocolitis than anti-PD-1/PD-L1 therapy, but no significant difference between the onset time of gastrointestinal perforation and intestinal obstruction was observed.

We also analyzed cases of ICI-associated megacolon, which were very rare in the clinical setting, and had only been recorded as case reports in previous research (Cho and Choi, 2020). Fifteen megacolon cases are featured herein, most of which involved

patients with lung cancer or malignant melanoma, and occurred in anti-CTLA-4 therapy (ipilimumab). Interestingly, ICI-associated megacolon was mainly reported from Europe but not Americas. The possible reason is that megacolon is commonly named grade 4 colitis in Americas, and has been described similarly in previous research (Wang et al., 2017). Clinically toxic megacolon requires rapid multidisciplinary assessment, and individual treatments need to be developed based on the underlying causes (Leppkes et al., 2015). If the cause is likely an infection or inflammation, perioperative morbidity and mortality can be reduced by conservative treatment. The effect of treatment needs to be re-evaluated after 72 h and after 7 d to further ensure patient safety. Thus, the toxic megacolon adverse event needs to be closely monitored during treatment by ICIs, especially by anti-CTLA-4. The risk factors of ICI-related megacolon are not yet clear, and hence they need to be investigated in future clinical trials. It was observed in our study that most patients of the enterocolitis, intestinal obstruction, and duodenitis cases were recovered or resolved after precise treatment, while most of the gastrointestinal perforation cases had fatal consequences. The number of recovery reports for ICI-associated enterocolitis was found to be larger compared to ICI-associated gastrointestinal perforation, intestinal obstruction, duodenitis, and megacolon combined. Therefore, ICI-related enterocolitis is treated conservatively with most patients capable of recovery, and there is usually no need to discontinue the drug (Zhang ML et al., 2020). Additionally, one of the most common drug side effects, esophagitis, was absent in gastrointestinal irAEs of our comprehensive assessment, demonstrating that the esophagus is likely not involved in gastrointestinal irAEs associated with ICIs therapy. Thus, it seems fortunate that the esophagus, an integral section of the gastrointestinal tract, appears to be spared in the procession of ICI therapy.

The VigiBase database has some limitations, which are also important to mention for the scope of this study. First, detailed information on clinical data, which may help to better evaluate patient responses related to irAEs, was missing from the VigiBase database. Second, when a report involved several drugs and/or several adverse events, we treated the adverse drug event pair as the basic unit rather than the reported event; the results of this pharmacovigilance analysis may thus be biased. Third, case reports of gastrointestinal disease associated with ICI therapies may not have been submitted to the VigiBase database, leading to a further bias in the database. Finally, the IC value does not indicate a causal relationship between ICIs and irAEs, but shows the related dependence of the ICI drugs and adverse event reports. In contrast to existing studies, however, the intensity of the large number of records at the national level supports our research aimed at quantifying the potential risks, but the true risks of these adverse events should be determined in prospective studies. Hence, a complete understanding of the limitations of VigiBase can help us better analyze ADRs, and produce useful clinical research hypotheses.

The present study shows that the number of gastrointestinal irAEs, including enterocolitis, gastrointestinal perforation, duodenitis, and intestinal obstruction cases, has been rising dramatically, with several reported events of megacolon, which is rare in the clinical setting. Most gastrointestinal irAEs occur early during the course of ICI therapy. Consequently, it is important to raise an awareness of gastrointestinal irAEs associated with treatment by the ICI therapy of some advanced malignant tumors.

## Author contributions

The study design was created by Xiahong LIN. Data collection and analysis was performed by Sifu HUANG, Xuefeng BAI, and Kainan ZHENG. Taiyong FANG and Yanta GUO conducted the literature search. Sifu HUANG and Xuefeng BAI wrote and edited the manuscript, and they contributed equally to this study. Xiahong LIN, Sifu HUANG, and Xuefeng BAI were responsible for the final modification of the manuscript. All authors have read and approved the final version of the manuscript.

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