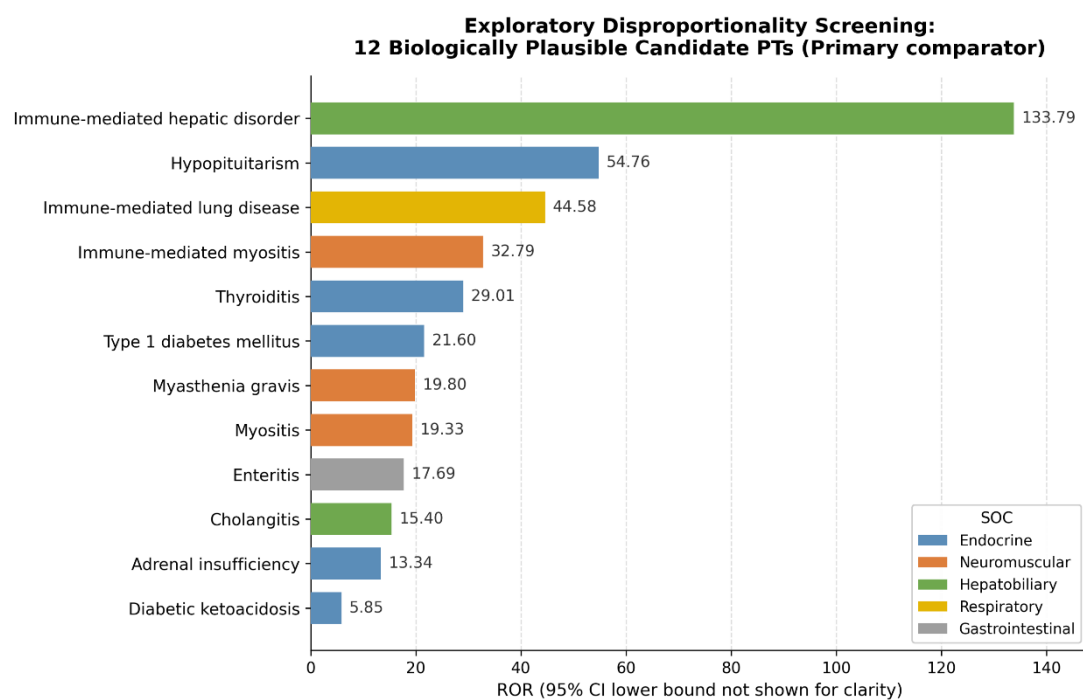


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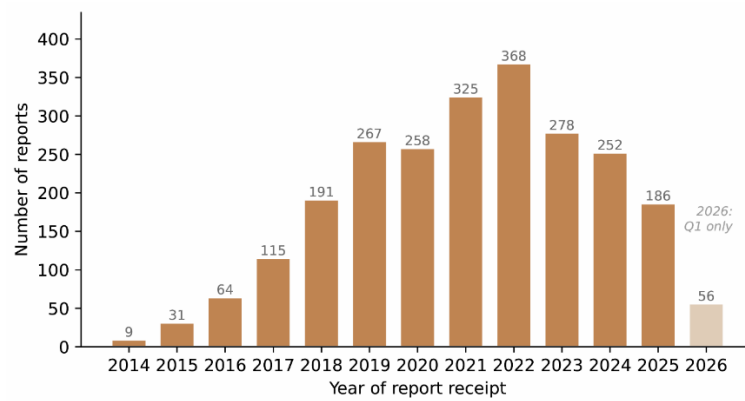
Supplementary materials for: Immune checkpoint inhibitor adverse events in colorectal cancer: a disproportionality analysis of FAERS with cross-database validation in JADER. Yunfei Yan, Wenjing Yue, Hua Song, Zirong Li, Wanhui Li, Xinyi Liu, Jianbo Pan, Shuang Cai (Peking Union Medical College Hospital).

Supplementary Fig. S1. Exploratory disproportionality screening of other MedDRA preferred terms (showing 12 biologically plausible confirmed candidates, using the primary comparator). PTs with coding artifacts or disease confounding are not displayed. All findings are hypothesis-generating only.



