

Immune checkpoint inhibitor adverse events in colorectal cancer: a disproportionality analysis of FAERS with cross-database validation in JADER

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Abstract

Background: Colorectal cancer (CRC) background symptomatology may confound immune checkpoint inhibitor (ICI) safety signals, but no colorectal cancer-specific pharmacovigilance analysis exists. The aim was to characterize adverse-event reporting for pembrolizumab and nivolumab in CRC using the FDA Adverse Event Reporting System (FAERS) with a disease-matched comparator, and to validate the findings externally in an independent national database.

Methods: This disproportionality analysis queried FAERS via the openFDA interface for CRC-indication reports with pembrolizumab or nivolumab as primary suspect (PS) drug. Ten predefined immune-related adverse events (irAEs) were evaluated with the proportional reporting ratio, reporting odds ratio (ROR), and information component, requiring concordance of all three. Comparators were all other FAERS reports (primary) and CRC non-ICI reports (sensitivity); all remaining preferred terms were screened. External validation used the Japanese Adverse Drug Event Report database (JADER; 587 identically constructed CRC-ICI suspected-drug reports) with prespecified replication criteria, plus drug-level corroboration in VigiAccess. No case-by-case analysis was performed.

Results: The FAERS cohort comprised 2,400 PS reports (August 2014–March 2026). Seven confirmed signals were identified: myocarditis (ROR 31.16, 95% CI 23.33–41.61), colitis (17.35, 14.08–21.37), hypothyroidism (10.54, 7.71–14.41), pneumonitis (9.59, 7.73–11.89), hyperthyroidism (8.60, 5.26–14.06), hepatitis (5.25, 4.14–6.66), and nephritis (4.62, 2.62–8.15). Diarrhea and rash were weakly positive against the full-database comparator but reversed against the CRC non-ICI comparator (0.36, 0.74), indicating indication confounding. Six of the seven confirmed signals replicated in JADER under both comparators; nephritis was not assessable (no mapped cases), and the diarrhea reversal replicated qualitatively. JADER high-frequency endocrine events corroborated the exploratory adrenal, pituitary, and type 1 diabetes candidates.

Conclusions: ICI toxicity reporting in CRC follows an organ-prioritized, cross-database-validated pattern warranting targeted monitoring; disease-matched comparators are necessary in tumor-specific pharmacovigilance to avoid signal misattribution.

1 Background

Colorectal cancer (CRC) is a leading cause of cancer incidence and mortality worldwide (1.90 million new cases and over 900,000 deaths in 2022) [1]. Immune checkpoint inhibitors (ICIs) have reshaped metastatic CRC treatment, particularly in microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) tumors: pembrolizumab prolonged progression-free survival in KEYNOTE-177 [2] and nivolumab produced durable responses in CheckMate-142 [3], establishing both as standard therapy for MSI-H/dMMR CRC. ICI benefit is coupled with immune-related adverse events (irAEs), toxicities arising from dysregulated immune activation against healthy tissues [4], differing from chemotherapy toxicities in latency, unpredictability, and potential chronicity [5, 6]. Most are low-grade, but fatality rates reach 0.36% for anti-PD-1 monotherapy and 1.23% for combination blockade, with myocarditis carrying the highest risk [7]; guidelines mandate early recognition, graded immunosuppression, and multidisciplinary surveillance [8, 9]. Randomized trials cannot fully characterize rare or late-onset toxicities; disproportionality analysis of the US FDA Adverse Event Reporting System (FAERS) is established for population-level signal detection [10, 11]. Pan-cancer FAERS analyses have broadly characterized ICI toxicity [12, 13], with updated comprehensive surveys confirming and extending these patterns [14, 15], and organ-specific pharmacovigilance studies have examined individual toxicities such as cardiovascular events [16]. Tumor-specific analyses have recently emerged in non-small cell lung cancer [17], small-cell lung cancer [18], melanoma [19], renal cell carcinoma [20], esophageal cancer [21], and bladder cancer [22]. A small number of these studies adopted disease-matched referents—a chemotherapy-only referent population in small-cell lung cancer [18] and a tumor-wide reporting background in melanoma [19]—and a confounding-aware design using tumor-type-specific, ICI-naïve referents was recently demonstrated for endocrine malignancies [23]. Nevertheless, no CRC-specific ICI signal analysis had been reported as of September 2026. This gap matters because the CRC background symptom profile (e.g., diarrhea or rash from cytotoxic or targeted therapy) may confound signals observed in pan-cancer analyses.

This study conducted a CRC-specific pharmacovigilance analysis of pembrolizumab- and nivolumab-related adverse events using FAERS, aiming to detect signals for 10 predefined irAEs under a dual-control design (all other database reports; CRC non-ICI comparator) using three concordant algorithms, and to generate hypotheses through exploratory screening of all remaining preferred terms (PTs).

2 Methods

2.1 Data source

This retrospective disproportionality analysis used the US FDA Adverse Event Reporting System (FAERS), a public spontaneous reporting database for post-marketing safety signal detection [10]. Data were obtained through the openFDA application programming interface drug/event endpoint [24]. Reports received between August 13, 2014, and March 31, 2026, were included (database: 20,328,575 reports).

2.2 Drugs and indications

Pembrolizumab and nivolumab were selected as the only two ICIs approved for MSI-H/dMMR metastatic CRC [2, 3]. Each drug was queried by generic and trade names (pembrolizumab + KEYTRUDA, Merck & Co., Inc., Rahway, NJ, USA; nivolumab + OPDIVO, Bristol-Myers Squibb Company, Princeton, NJ, USA). Five indication terms ("colorectal cancer," "colon cancer," "rectal cancer," "colorectal adenocarcinoma," "rectal adenocarcinoma") in the drug indication field cross-combined with the 2 drugs into 10 query groups, returning 2,674 raw reports (Fig. 1); retrieved reports were then matched against 22 extended indication terms (variants; Table S3).

2.3 Cohort definition

Duplicate versions were removed per the FDA-recommended procedure: grouping by safetyreportid, retaining the most recent receivedate, and resolving ties by the highest safetyreportversion; this removed 52 duplicates, leaving 2,622 unique reports. Only reports whose ICI record contained a CRC indication term were retained (n = 2,497); 125 reports with blank (n = 57), unknown (n = 45), or other-disease (n = 23) indications were conservatively excluded. The cohort was restricted to primary suspect (PS) reports [22], yielding 2,400 reports (97 non-PS excluded). Ages were harmonized per ICH E2B(R2) unit codes (800 = decade, 801 = year, 802 = month, 803 = week, 804 = day, 805 = hour) [24]; implausible values (> 110 or < 0 years) were set to missing.

