

READUS-PV Checklist

Manuscript: Immune checkpoint inhibitor adverse events in colorectal cancer: a disproportionality analysis of FAERS with cross-database validation in JADER **Authors:** Yunfei Yan, Wenjing Yue, Hua Song, Zirong Li, Wanhui Li, Xinyi Liu, Jianbo Pan, Shuang Cai (Peking Union Medical College Hospital) **Target journal:** BMC Cancer (Research article) **Checklist:** The REporting of A Disproportionality analysis for drUg Safety signal detection using individual case safety reports in PharmacoVigilance (READUS-PV; Fusaroli M, et al. Drug Saf. 2024;47(6):575-584)

Note: Supplementary materials are provided as additional files: Supplementary Figures S1–S2 (separate image files); Supplementary Tables S1–S6 (CSV files; a formatted Word version of Tables S4–S6 is additionally provided); Supplementary Data File S1 (complete 382-PT screening results including FDR q-values, CSV), Data File S2 (JADER PT mapping audit, 316 PTs, CSV) and Data File S3 (JADER indication-vocabulary audit, 293 strings, CSV). “N/A” marks items not applicable to this study, as permitted by the “if performed / if applicable” wording of the guideline. Section numbers refer to the manuscript structure: 1 Background, 2 Methods (2.1–2.8), 3 Results (3.1–3.6), 4 Discussion (4.1 Statement of key findings, 4.2 Interpretation, 4.3 Strengths and weaknesses, 4.4 Further research), 5 Conclusions, followed by List of abbreviations and Declarations. Tables 1–4 and the 2×2 contingency table appear after the References; figure files are uploaded separately, with legends in the Figure Legends section. Version 1 of the manuscript adds external validation in JADER and VigiAccess (Sections 2.8 and 3.6, Table 4, Figure 3).

Table 1. READUS-PV checklist (main body)

Section and topic	Item #	Checklist item	Location in manuscript / notes
Title	1a	If disproportionality analyses are a prominent component of the published study, the study should be identified as a “disproportionality analysis.” The type of data and name of the database(s) should be specified.	Title page: “...a disproportionality analysis of FAERS with cross-database validation in JADER” — both databases named in the title; full database names (FDA Adverse Event Reporting System; Japanese Adverse Drug Event Report database) spelled out in the Abstract.
	1b	Report the name of adverse event(s) and/or drug(s) under study, when applicable.	Title page: “Immune checkpoint inhibitor adverse events”; the two drugs (pembrolizumab, nivolumab) are named in the Abstract and Sections 1 and 2.2.

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Introduction — Background	2a	Describe the drug(s) and its utilization, the nature of the adverse event(s) under study and its frequency, and the existing knowledge on the drug–event combination.	Section 1, paras. 1–2: ICI use in CRC (MSI-H/dMMR indications), nature and frequency of irAEs, and existing evidence.
	2b	Specify the rationale for performing the analysis, e.g., as part of routine pharmacovigilance, to investigate an overall safety profile, or to assess a pre-specified hypothesis.	Section 1, final para.: no CRC-specific disproportionality analysis reported; CRC background symptomatology may confound pan-cancer signals; pre-specified profiling of 10 irAEs with a dual-comparator stress test.
	2c	Explain why individual case safety report databases and disproportionality analysis are suitable to fill the knowledge gap.	Section 1: randomized trials cannot fully characterize rare or late-onset toxicities; disproportionality analysis of spontaneous reporting systems is established for population-level signal detection.
Introduction — Objectives	3	State specific objectives, identifying the adverse event(s), the drug(s), and the reference group, including any pre-specified hypothesis, if applicable.	Section 1, final paragraph (study aim): 10 predefined irAEs for pembrolizumab/nivolumab; primary reference = all other FAERS reports; sensitivity reference = CRC non-ICI reports; exploratory screen pre-specified as hypothesis-generating.
Methods — Study design	4a	Identify the study (i.e., “disproportionality analysis”) and the type of data used (e.g., “individual case safety reports”).	Section 2.1: retrospective disproportionality analysis of individual case safety reports.
	4b	Provide an outline of the entire study design, including primary and sensitivity analyses performed, and other	Sections 2.1–2.6: primary analysis (10 predefined irAEs, full-database comparator), sensitivity analysis (CRC non-ICI comparator), exploratory all-

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		designs such as case-by-case analysis or literature review.	PT screening with FDR correction and prespecified pseudo-signal adjudication; Section 2.8: external validation in JADER (identical cohort construction, prespecified replication criterion, dual comparators) and VigiAccess (drug-level corroboration); post hoc analyses (PS-restricted comparators, PT-subset analysis, drug-stratified analysis; Tables S4–S6); no case-by-case analysis or literature review (rationale in Section 4.4).
Methods — Data description, access, and pre-processing	5a	Specify the name of the database(s), the database(s) custodian, and the coverage. Specify the type/number of drugs included within the database and the thesaurus, taxonomies, or ontologies used for coding drugs and events.	Sections 2.1, 2.2 & 2.4: FAERS (custodian: US FDA; US and international reports) accessed via the openFDA API; events coded with MedDRA preferred terms; drugs identified by brand (KEYTRUDA, OPDIVO) and generic names. Section 2.8: JADER (custodian: PMDA; Japanese national reports), four relational tables, events coded with MedDRA/J PTs; VigiAccess (custodian: WHO-Uppsala Monitoring Centre), aggregated drug-level data by active ingredient.
	5b	Specify the extraction dates and describe and justify all choices used for data pre-processing, including any data transformation or exclusion, if appropriate.	Sections 2.1 & 2.3: data span August 13, 2014–March 31, 2026 (database locked March 31, 2026); post hoc verification queries on August 28, 2026 (Tables S4, S6); FDA-recommended deduplication; exclusion of blank/unknown/other-disease indications; primary-suspect restriction — each justified. Section 2.8: JADER version pmdacasereport202608