All associations are hypothesis-generating only. PTs with coding artifacts or disease confounding are not shown.
Source: FAERS via openFDA API; primary comparator (N = 20,328,575).

Supplementary Fig. S2. Annual FAERS ICI-CRC adverse event reports, 2014–2026. Report counts peaked at 368 in 2022; 2026 data cover only the first quarter (n = 56). FAERS, FDA Adverse Event Reporting System; ICI, immune checkpoint inhibitor; CRC, colorectal cancer.



Supplementary Table S1. Exploratory screening results: 12 biologically plausible confirmed candidates and 6 excluded pseudo-signals

Biologically plausible confirmed candidates (12, all hypothesis-generating)

Preferred Term (PT)	ROR	95% CI	SOC
Immune-mediated hepatic disorder	133.79	92.51–193.50	Hepatobiliary
Hypopituitarism	54.76	30.23–99.20	Endocrine
Immune-mediated lung disease	44.58	23.13–85.94	Respiratory
Immune-mediated myositis	32.79	17.60–61.10	Neuromuscular
Thyroiditis	29.01	15.57–54.05	Endocrine
Type 1 diabetes mellitus	21.60	12.99–35.91	Endocrine
Myasthenia gravis	19.80	12.45–31.50	Neuromuscular
Myositis	19.33	12.44–30.03	Neuromuscular
Enteritis	17.69	10.25–30.53	Gastrointestinal
Cholangitis	15.40	8.51–27.86	Hepatobiliary
Adrenal insufficiency	13.34	8.39–21.22	Endocrine
Diabetic ketoacidosis	5.85	3.58–9.56	Endocrine

Excluded pseudo-signals and non-toxicity terms (6)

Preferred Term (PT)	ROR	Exclusion reason
Pulmonary ossification	9,744.08	Only 30 background reports; statistical artifact

Carcinoembryonic antigen increased	35.83	Tumor marker monitoring, not a toxicity event
Large intestinal obstruction	35.08	Confounded by underlying disease/disease progression
Large intestine perforation	12.42	Confounded by underlying disease/disease progression
Immune-mediated adverse reaction	71.42	Non-specific term, no organ attribution
Therapy partial responder	13.28	Efficacy outcome term, not an adverse event

Note: These 12 are the strongest of the 32 retained biologically plausible candidates; complete screening results for all 382 PTs (including 140 PTs partially meeting criteria) are provided in Supplementary Data File S1. All associations are hypothesis-generating.

Supplementary Table S2. MedDRA preferred term mapping for 10 predefined irAEs

SOC	irAE (consolidated)	Cases	% of cohort	Constituent PTs (n)
Gastrointestinal	Colitis	92	3.8%	Colitis (43); Immune-mediated enterocolitis (37); Enterocolitis (11); Autoimmune colitis (3)
Gastrointestinal	Diarrhea	103	4.3%	Diarrhoea (102); Diarrhoea haemorrhagic (1)
Skin	Rash	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	23	1.0%	Pruritus (23)
Endocrine	Hypothyroidism	40	1.7%	Hypothyroidism (31); Immune-mediated hypothyroidism (8); Autoimmune hypothyroidism (1)
Endocrine	Hyperthyroidism	16	0.7%	Hyperthyroidism (12); Thyrotoxic crisis (3); Graves' disease (2)

Respiratory	Pneumonitis	86	3.6%	Pneumonitis (59); Interstitial lung disease (23); Immune-mediated pneumonitis (2); Acute interstitial pneumonitis (1); Organising pneumonia (1)
Hepatobiliary	Hepatitis	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	47	2.0%	Immune-mediated myocarditis (28); Myocarditis (17); Autoimmune myocarditis (1); Myocarditis-myositis-myasthenia gravis overlap syndrome (1)
Renal	Nephritis	12	0.5%	Nephritis (10); Immune-mediated nephritis (1); Tubulointerstitial nephritis (1)

Note: Individual PT counts are mutually non-exclusive; a single report may be counted under multiple PTs, so PT-level counts may exceed the consolidated row count.