2.4 Event definitions

Ten immune-related adverse events (irAEs) were predefined across 7 System Organ Classes (SOCs): colitis, diarrhea, rash, pruritus, hypothyroidism, hyperthyroidism, pneumonitis, hepatitis, myocarditis, and nephritis, based on the ASCO and ESMO management guidelines [8, 9] and the published single-malignancy FAERS template, which predefines a fixed panel to control multiple testing [22]. Each irAE was mapped to validated MedDRA preferred term (PT) lists (e.g., colitis: "Colitis," "Immune-mediated enterocolitis," "Enterocolitis," and "Autoimmune colitis"; complete mapping in Table S2), and cases were identified by PT matching in each report's reaction field.

2.5 Disproportionality analysis

Two comparators were defined. The primary comparator comprised all other reports (N = 20,328,575; comparator count = N - 2,400). The sensitivity comparator comprised CRC reports not mentioning any ICI (n = 100,520), non-overlapping with the case set by construction; it tests whether signals persist against a non-ICI CRC therapeutic background. Background PT counts were obtained through openFDA count queries on the exact PT sub-field (.exact) to avoid token-matching inflation. For each irAE, a 2x2 table was constructed: a = case reports containing the PT; b = case reports not containing it; primary comparator, c = background count - a, d = (20,328,575 - 2,400) - c; sensitivity comparator, c = CRC non-ICI count, d = 100,520 - c.

$PRR = [a/(a + b)] / [c/(c + d)]$, 95% confidence interval (CI) = $\exp\{\ln(PRR) \pm 1.96 \times \sqrt{1/a + 1/c - 1/(a + b) - 1/(c + d)}\}$

$ROR = (a \times d) / (b \times c)$, 95% CI = $\exp\{\ln(ROR) \pm 1.96 \times \sqrt{1/a + 1/b + 1/c + 1/d}\}$

$IC = \log 2[(a + 0.5)/(E + 0.5)]$, where $E = (a + b)(a + c)/N_{total}$ is the expected count under the independence assumption; IC025 is the lower bound of the 95% CI for IC, $IC025 = IC - 2 \times (1/\ln 2) \times \sqrt{1/(a + 0.5) + 1/(E + 0.5)}$

Three disproportionality algorithms were employed: the proportional reporting ratio (PRR) [25], the reporting odds ratio (ROR) [26], and the information component (IC) from the Bayesian Confidence Propagation Neural Network [27]. For PRR and ROR, the Haldane–Anscombe 0.5 correction was applied only when any cell count was zero; for IC, + 0.5 shrinkage was applied in all calculations. The IC formulation is the standard operational approximation of the full BCPNN posterior [27]; a post hoc recalculation using the exact Bayesian posterior variance (digamma/trigamma functions; priors $\alpha_1 = 0.5$, $\alpha_2 = 1.5$, $\beta = \gamma = 1$) yielded uniformly higher IC025 values across all 58 irAE–comparator combinations and changed no signal classification; the reported intervals are therefore conservative. A confirmed signal required simultaneous satisfaction of $a \geq 3$, $PRR \geq 2$, $PRR025 > 1$, $ROR025 > 1$, and $IC025 > 0$ (concordance across all three algorithms) [11, 22]; associations meeting criteria only partially were classified as hypothesis-generating. The term “confirmed signal” is used in the operational pharmacovigilance sense—a statistical determination meeting prespecified concordance criteria—and does not imply causality [10].

2.6 Exploratory screening

An exploratory screening was prespecified: using the same signal criteria, all other PTs with at least 3 cases in the cohort were tested against the primary comparator. Administrative, product-quality, and procedural PTs and the non-informative term “Death” were excluded a priori; therapeutic-outcome terms meeting the criteria (e.g., “Therapy partial responder”) were retained in the results (Table S1) but excluded from biological interpretation. Pseudo-signal adjudication followed a prespecified rule: PTs directly attributable to the underlying malignancy or its management (e.g., obstruction, perforation, tumor-marker changes) and non-specific or efficacy terms were excluded from biological interpretation; PTs with literature support for an immune-mediated mechanism were retained as candidates. Screening p-values (two-sided Fisher exact tests) underwent Benjamini–Hochberg false-discovery-rate correction across all tested PTs. All screening associations were treated as hypothesis-generating. The 10 predefined irAEs were additionally analyzed against the CRC non-ICI comparator as a sensitivity analysis.

2.7 Reporting and software

This study followed the READUS-PV reporting standard [28]. Analyses used Python 3.12 (pandas; matplotlib); the cross-database forest plot (Fig. 3) was generated with R 4.6.1 (packages: ggplot2, dplyr, tidyr, forcats, scales). All query strings, parameters, and code are reproducible per the above specifications.

Table 3

Disproportionality analysis of predefined irAEs: primary analysis (FAERS full-database comparator) and sensitivity analysis (CRC non-ICI comparator)

irAE	SOC	a	Primary ROR (95% CI)	Primary PRR (95% CI)	Primary IC (IC025)	Primary Assessment	Sensitivity ROR (95% CI)	Sensitivity Assessment
Colitis	GI	92	17.35 (14.08–21.37)	16.72 (13.68–20.43)	3.94 (2.73)	Confirmed	5.33 (4.28–6.65)	Confirmed
Diarrhea	GI	103	1.37 (1.13–1.67)	1.36 (1.12–1.64)	0.44 (0.00)	Hypothesis-generating	0.36 (0.30–0.44)	None
Rash	Skin	112	1.48 (1.22–1.79)	1.46 (1.21–1.74)	0.54 (0.11)	Hypothesis-generating	0.74 (0.61–0.89)	None
Pruritus	Skin	23	0.52 (0.34–0.78)	0.52 (0.35–0.78)	–0.92 (–1.66)	None	0.57 (0.38–0.87)	None
Hypothyroidism	Endocrine	40	10.54 (7.71–14.41)	10.38 (7.63–14.12)	3.22 (1.76)	Confirmed	15.06 (10.48–21.65)	Confirmed
Hyperthyroidism	Endocrine	16	8.60 (5.26–14.06)	8.55 (5.24–13.93)	2.80 (0.79)	Confirmed	30.66 (16.08–58.45)	Confirmed
Pneumonitis	Respiratory	86	9.59 (7.73–11.89)	9.28 (7.54–11.42)	3.15 (2.17)	Confirmed	2.37 (1.90–2.96)	Confirmed
Hepatitis	Hepatobiliary	70	5.25 (4.14–6.66)	5.13 (4.07–6.46)	2.32 (1.48)	Confirmed	3.20 (2.50–4.09)	Confirmed
Myocarditis	Cardiac	47	31.16 (23.33–41.61)	30.57 (23.02–40.59)	4.54 (2.48)	Confirmed	23.60 (16.49–33.78)	Confirmed
Nephritis	Renal	12	4.62 (2.62–8.15)	4.60 (2.62–8.09)	2.01 (0.18)	Confirmed	7.65 (4.13–14.17)	Confirmed

Abbreviations: ROR, reporting odds ratio; PRR, proportional reporting ratio; IC, information component; IC025, lower bound of the 95% CI for IC; CI, confidence interval; a, case count. Bold rows indicate 7 confirmed signals. A confirmed signal was defined as a ≥ 3 with all three algorithms positive (PRR ≥ 2 and PRR025 > 1 , ROR025 > 1 , IC025 > 0); otherwise classified as hypothesis-generating or absent.

Table 4
Cross-database concordance of predefined irAE signals: FAERS (n = 2,400) versus JADER (n = 587)

irAE	FAERS ROR (95% CI)	FAERS ROR (95% CI)	JADER ROR (95% CI)	JADER ROR (95% CI)	Verdict
	full-database	CRC non-ICI	full-database	CRC non-ICI	
Colitis	17.35 (14.08–21.37)	5.33 (4.28–6.65)	15.09 (11.59–19.65)	11.98 (8.84–16.24)	Replicated
Hypothyroidism	10.54 (7.71–14.41)	15.06 (10.48–21.65)	11.43 (8.59–15.21)	15.84 (11.24–22.32)	Replicated
Hyperthyroidism	8.60 (5.26–14.06)	30.66 (16.08–58.45)	10.56 (6.60–16.91)	136.11 (45.92–403.46)	Replicated
Pneumonitis	9.59 (7.73–11.89)	2.37 (1.90–2.96)	2.84 (2.23–3.62)	3.01 (2.34–3.87)	Replicated
Hepatitis	5.25 (4.14–6.66)	3.20 (2.50–4.09)	3.13 (2.27–4.32)	6.42 (4.52–9.11)	Replicated
Myocarditis	31.16 (23.33–41.61)	23.60 (16.49–33.78)	9.28 (5.64–15.27)	6.67 (3.86–11.54)	Replicated
Nephritis	4.62 (2.62–8.15)	7.65 (4.13–14.17)	NE (0 cases)	NE (0 cases)	Not assessable
Diarrhea	1.37 (1.13–1.67)	0.36 (0.30–0.44)	1.74 (1.02–2.96)	0.82 (0.48–1.40)	Reversal replicated (qualitative)
Rash	1.48 (1.22–1.79)	0.74 (0.61–0.89)	1.94 (1.24–3.03)	4.50 (2.79–7.25)	Divergent (Section 4.2)
Pruritus	0.52 (0.34–0.78)	0.57 (0.38–0.87)	1.20 (0.39–3.74)	2.00 (0.62–6.47)	Null in both databases
Abbreviations: ROR, reporting odds ratio; CI, confidence interval; NE, not estimable (no mapped preferred-term cases in the JADER cohort); CRC, colorectal cancer; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event. Replication was prespecified as a direction-consistent estimate with ROR ₀₂₅ > 1 under the full-database comparator. JADER estimates use the main preferred-term mapping; excluding uncertain-confidence mappings did not change any verdict. Event labels in the text and tables use US spelling; figure row labels and mapped MedDRA/J preferred terms retain the original MedDRA spelling (e.g., Diarrhoea).					

2.8 External validation in JADER and VigAccess

External validation used the Japanese Adverse Drug Event Report database (JADER), a national spontaneous reporting system maintained by the Pharmaceuticals and Medical Devices Agency (PMDA) [29]. The complete public dataset (version pmdacasereport202608; 1,049,684 unique reports, April 2004–March 2026) was downloaded from the PMDA portal on 13 September 2026 and analysed following published guidance for JADER research [30]. JADER comprises four relational tables (demographics, drugs, reactions, and medical histories); adverse events are coded as Medical Dictionary for Regulatory Activities/Japanese (MedDRA/J) preferred terms (PTs).

The validation cohort was constructed with rules identical to the FAERS pipeline: reports in which pembrolizumab or nivolumab (identified by generic or brand name) was the suspected drug; a colorectal cancer (CRC) indication identified from Japanese indication terms (colon, rectal, or large-intestine carcinoma; phrases explicitly denoting non-CRC primaries excluded); report-level deduplication retaining the latest version. Reports were included from 2018 Q4—the quarter of the first Japanese approval of pembrolizumab for microsatellite instability–high solid tumours, which first made immune checkpoint inhibitor treatment of CRC routine clinical practice in Japan—through 2026 Q1 (the data lock of the database version used). All 293 verbatim indication strings in the candidate set were manually adjudicated (Data File S3); 13 reports of

non-CRC primaries (e.g., anorectal melanoma, uterine, small-intestinal, and neuroendocrine malignancies, and one text-matching artefact) were excluded, yielding 587 reports (pembrolizumab 326; nivolumab 261).

All 316 unique PTs recorded in the validation cohort were enumerated and mapped to the 10 predefined immune-related adverse event (irAE) groups before analysis; mapping confidence was graded (exact MedDRA/J equivalent, best semantic match, or uncertain), and a sensitivity analysis excluded uncertain mappings (Supplementary Note S1; Data File S2). Disproportionality was quantified with the same three algorithms and dual comparators: all other JADER reports (n = 1,049,097) and a JADER-internal CRC non-ICI comparator (n = 17,214; CRC-indication reports without ICI exposure in the same window). Prespecified replication required a direction-consistent estimate with the lower 95% confidence bound of the reporting odds ratio (ROR) above 1 under the full-database comparator. Drug-level corroboration used VigAccess (WHO-Uppsala Monitoring Centre) [31], queried on 13 September 2026, which provides aggregated system-organ-class counts by active ingredient.

3 Results

3.1 Cohort characteristics

The case selection flow is shown in Fig. 1: of 2,674 raw reports, 52 duplicates were removed (2,622 unique reports); restriction to CRC indication retained 2,497; after excluding 125 unmatched indications (57 blank, 45 unknown, 23 other-disease) and 97 non-PS reports, the cohort comprised 2,400 ICI-CRC PS reports. Baseline characteristics are in Table 1.

Table 1 Characteristics of 2,400 ICI-CRC primary suspect reports		
ICI-CRC cohort	irAE PT present	irAE PT absent
	a	b
Comparator reports	c	d

Category	Variable	n (%)
Total	Reports	2,400 (100.0%)
ICI	Nivolumab	1,242 (51.7%)
ICI	Pembrolizumab	1,143 (47.6%)
ICI	Nivolumab + Pembrolizumab	15 (0.6%)
Sex	Male	1,269 (52.9%)
Sex	Female	975 (40.6%)
Sex	Unknown	156 (6.5%)
Age	Median (IQR), years (valid n = 1,850)	62 (51–72)
Age group	< 65 years	1,044 (43.5%)
Age group	≥ 65 years	806 (33.6%)
Age group	Unknown	550 (22.9%)
Region	United States	1,116 (46.5%)
Region	Japan	316 (13.2%)
Region	France	125 (5.2%)
Region	Other countries/regions	720 (30.0%)
Region	Missing	123 (5.1%)
Seriousness	Serious	2,083 (86.8%)
Seriousness	Non-serious/Unknown	317 (13.2%)
Outcome	Death	583 (24.3%)
Outcome	Hospitalization	1,072 (44.7%)
Outcome	Life-threatening	169 (7.0%)
Outcome	Disability	28 (1.2%)
Outcome	Other serious	1,610 (67.1%)
Reporter	Other health professional	909 (37.9%)
Reporter	Physician	848 (35.3%)
Reporter	Consumer	477 (19.9%)
Reporter	Pharmacist	159 (6.6%)
Reporter	Unknown	5 (0.2%)
Reporter	Lawyer	2 (0.1%)
Concomitant drugs	Other antineoplastic agents (heuristic)	322 (13.4%)
Concomitant drugs	None/Unknown	2,078 (86.6%)
Abbreviations: ICI, immune checkpoint inhibitor; CRC, colorectal cancer; IQR, interquartile range. Outcome categories are mutually non-exclusive.		