Supplementary Table S3. Extended vocabulary of 22 CRC indication terms for case identification

No.	Indication term	Type	Usage
1	colorectal cancer	Standard	API search + case matching
2	colon cancer	Standard	API search + case matching
3	rectal cancer	Standard	API search + case matching
4	colorectal adenocarcinoma	Standard	API search + case matching
5	rectal adenocarcinoma	Standard	API search + case matching
6	bowel cancer	Extended	Case matching
7	colorectal carcinoma	Extended	Case matching
8	colonic cancer	Extended	Case matching
9	colonic adenocarcinoma	Extended	Case matching
10	colon adenocarcinoma	Extended	Case matching
11	colonic carcinoma	Extended	Case matching
12	rectal carcinoma	Extended	Case matching
13	rectum cancer	Extended	Case matching
14	sigmoid	Extended	Case matching
15	sigmoid colon cancer	Extended	Case matching

16	sigmoid adenocarcinoma	Extended	Case matching
17	caecal	Extended	Case matching
18	caecal cancer	Extended	Case matching
19	caecum cancer	Extended	Case matching
20	caecal adenocarcinoma	Extended	Case matching
21	colorectal neoplasm	Extended	Case matching
22	bowel neoplasm	Extended	Case matching

Note: Terms 1–5 were used for the initial openFDA API search; terms 6–22 are extended matching terms used for case matching against the indication field of ICI drug records in retrieved reports. Extended terms include spelling variants and anatomical variants.

Supplementary Table S4. Post hoc sensitivity analysis of the 10 predefined immune-related adverse events with both comparators restricted to primary suspect reports

irAE	Cases (a)	Primary	Verdict	CRC non-ICI	Verdict
		comparator, PS- restricted: ROR (95% CI)		comparator, PS- restricted: ROR (95% CI)	
Colitis	92	17.57 (14.26– 21.64)	confirmed	5.46 (4.38–6.80)	confirmed
Diarrhoea	103	1.40 (1.15–1.70)	hypothesis- generating	0.37 (0.30–0.45)	none
Rash	112	1.37 (1.13–1.66)	hypothesis- generating	0.69 (0.57–0.83)	none
Pruritus	23	0.53 (0.35–0.79)	none	0.58 (0.39–0.88)	none
Hypothyroidism	40	10.72 (7.84–14.66)	confirmed	15.33 (10.66– 22.04)	confirmed
Hyperthyroidism	16	8.58 (5.25–14.03)	confirmed	32.69 (17.04– 62.73)	confirmed
Pneumonitis	86	9.59 (7.73–11.89)	confirmed	2.38 (1.91–2.97)	confirmed

irAE	Cases (a)	Primary	Verdict	CRC non-ICI	Verdict
		comparator, PS- restricted: ROR (95% CI)		comparator, PS- restricted: ROR (95% CI)	
Hepatitis	70	5.10 (4.02–6.47)	confirmed	3.19 (2.49–4.08)	confirmed
Myocarditis	47	31.77 (23.79– 42.43)	confirmed	24.02 (16.78– 34.39)	confirmed
Nephritis	12	4.69 (2.66–8.27)	confirmed	7.79 (4.20–14.42)	confirmed

Note: The case set was unchanged (2,400 primary suspect reports). Both comparators were restricted to reports listing a primary suspect drug (openFDA queries on August 28, 2026: full-database comparator N = 20,663,429; colorectal cancer non-ICI comparator n = 102,314); comparator totals slightly exceed the locked analysis set owing to database growth after March 31, 2026. Verdicts used the same concordance criteria as the primary analysis (confirmed signal: $a \geq 3$, $PRR \geq 2$, $PRR025 > 1$, $ROR025 > 1$, and $IC025 > 0$). All seven confirmed signals and every signal classification remained unchanged under both restricted comparators.