Nivolumab and pembrolizumab accounted for comparable proportions (51.7% and 47.6%); 15 reports (0.6%) mentioned both (Table 1). Males comprised 52.9%; median age was 62 years (IQR 51–72; 1,850 reports with valid age). Most reports were serious (86.8%), with death in 24.3%. Physicians and other health professionals filed 35.3% and 37.9%. The United States contributed most (1,116; 46.5%), followed by Japan (316; 13.2%) and France (125; 5.2%). Annual counts rose from 9 (2014) to 368 (2022), then fell to 186 in 2025; the 56 reports in 2026 cover the first quarter only (Figure S2).

3.2 Predefined irAE distribution

Table 2 presents the distribution of the 10 predefined immune-related adverse events (irAEs) (PT mapping in Table S2).

Table 2
Case counts for 10 predefined irAE groups (n = 2,400)

System Organ Class (SOC)	irAE / PT	Cases	% of cohort
Gastrointestinal	Colitis (consolidated)	92	3.8%
	Colitis	43	
	Immune-mediated enterocolitis	37	
	Enterocolitis	11	
	Autoimmune colitis	3	
Gastrointestinal	Diarrhea (consolidated)	103	4.3%
	Diarrhoea	102	
	Diarrhoea haemorrhagic	1	
Skin	Rash (consolidated)	112	4.7%
	Rash	57	
	Immune-mediated dermatitis	15	
	Rash maculo-papular	13	
	Rash pruritic	9	
	Rash papular	4	
	Toxic skin eruption	3	
	Dermatitis acneiform	3	
	Rash generalised	2	
	Rash macular	2	
	Dermatitis allergic	2	
	Dermatitis psoriasiform	2	
	Drug eruption	2	
	Dermatitis	1	
	Rash erythematous	1	
	Rash pustular	1	
	Rash vesicular	1	
Skin	Pruritus (consolidated)	23	1.0%
	Pruritus	23	
Endocrine	Hypothyroidism (consolidated)	40	1.7%
	Hypothyroidism	31	
	Immune-mediated hypothyroidism	8	
	Autoimmune hypothyroidism	1	
Abbreviations: irAE, immune-related adverse event; PT, preferred term; SOC, System Organ Class. Bold rows represent consolidated irAE groups; constituent PTs are listed below each. Individual PT counts are mutually non-exclusive.			

System Organ Class (SOC)	irAE / PT	Cases	% of cohort
Endocrine	Hyperthyroidism (consolidated)	16	0.7%
	Hyperthyroidism	12	
	Thyrotoxic crisis	3	
	Graves' disease	2	
Respiratory	Pneumonitis (consolidated)	86	3.6%
	Pneumonitis	59	
	Interstitial lung disease	23	
	Immune-mediated pneumonitis	2	
	Acute interstitial pneumonitis	1	
	Organising pneumonia	1	
Hepatobiliary	Hepatitis (consolidated)	70	2.9%
	Hepatitis	20	
	Immune-mediated hepatitis	19	
	Autoimmune hepatitis	8	
	Hepatotoxicity	8	
	Drug-induced liver injury	7	
	Hepatitis cholestatic	4	
	Liver injury	3	
	Hepatitis toxic	3	
	Mixed liver injury	1	
Cardiac	Myocarditis (consolidated)	47	2.0%
	Immune-mediated myocarditis	28	
	Myocarditis	17	
	Autoimmune myocarditis	1	
	Myocarditis-myositis-myasthenia gravis overlap syndrome	1	
Renal	Nephritis (consolidated)	12	0.5%
	Nephritis	10	
	Immune-mediated nephritis	1	
	Tubulointerstitial nephritis	1	
Abbreviations: irAE, immune-related adverse event; PT, preferred term; SOC, System Organ Class. Bold rows represent consolidated irAE groups; constituent PTs are listed below each. Individual PT counts are mutually non-exclusive.			

Rash was the most common predefined irAE (112 cases; 4.7%), followed by diarrhea (103; 4.3%), colitis (92; 3.8%), pneumonitis (86; 3.6%), and hepatitis (70; 2.9%). Myocarditis totaled 47 cases (2.0%), 28 coded to the specific PT “immune-mediated myocarditis.” Hypothyroidism (40; 1.7%) and hyperthyroidism (16; 0.7%, including 3 thyrotoxic crisis reports) were

less frequent; pruritus (23; 1.0%) and nephritis (12; 0.5%) were least common. Explicitly immune-mediated PTs accounted for substantial proportions (e.g., 37 of 92 colitis cases), supporting face validity of the mapping.

3.3 Primary analysis

Estimates against the full-database comparator are presented in Table 3 and Fig. 2.

Seven of the 10 predefined irAEs met the confirmed-signal criteria. Myocarditis showed the strongest association (ROR 31.16, 95% CI 23.33–41.61; IC 4.54, IC025 2.48), followed by colitis (ROR 17.35, 95% CI 14.08–21.37), hypothyroidism (10.54, 7.71–14.41), pneumonitis (9.59, 7.73–11.89), hyperthyroidism (8.60, 5.26–14.06), hepatitis (5.25, 4.14–6.66), and nephritis (4.62, 2.62–8.15). Diarrhea (1.37, 1.13–1.67) and rash (1.48, 1.22–1.79) were weakly positive (hypothesis-generating); pruritus was negatively associated (0.52, 0.34–0.78) (Fig. 2). ROR and PRR estimates were nearly identical and all IC025 values exceeded zero.

3.4 Sensitivity analysis

All 7 confirmed signals persisted under the CRC non-ICI comparator (Table 3, right columns): hyperthyroidism (ROR 30.66, 95% CI 16.08–58.45), myocarditis (23.60, 16.49–33.78), hypothyroidism (15.06, 10.48–21.65), nephritis (7.65, 4.13–14.17), colitis (5.33, 4.28–6.65), hepatitis (3.20, 2.50–4.09), and pneumonitis (2.37, 1.90–2.96). Diarrhea and rash reversed (0.36, 0.30–0.44; 0.74, 0.61–0.89) and pruritus remained negative (0.57, 0.38–0.87), indicating that their mild primary elevations reflect CRC background reporting rather than ICI-specific toxicity. A post hoc analysis restricting both comparators to reports listing a primary suspect drug (queries August 28, 2026: N = 20,663,429 full-database; n = 102,314 CRC non-ICI) left all seven signals and every signal classification unchanged (Table S4).

3.5 Exploratory screening

Among the 382 PTs screened (Figure S1; Table S1; complete results in Supplementary Data File S1), 38 met all concordance criteria (confirmed candidates) and 140 met criteria partially; all were prespecified as hypothesis-generating. All 38 confirmed candidates remained statistically significant after Benjamini–Hochberg false-discovery-rate correction across the 382 tests (all $q < 4.2 \times 10^{-4}$; q-values in Data File S1). Six criterion-meeting PTs were excluded from biological interpretation per the prespecified adjudication rule: pulmonary ossification (ROR 9,744.08; 30 background reports) lacks plausibility; carcinoembryonic antigen increased (35.83) reflects tumor-marker monitoring; large intestinal obstruction (35.08) and perforation (12.42) were confounded by the underlying malignancy; immune-mediated adverse reaction (71.42) and therapy partial responder (13.28) are non-specific or efficacy terms. The strongest retained candidates were immune-mediated hepatic disorder (ROR 133.79, 95% CI 92.51–193.50), hypopituitarism (54.76), immune-mediated lung disease (44.58), immune-mediated myositis (32.79), thyroiditis (29.01), type 1 diabetes mellitus (21.60), myasthenia gravis (19.80), myositis (19.33), enteritis (17.69), cholangitis (15.40), adrenal insufficiency (13.34), and diabetic ketoacidosis (5.85).

3.6 External validation in JADER and VigAccess

The JADER validation pipeline identified 69,290 reports naming pembrolizumab or nivolumab, of which 66,438 listed either drug as a suspected drug, 606 carried a CRC indication, and 600 fell within the 2018Q4–2026Q1 window; after manual adjudication of all 293 verbatim indication strings (13 non-CRC primaries excluded), the validation cohort comprised 587 CRC-ICI suspected-drug reports (pembrolizumab 326; nivolumab 261; 52.6% male; median age 70 years), containing 1,115 adverse-event records and 316 unique PTs. Six of the seven FAERS confirmed signals replicated under the prespecified criterion (direction-consistent, ROR025 > 1, full-database comparator): colitis (ROR 15.09, 95% CI 11.59–19.65), hypothyroidism (11.43, 8.59–15.21), hyperthyroidism (10.56, 6.60–16.91), pneumonitis (2.84, 2.23–3.62), hepatitis (3.13, 2.27–4.32), and myocarditis (9.28, 5.64–15.27); all six remained significant under the JADER-internal CRC non-ICI comparator (Table 4; Fig. 3; complete estimates for all three algorithms under both comparators in Table S7). Nephritis was not assessable: no cohort PT mapped to the nephritis group (the semantically nearest PT, immune-mediated renal disorder, was conservatively not mapped). Excluding the three uncertain-confidence PT mappings did not change any replication verdict.

The diarrhea reversal replicated qualitatively: weakly positive against the full-database comparator (ROR 1.74, 95% CI 1.02–2.96) and null against the CRC non-ICI comparator (0.82, 0.48–1.40), mirroring the FAERS pattern (1.37 → 0.36). Rash diverged across databases (1.94 → 4.50 in JADER versus 1.48 → 0.74 in FAERS) and is examined in Section 4.2. Pruritus was null in both databases.

JADER high-frequency events outside the 10 predefined groups corroborated the FAERS exploratory endocrine cluster: adrenal insufficiency–spectrum PTs (94 records, including adrenal insufficiency 43 and immune-mediated adrenal insufficiency 31), hypopituitarism/hypophysitis–spectrum PTs (25 records, including hypopituitarism 15), and type 1 diabetes/diabetic ketoacidosis–spectrum PTs (41 records, including type 1 diabetes 22 and diabetic ketoacidosis 13), consistent with the FAERS candidates adrenal insufficiency, hypopituitarism, type 1 diabetes, and diabetic ketoacidosis (Figure S1; Table S8). At drug level, VigAccess queries (13 September 2026) returned 126,262 pembrolizumab and 120,192 nivolumab reports, with endocrine, gastrointestinal, respiratory, and skin system-organ classes predominating—qualitatively concordant with the two database-specific signal spectra.

4 Discussion

4.1 Statement of key findings

This CRC-focused analysis incorporated 2,400 immune checkpoint inhibitor (ICI) primary suspect reports. Seven of 10 predefined immune-related adverse events (irAEs) met the confirmed-signal criteria—myocarditis, colitis, hypothyroidism, pneumonitis, hyperthyroidism, hepatitis, and nephritis—consistent with the established organ distribution of checkpoint blockade toxicity [4, 5, 6] and guideline surveillance priorities [8, 9]; all 7 persisted under the CRC non-ICI comparator. The most notable finding is the divergence between reporting frequency and disproportionality for myocarditis: only 47 reports (2.0%), yet the strongest association (ROR 31.16). ICI myocarditis is uncommon but carries the highest irAE fatality rate [7, 32]; rarity in spontaneous reports should not be equated with dismissible clinical priority. Diarrhea and rash, the most frequent predefined events (103 and 112 cases), were weakly positive under the full-database comparator but reversed under the CRC non-ICI comparator, and pruritus was negative under both (Section 4.2)—the principal methodological finding.

External validation strengthens these findings: six of the seven confirmed signals replicated in an independently constructed JADER cohort (587 CRC-ICI suspected-drug reports) under the prespecified criterion and under both comparators (Section 3.6); nephritis was not assessable because no cohort preferred term (PT) mapped to the group. The diarrhea reversal—the principal methodological observation—replicated qualitatively (1.74 → 0.82), providing cross-database evidence that the attenuation reflects CRC background reporting rather than a database-specific artifact.