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Supplementary Table S5. Post hoc subset analysis of the 10 predefined immune-related adverse events by immune-specific versus non-specific preferred terms

irAE	PT subset	Preferred terms included	Cases (a)	Primary comparator: ROR (95% CI)	Verdict	CRC non-ICI comparator: ROR (95% CI)	Verdict
Colitis	immune-specific	Immune-mediated enterocolitis; Autoimmune colitis	40	86.04 (62.85–117.78)	confirmed	578.59 (178.86–1871.65)	confirmed
Colitis	non-specific	Colitis; Enterocolitis	54	11.11 (8.48–14.56)	confirmed	3.14 (2.37–4.15)	confirmed
Diarrhoea	immune-specific	(none)	0	n/a (no PT mapped to this subset)	n/a	n/a (no PT mapped to this subset)	n/a
Diarrhoea	non-specific	Diarrhoea; Diarrhoea haemorrhagic	103	1.40 (1.15–1.70)	hypothesis-generating	0.37 (0.30–0.45)	none
Rash	immune-specific	Immune-mediated dermatitis	15	143.15 (85.81–238.81)	confirmed	644.10 (85.04–4878.25)	confirmed
Rash	non-specific	Rash; Rash maculo-papular; Rash pruritic; Rash papular; Toxic skin eruption; Dermatitis acneiform; Rash generalised; Rash macular; Dermatitis allergic; Dermatitis psoriasiform; Drug eruption; Dermatitis; Rash erythematous; Rash pustular; Rash vesicular	98	1.20 (0.98–1.46)	none	0.60 (0.49–0.73)	none

irAE	PT subset	Preferred terms included	Cases (a)	Primary comparator: ROR (95% CI)	Verdict	CRC non-ICI comparator: ROR (95% CI)	Verdict
Pruritus	immune-specific	(none)	0	n/a (no PT mapped to this subset)	n/a	n/a (no PT mapped to this subset)	n/a
Pruritus	non-specific	Pruritus	23	0.53 (0.35–0.79)	none	0.58 (0.39–0.88)	none
Hypothyroidism	immune-specific	Immune-mediated hypothyroidism; Autoimmune hypothyroidism	9	60.70 (31.47–117.07)	confirmed	undefined (comparator count = 0)	not assessable
Hypothyroidism	non-specific	Hypothyroidism	31	8.61 (6.04–12.28)	confirmed	11.85 (7.95–17.66)	confirmed
Hyperthyroidism	immune-specific	(none)	0	n/a (no PT mapped to this subset)	n/a	n/a (no PT mapped to this subset)	n/a
Hyperthyroidism	non-specific	Hyperthyroidism; Thyrotoxic crisis; Graves' disease	16	8.56 (5.24–14.00)	confirmed	32.72 (17.05–62.79)	confirmed
Pneumonitis	immune-specific	Immune-mediated pneumonitis	2	74.38 (18.48–299.36)	none	undefined (comparator count = 0)	not assessable
Pneumonitis	non-specific	Pneumonitis; Interstitial lung disease; Acute interstitial pneumonitis; Organising pneumonia	84	9.39 (7.55–11.67)	confirmed	2.32 (1.86–2.90)	confirmed
Hepatitis	immune-specific	Immune-mediated hepatitis; Autoimmune hepatitis	27	26.91 (18.41–39.35)	confirmed	194.20 (80.10–470.80)	confirmed
Hepatitis	non-specific	Hepatitis; Hepatotoxicity; Drug-induced liver injury; Hepatitis	45	3.49 (2.60–4.68)	confirmed	2.04 (1.51–2.76)	confirmed

irAE	PT subset	Preferred terms included	Cases (a)	Primary comparator: ROR (95% CI)	Verdict	CRC non-ICI comparator: ROR (95% CI)	Verdict
Myocarditis	immune-specific	cholestatic; Liver injury; Hepatitis toxic; Mixed liver injury Immune-mediated myocarditis; Autoimmune myocarditis	29	148.33 (102.53–214.57)	confirmed	250.51 (96.89–647.74)	confirmed
Myocarditis	non-specific	Myocarditis; Myocarditis-myositis-myasthenia gravis overlap syndrome	18	13.78 (8.67–21.93)	confirmed	9.67 (5.79–16.14)	confirmed
Nephritis	immune-specific	Immune-mediated nephritis	1	19.34 (2.72–137.64)	none	undefined (comparator count = 0)	not assessable
Nephritis	non-specific	Nephritis; Tubulointerstitial nephritis	11	4.38 (2.42–7.92)	confirmed	7.14 (3.77–13.54)	confirmed