4.2 Interpretation

The myocarditis findings are consistent with a WHO Vigibase analysis demonstrating cardiovascular irAE disproportionality with high fatality [16] and a pan-cancer FAERS study identifying myocarditis among the most disproportionately reported cardiac events [33]; fulminant checkpoint-associated myocarditis [32] ranks highest in irAE fatality [7]. Our CRC-restricted estimate (ROR 31.16) exceeds typical pan-cancer levels, potentially reflecting enrichment of explicitly immune-mediated preferred terms (PTs). A post hoc subset analysis showed that immune-specific and non-specific PT subsets each independently met confirmed-signal criteria (myocarditis: ROR 148.33, 95% CI 102.53–214.57 and 13.78, 8.67–21.93; colitis: 86.04 and 11.11; Table S5); the pooled estimate reflects a coding-practice gradient rather than a mapping artifact. The colitis signal (17.35) is consistent with pan-cancer gastrointestinal toxicity analyses [34], dedicated immune-mediated enterocolitis studies [35], and earlier work [12, 13]; a digestive-tumor FAERS study included CRC only as a subgroup [36], leaving this the first CRC-specific analysis. The endocrine signals (10.54; 8.60) align with meta-analytic evidence on PD-1 inhibitor endocrinopathy [37], and the exploratory type 1 diabetes candidate extends the spectrum of checkpoint-induced insulin-dependent diabetes [38]. This study follows the single-malignancy template of Gokhale and Zapata (365 bladder cancer reports) [22], adding a tumor-specific non-ICI comparator, trade-name-inclusive searching (2,400 reports), and systematic 382-PT screening.

The dual-control design quantifies indication confounding: switching comparators, diarrhea shifted from ROR 1.37 to 0.36 and rash from 1.48 to 0.74. The most parsimonious explanation is background over-reporting in CRC populations (fluoropyrimidine and epidermal growth factor receptor-targeted therapy, disease burden, monitoring intensity), with ICIs adding no disproportionate reporting above this background. Conversely, sensitivity estimates for hypothyroidism, hyperthyroidism, and nephritis increased (15.06, 30.66, 7.65), suggesting full-database dilution of ICI-specific associations. Tumor-specific studies relying solely on full-database comparators may thus overestimate common events and underestimate rare specific ones; dual reporting should be considered standard practice [11, 26, 39].

Exploratory screening identified an internally consistent endocrine cluster: hypopituitarism (ROR 54.76), thyroiditis (29.01), adrenal insufficiency (13.34), type 1 diabetes mellitus (21.60), and diabetic ketoacidosis (5.85), corroborating the recognized ICI endocrinopathy spectrum [8, 9, 37, 38]. Neuromuscular candidates (myasthenia gravis 19.80; myositis 19.33; immune-mediated myositis 32.79) and cholangitis (15.40) are biologically plausible extensions of known irAEs [4, 5]; the strongest candidates clustered within immune-mediated hepatobiliary and pulmonary spectra (133.79 and 44.58). These candidates are strictly hypothesis-generating: multiplicity alone can produce extreme estimates despite false-discovery-rate correction, and coding artifacts were excluded (Section 3.5); all require external validation [40].

The cross-database comparison also delineates the boundary of the comparator logic. Rash did not show the FAERS reversal in JADER (1.94 → 4.50 versus 1.48 → 0.74): the JADER rash cluster was dominated by explicitly immune-mediated dermatitis terms, whereas the Japanese CRC comparator background—unlike its FAERS counterpart—contains proportionally less targeted-therapy skin toxicity, so the disease-matched comparator no longer cancels the drug-attributable component. This divergence indicates that reversal patterns are comparator- and coding-context-dependent and should be interpreted per database rather than assumed transportable. In contrast, the exploratory endocrine cluster proved transportable: adrenal insufficiency–spectrum, hypopituitarism/hypophysitis–spectrum, and type 1 diabetes–spectrum PTs were among the most frequent JADER events (94, 25, and 41 records), independently corroborating the FAERS candidates adrenal insufficiency, hypopituitarism, type 1 diabetes, and diabetic ketoacidosis [8, 9, 37, 38].

4.3 Strengths and weaknesses

Several limitations apply. FAERS is subject to underreporting, notoriety bias, and the Weber effect; disproportionality metrics cannot estimate incidence and do not establish causality [10, 40]. Indication identification relied on free-text fields: 125 unmatched reports were conservatively excluded and true CRC cases may have been lost, though the sensitivity comparator was likewise CRC-restricted, partially mitigating this. De-duplication was asymmetric: case reports were de-duplicated per FDA recommendations, whereas background counts are openFDA aggregates that cannot be de-duplicated; resulting inflation would dilute estimates (likely conservative). Concomitant medications (heuristically identified in 13.4% of reports) were not formally adjusted for. Ipilimumab was co-reported in 484 reports (20.2%), reflecting nivolumab–ipilimumab combination use in MSI-H/dMMR CRC [3], and was enriched among colitis (38.0%) and hyperthyroidism (62.5%) case sets; combination therapy could not be separated from anti-PD-1 monotherapy, and drug-level estimates against each drug's own background attenuated toward unity (Table S6)—expected comparator enrichment in within-drug analyses rather than evidence against the pooled signals. Finally, 2026 data cover only the first quarter (database locked March 31, 2026).

The validation analysis adds its own limitations. The JADER cohort was modest (587 reports), so estimates are imprecise for rare events (hyperthyroidism had only 4 comparator cases under the CRC non-ICI analysis) and nephritis could not be evaluated. MedDRA/J PTs lack direct MedDRA codes in the public CSV release; three mappings were graded uncertain and were tested by sensitivity analysis, but residual misclassification cannot be excluded. JADER does not support the same indication-vocabulary audit depth as FAERS free text, and VigAccess provides only drug-level aggregates without indication stratification, so its role was restricted to qualitative corroboration. The observation windows differed by design (FAERS from August 2014, following the first US immune checkpoint inhibitor approval; JADER from 2018 Q4, following the first Japanese approval relevant to colorectal cancer); the validation therefore tests signal replication within each country's routine-practice era rather than calendar-aligned periods, and cross-database estimates are compared qualitatively rather than pooled.

4.4 Further research

FAERS-based disproportionality publications have grown rapidly (approximately 100 in 2021 to over 600 in 2024), many with methodological deficiencies [41]. Against the criteria of Khouri et al., this study adheres to READUS-PV [28] with a completed checklist; fully discloses query strings, deduplication rules, PT mapping, and indication vocabulary; and its dual-control design constitutes the advocated “stress test of expected biases”—the diarrhea/rash reversals ($1.37 \rightarrow 0.36$; $1.48 \rightarrow 0.74$) directly quantify indication confounding. It consistently distinguishes signals from causal relationships (“confirmed signal,” never “confirmed association” [10, 40, 42]), integrates fatality and mechanistic evidence into interpretation [7, 32, 37, 38], and is concordant with VigiBase and pan-cancer evidence [16, 33, 34]; screening candidates are explicitly hypothesis-generating with coding-artifact exclusion, in contrast to practices criticized by Khouri et al. [41]. Gaps: the analysis plan was specified a priori but not publicly preregistered, and—although the primary signals are now cross-database validated—triangulation with registry or claims data remains absent. In addition, no case-by-case analysis was performed: publicly available FAERS data are de-identified and lack clinical narratives and complete medical histories, precluding meaningful case-level causality assessment [41]. To partially compensate, we restricted the cohort to primary suspect reports, applied FDA deduplication rules, and adjudicated the biological plausibility of all newly detected candidate signals. Future research should integrate multi-source evidence to advance the assessment from signal to causality.

5 Conclusions

Among 2,400 immune checkpoint inhibitor (ICI) primary suspect reports in colorectal cancer (CRC), 7 of 10 predefined immune-related adverse events (irAEs) were confirmed signals, strongest for myocarditis (ROR 31.16, 95% CI 23.33–41.61), consistent with prior ICI cardiac toxicity evidence [16]. The apparent diarrhea and rash signals disappeared under the CRC non-ICI comparator, suggesting background confounding rather than ICI-attributable risk. Clinically, CRC patients receiving pembrolizumab or nivolumab warrant organ-prioritized irAE monitoring; methodologically, disease-matched comparators are necessary in tumor-specific pharmacovigilance to avoid signal misattribution [11, 26, 39]. Future work should add time-to-onset analysis, extend external validation to additional sources (e.g., VigiBase, registry or claims data), and pursue prospective surveillance of priority organ toxicities.

Abbreviations

API, application programming interface; BCPNN, Bayesian confidence propagation neural network; CI, confidence interval; CRC, colorectal cancer; dMMR, mismatch repair-deficient; FAERS, US FDA Adverse Event Reporting System; FDA, US Food and Drug Administration; IC, information component; ICH, International Council for Harmonisation; ICI, immune checkpoint inhibitor; IQR, interquartile range; irAE, immune-related adverse event; MedDRA, Medical Dictionary for Regulatory Activities; MSI-H, microsatellite instability-high; PRR, proportional reporting ratio; PS, primary suspect; PT, preferred term; ROR, reporting odds ratio; SOC, System Organ Class; WHO, World Health Organization.

Declarations

Ethics approval and consent to participate

The data analyzed in this study are from the publicly available, de-identified US FDA Adverse Event Reporting System (FAERS); therefore, institutional review board approval was not required.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Author Contribution

Y.Y., W.Y. and J.P. wrote the main manuscript text. Y.Y. performed the FAERS analyses. W.L., X.L. and S.C. prepared the data and performed the validation analyses. H.S. and Z.L. supervised the study. All authors reviewed the manuscript.

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Data Availability

All data analyzed in this study are from publicly available pharmacovigilance databases. FAERS data were obtained via the openFDA API (<https://open.fda.gov/>) and JADER data from the PMDA website (<https://www.pmda.go.jp/>, release pmdacasereport202608). The derived analysis datasets supporting the results are included in the article and its supplementary files (Data Files S1-S3; Tables S1-S8; Notes S1-S2). Analysis code is available from the corresponding author upon reasonable request.

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Figures

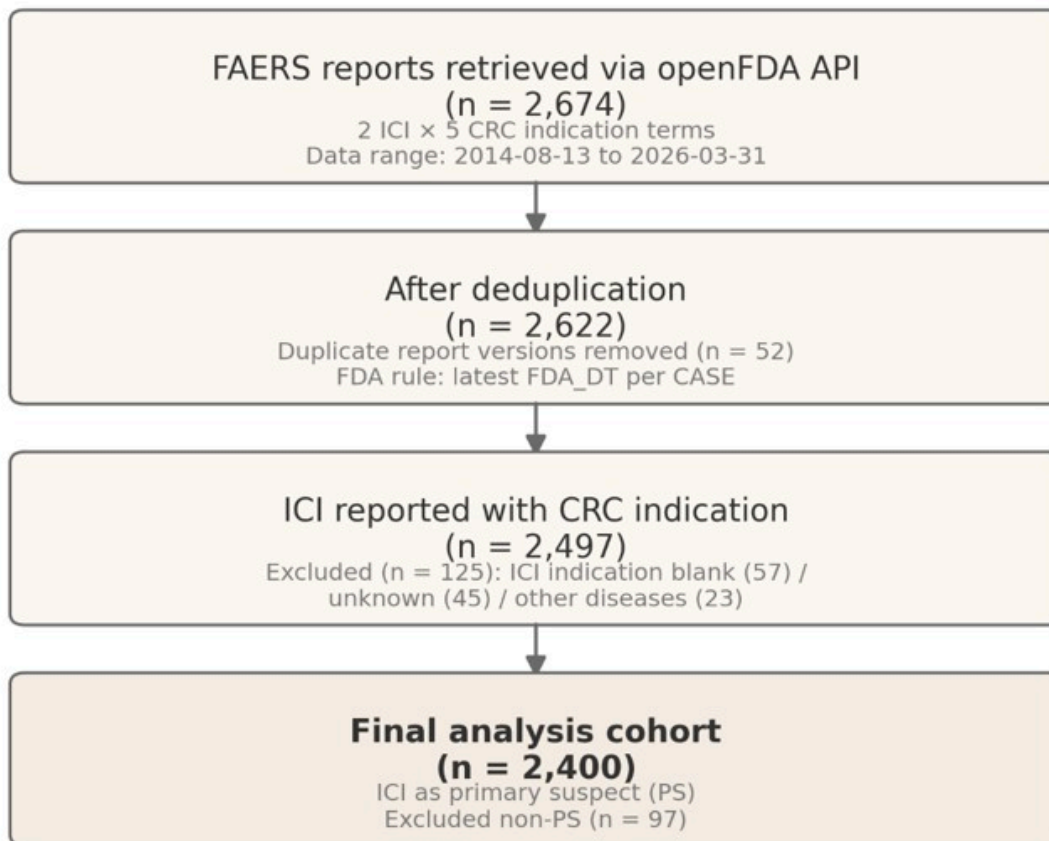


Figure 1

Report screening flowchart. A total of 2,674 records were retrieved; 52 duplicate versions were removed per FDA deduplication rules (2,622 retained); 125 reports without ICI-CRC indication were excluded (2,497 retained); 97 non-primary-suspect reports were excluded, yielding a final primary suspect (PS) cohort of 2,400 reports. ICI, immune checkpoint inhibitor; CRC, colorectal cancer; PS, primary suspect. Row labels retain the original MedDRA preferred-term spelling (e.g., Diarrhoea).