Note: Immune-specific subsets comprise preferred terms (PTs) explicitly denoting an immune-mediated or autoimmune mechanism (e.g., “Immune-mediated myocarditis,” “Autoimmune colitis”); non-specific subsets comprise all remaining PTs of each irAE mapping (complete mapping in Table S2). Subset case counts are mutually non-exclusive when a report contains PTs from both subsets (overlaps: colitis n = 2, rash n = 1, hepatitis n = 2). “n/a”: no PT mapped to the subset; “undefined”: comparator count of zero precluding estimation. Extreme ROR estimates in immune-specific subsets (e.g., colitis 578.59, rash 644.10) arise from near-zero comparator counts of these narrowly mapped PTs in the CRC non-ICI comparator and should be interpreted as directional only. Verdicts used the same concordance criteria as the primary analysis. For myocarditis and colitis, both subsets independently met confirmed-signal criteria, indicating that the pooled signals do not arise from preferential coding of immune-mediated terms.

Supplementary Table S6. Post hoc within-drug disproportionality analysis of the 10 predefined immune-related adverse events for nivolumab and pembrolizumab, with ipilimumab co-reporting in the pooled cohort

irAE	Drug	Cases with event (a)	Drug-specific PS background (N)	Within-drug ROR (95% CI)	Verdict	Ipilimumab co-mentioned in irAE case set, n (%)
Colitis	nivolumab	55	96,839	0.93 (0.71–1.22)	none	35 (38.0%)

irAE	Drug	Cases with event (a)	Drug-specific PS background (N)	Within-drug ROR (95% CI)	Verdict	Ipilimumab co-mentioned in irAE case set, n (%)
Colitis	pembrolizumab	40	104,914	1.05 (0.76–1.44)	none	35 (38.0%)
Diarrhoea	nivolumab	53	96,839	0.75 (0.57–0.99)	none	19 (18.4%)
Diarrhoea	pembrolizumab	51	104,914	0.79 (0.59–1.04)	none	19 (18.4%)
Rash	nivolumab	61	96,839	0.82 (0.63–1.06)	none	27 (24.1%)
Rash	pembrolizumab	52	104,914	0.66 (0.50–0.87)	none	27 (24.1%)
Pruritus	nivolumab	14	96,839	0.60 (0.35–1.01)	none	5 (21.7%)
Pruritus	pembrolizumab	9	104,914	0.46 (0.24–0.88)	none	5 (21.7%)
Hypothyroidism	nivolumab	9	96,839	0.27 (0.14–0.53)	none	6 (15.0%)
Hypothyroidism	pembrolizumab	31	104,914	0.76 (0.53–1.08)	none	6 (15.0%)
Hyperthyroidism	nivolumab	10	96,839	0.72 (0.39–1.35)	none	10 (62.5%)
Hyperthyroidism	pembrolizumab	6	104,914	0.54 (0.24–1.21)	none	10 (62.5%)
Pneumonitis	nivolumab	40	96,839	0.74 (0.54–1.01)	none	25 (29.1%)

irAE	Drug	Cases with event (a)	Drug-specific PS background (N)	Within-drug ROR (95% CI)	Verdict	Ipilimumab co-mentioned in irAE case set, n (%)
Pneumonitis	pembrolizumab	47	104,914	0.83 (0.62–1.11)	none	25 (29.1%)
Hepatitis	nivolumab	37	96,839	0.85 (0.61–1.19)	none	24 (34.3%)
Hepatitis	pembrolizumab	34	104,914	0.82 (0.58–1.15)	none	24 (34.3%)
Myocarditis	nivolumab	20	96,839	0.93 (0.60–1.45)	none	11 (23.4%)
Myocarditis	pembrolizumab	29	104,914	1.24 (0.86–1.80)	none	11 (23.4%)
Nephritis	nivolumab	2	96,839	0.16 (0.04–0.65)	none	1 (8.3%)
Nephritis	pembrolizumab	10	104,914	0.54 (0.29–1.01)	none	1 (8.3%)