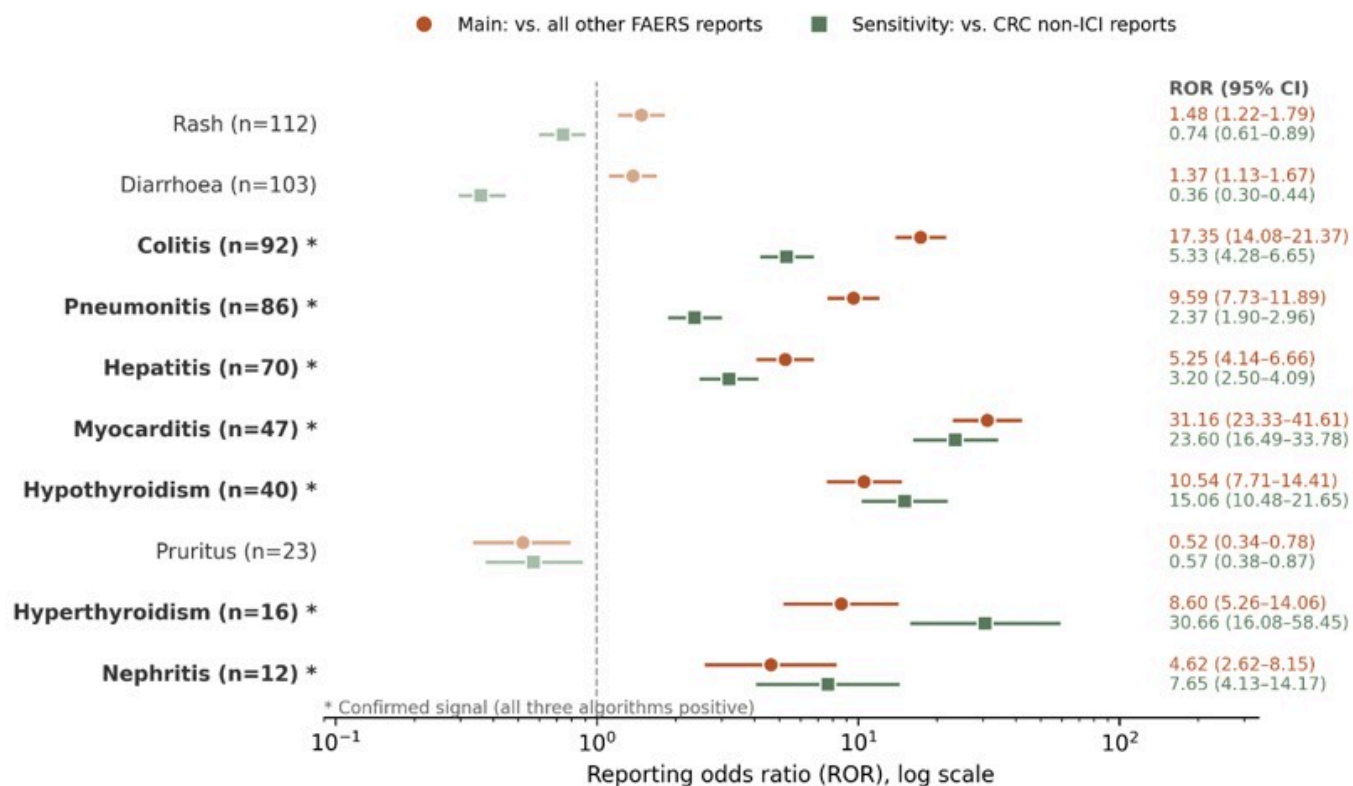


Figure 2

Forest plot of reporting odds ratios (RORs, 95% confidence intervals, log scale) for 10 predefined immune-related adverse events. Primary analysis used all other FAERS reports as the comparator (circles); sensitivity analysis used CRC non-ICI comparator reports (squares). Asterisks indicate confirmed signals ($a \geq 3$, PRR, ROR, and IC all positive). Note the disappearance of diarrhea and rash signals in the sensitivity analysis. Row labels retain the original MedDRA preferred-term spelling (e.g., Diarrhoea).

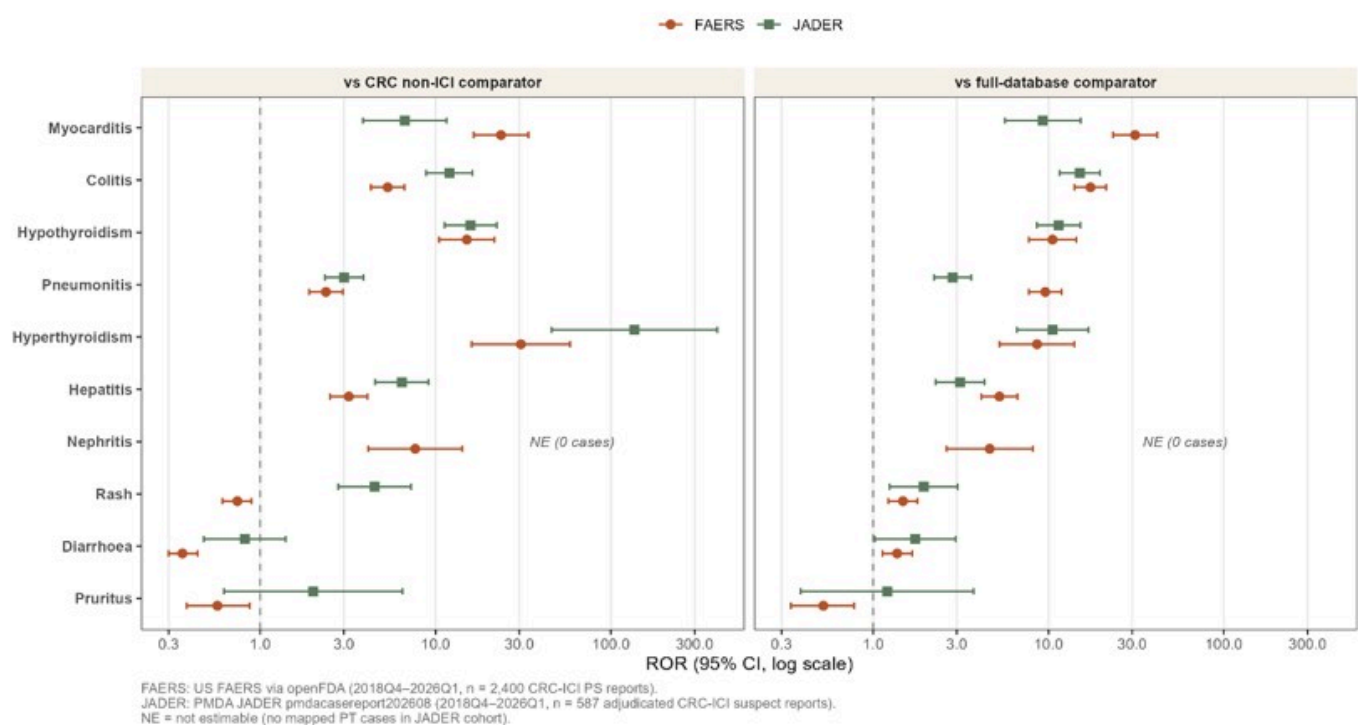


Figure 3

Forest plot comparing reporting odds ratios (RORs, 95% confidence intervals, log scale) for the 10 predefined immune-related adverse events between FAERS (n = 2,400) and JADER (n = 587), under the full-database comparator (left panel) and the CRC non-ICI comparator (right panel). Circles denote FAERS estimates and squares denote JADER estimates. Nephritis was not estimable in JADER (no mapped preferred-term cases; NE, not estimable). FAERS estimates from Table 3; JADER estimates from Table 4 (main preferred-term mapping).

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