Note: Drug-specific cohorts comprised FAERS reports listing the respective drug as primary suspect (openFDA queries on August 28, 2026; nivolumab N = 96,839; pembrolizumab N = 104,914; 15 dual-agent reports are counted in both cohorts). The within-drug comparator consists of reports of the same drug without the event; estimates therefore attenuate toward unity (comparator enrichment) and are not comparable to the pooled dual-control analysis. Ipilimumab co-reporting was tabulated within each irAE case set of the pooled 2,400-report cohort (overall 484/2,400, 20.2%).

Supplementary Note S1. External validation in JADER and VigAccess

The JADER validation cohort was constructed from the complete public release (version pmdacasereport202608; 1,049,684 unique reports, April 2004–March 2026; downloaded 13 September 2026) with rules mirroring the FAERS pipeline: 69,290 reports naming pembrolizumab or nivolumab → 66,438 suspected-drug (被疑薬) reports → 606 with a colorectal-cancer indication (Japanese terms for colon, rectal, or large-intestine carcinoma) → 600 within the 2018Q4–2026Q1 window (start aligned to the first Japanese approval of pembrolizumab for MSI-H solid tumours, December 2018) → 587 after manual adjudication of all 293 verbatim indication strings (13 non-CRC primaries excluded: 6 anorectal/large-intestine melanoma, 2 uterine, 2 small-

22 intestinal/duodenal, 1 rectal neuroendocrine carcinoma, 1 bladder-cancer text artefact). The cohort contained 1,115 adverse-event records and 316 unique
 23 MedDRA/J preferred terms (pembrolizumab 326; nivolumab 261; 52.6% male; median age 70 years).

24 All 316 PTs were mapped to the 10 predefined irAE groups before analysis, blind to the outcome estimates; mapping confidence was graded exact
 25 MedDRA/J equivalent, best semantic match, or uncertain (uncertain: 腸炎 [enteritis], 発疹 [rash], 肝障害 [liver disorder]). Mapped records per group:
 26 pneumonitis 75, colitis 62, hypothyroidism 52, hepatitis 40, rash 20, hyperthyroidism 18, myocarditis 16, diarrhoea 14, pruritus 3, nephritis 0. The complete
 27 PT-level mapping with adjudication is provided in Data File S2; the complete indication-vocabulary adjudication in Data File S3. High-frequency clusters
 28 outside the predefined groups (adrenal insufficiency–spectrum 94 records, hypopituitarism/hypophysitis–spectrum 25, type 1 diabetes/diabetic ketoacidosis–
 29 spectrum 41) corroborated the FAERS exploratory endocrine candidates (Supplementary Fig. S1).

30 VigiAccess (WHO-Uppsala Monitoring Centre) was queried on 13 September 2026 for drug-level corroboration: pembrolizumab 126,262 reports; nivolumab
 31 120,192 reports; endocrine, gastrointestinal, respiratory, and skin system-organ classes predominated for both agents, qualitatively concordant with the
 32 FAERS and JADER signal spectra. VigiAccess provides drug-level aggregates without indication stratification and was not used for quantitative validation.

33 **Supplementary Table S7. JADER disproportionality estimates for the 10 predefined irAEs (main preferred-term mapping): ROR, PRR, and BCPNN**
 34 **information component under both comparators**

irAE	a	Full-database comparator: ROR (95% CI)	Full-database: PRR (95% CI)	Full-database: IC (IC025)	CRC non-ICI comparator: ROR (95% CI)	CRC non-ICI: PRR (95% CI)	CRC non-ICI: IC (IC025)
Colitis	62	15.09 (11.59– 19.65)	13.60 (10.74– 17.23)	3.76 (3.39)	11.98 (8.84– 16.24)	10.82 (8.18– 14.31)	3.03 (2.61)
Diarrhea	14	1.74 (1.02–2.96)	1.72 (1.03–2.89)	0.83 (0.08)	0.82 (0.48–1.40)	0.82 (0.49–1.39)	-0.23 (-0.99)
Rash	20	1.94 (1.24–3.03)	1.91 (1.24–2.94)	0.97 (0.33)	4.50 (2.79–7.25)	4.38 (2.76–6.95)	2.00 (1.33)
Pruritus	3	1.20 (0.39–3.74)	1.20 (0.39–3.72)	0.48 (-1.03)	2.00 (0.62–6.47)	2.00 (0.62–6.42)	1.14 (-0.43)
Hypothyroidism	52	11.43 (8.59– 15.21)	10.51 (8.10– 13.63)	3.40 (2.99)	15.84 (11.24– 22.32)	14.52 (10.52– 20.04)	3.33 (2.86)
Hyperthyroidism	18	10.56 (6.60–	10.27 (6.51–	3.39 (2.72)	136.11 (45.92–	131.96 (44.80–	4.61 (3.72)

		16.91)	16.21)		403.46)	388.71)	
Pneumonitis	75	2.84 (2.23–3.62)	2.61 (2.11–3.22)	1.39 (1.04)	3.01 (2.34–3.87)	2.75 (2.20–3.44)	1.39 (1.03)
Hepatitis	40	3.13 (2.27–4.32)	2.99 (2.21–4.03)	1.59 (1.13)	6.42 (4.52–9.11)	6.05 (4.35–8.41)	2.38 (1.89)
Myocarditis	16	9.28 (5.64–15.27)	9.05 (5.58–14.70)	3.21 (2.51)	6.67 (3.86–11.54)	6.52 (3.82–11.13)	2.49 (1.72)
Nephritis	0	NE (no mapped cases)	NE	NE	NE (no mapped cases)	NE	NE

Note: Full-database comparator = all other JADER reports in the database version ($n = 1,049,097$). CRC non-ICI comparator = JADER CRC-indication reports without ICI exposure in the same 2018Q4–2026Q1 window ($n = 17,214$). NE = not estimable (no preferred term mapped to the group in the validation cohort). Estimates for the noUncertain sensitivity mapping (excluding 腸炎, 発疹, 肝障害) are provided in the machine-readable file `jader_stage3_signals.csv`; no replication verdict changed under the sensitivity mapping. ROR, reporting odds ratio; PRR, proportional reporting ratio; IC, information component (Bayesian confidence propagation neural network, 0.5 continuity correction).

Supplementary Table S8. JADER high-frequency clusters outside the 10 predefined irAE groups corroborating the FAERS exploratory endocrine candidates

Cluster	Representative MedDRA/J preferred terms (records)	Total records	FAERS exploratory counterpart (Supplementary Table S1 / Fig. S1)
Adrenal insufficiency spectrum	副腎機能不全 Adrenal insufficiency (43); 免疫介在性副腎機能不全 Immune-mediated adrenal insufficiency (31); others (20)	94	Adrenal insufficiency (ROR 13.34)
Hypopituitarism / hypophysitis spectrum	下垂体機能低下症 Hypopituitarism (15); others (10)	25	Hypopituitarism (ROR 54.76)

Type 1 diabetes / diabetic ketoacidosis spectrum	1 型糖尿病 mellitus (22); 糖尿病性ケトアシドーシス Diabetic ketoacidosis (13); others (6)	Type 1 diabetes 41	Type 1 diabetes mellitus (ROR 21.60); Diabetic ketoacidosis (ROR 5.85)
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Note: JADER record counts are adverse-event records (a report may contribute multiple records). “Others” aggregates lower-frequency preferred terms of the same spectrum; the complete PT-level enumeration is provided in Data File S2. FAERS RORs are from the exploratory screening against the full-database comparator (hypothesis-generating).