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Methods — Variables definition			downloaded 13 September 2026 (1,049,684 reports); report-level deduplication retaining the latest version; 2018Q4–2026Q1 window (start aligned to the first Japanese approval of pembrolizumab for MSI-H solid tumours, December 2018, the onset of routine ICI use for CRC in Japan; observation windows differ from FAERS by design, justified in Section 4.3); manual adjudication of all 293 verbatim indication strings with 13 non-CRC exclusions (Data File S3); VigAccess queried 13 September 2026.
	6a	Describe the study population, including any restriction.	Sections 2.2–2.3 & 3.1: CRC-indication ICI primary-suspect reports; all restrictions enumerated.
	6b	Describe the nature and the meaning of key variables assessed in the work.	Sections 2.2–2.5: 22-term indication vocabulary (Table S3), suspect-role coding, 2×2 contingency cells.
	6c	Specify and justify any grouping of drugs or events. For drugs, specify and justify whether active ingredients/trade names/salts were considered and/or the selected role.	Sections 2.2–2.4: two ICIs analyzed as a class (same mechanism and CRC indications); trade names and active ingredients both queried; primary-suspect role selected; 10 irAE groups consolidated from MedDRA PTs per guideline-aligned mapping (Table S2).
	6d	Describe any additional data source used, the type of data, and how they interact with individual case safety reports.	Section 2.8: JADER (independent national spontaneous reporting system) used for external validation with identically constructed cohort and dual comparators; VigAccess (WHO-UMC aggregate counts) used for drug-level qualitative corroboration;

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			neither interacts with FAERS case-level data.
Methods — Statistical methods	7a	Present any descriptive analysis performed, specifying variables investigated, statistical tests, and significance thresholds.	Sections 3.1–3.2, Tables 1–2: descriptive counts and percentages; no inferential testing of baseline data.
	7b	Describe the measure(s) selected for the disproportionality analysis including any threshold used to identify signals of disproportionate reporting. Explain the reason for this choice if applicable.	Section 2.5: PRR, ROR, and IC with thresholds ($a \geq 3$, $PRR \geq 2$ with $PRR025 > 1$, $ROR025 > 1$, and $IC025 > 0$); concordance across all three algorithms required; choices referenced. Post hoc exact-BCPNN recalculation confirmed that reported intervals are conservative (Section 2.5).
	7c	Clearly describe any sensitivity analysis and any tool to control confounding, including any restriction, subgroup, stratification, adjustment, or interaction.	Sections 2.5–2.6: disease-matched CRC non-ICI comparator as the sensitivity analysis against indication confounding; Benjamini–Hochberg FDR correction across all screened PTs; post hoc PS-restricted comparators (Table S4), immune-specific/non-specific PT subsets (Table S5), and within-drug stratification with ipilimumab co-reporting (Table S6). Section 2.8: JADER-internal CRC non-ICI comparator ($n = 17,214$) plus sensitivity analysis excluding uncertain-confidence PT mappings.
	7d	Specify the variables and methods used for the case-by-case analysis, including any algorithm or criteria used to assess causality, if performed.	N/A — no case-by-case causality assessment performed (rationale in Section 4.4); prespecified biological-plausibility adjudication of exploratory candidates described in Sections 4.2 and 2.6.

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Results — Participants	7e	Specify any statistical methods used for other data sources.	Section 2.8: identical PRR/ROR/IC algorithms applied to JADER 2×2 contingency tables; prespecified replication criterion (direction-consistent, ROR025 > 1 under the full-database comparator); VigiAccess used descriptively only.
	8a	Specify the number of individual case safety reports included at each stage, including reasons for exclusion.	Section 3.1 & Figure 1: 2,674 retrieved → 2,622 after deduplication → 2,497 with CRC indication → 2,400 primary-suspect reports; reasons given for each exclusion. Section 3.6: JADER 69,290 ICI reports → 66,438 suspected-drug → 606 CRC-indication → 600 within window → 587 after adjudicated exclusions.
	8b	Provide key demographic and clinical characteristics of cases, if possible comparing cases with any appropriate reference group.	Section 3.1 & Table 1: age, sex, region, reporting year, reporter type, and outcomes; comparator-arm demographics are not retrievable from aggregate openFDA counts.
Results — Disproportionality analysis	9	Present all results including confidence intervals. Present also results of sensitivity analyses, if performed.	Section 3.3, Table 3 & Figure 2: primary estimates with 95% CIs; Section 3.4: sensitivity estimates; Section 3.5, Table S1 & Supplementary Data File S1: exploratory screening results; post hoc analyses in Tables S4–S6. Section 3.6, Table 4 & Figure 3: cross-database validation estimates with 95% CIs under both comparators, including the uncertain-mapping sensitivity analysis.
Results — Case-by-case analysis	10	Present the case-by-case analysis of key variables. Present the	N/A — no case-by-case analysis performed (rationale in Section 4.4); adjudication results

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		causality assessment, if applicable.	presented in Section 3.5 and Table S1 (excluded PTs with reasons).
Discussion — Key results	11	Discuss key results with reference to study objectives and contextualize them within the current literature and other consulted sources. Clearly discriminate between expected reactions and emerging safety signals.	Sections 4.1–4.2: results vs objectives (4.1, including the 6/7 cross-database replication); comparison with prior studies, indication-confounding interpretation, cross-database corroboration and the rash divergence, and established irAEs vs emerging hypothesis-generating candidates (4.2).
Discussion — External validity	12a	Discuss the external validity of the results to the general population.	Sections 4.3 & 5: extrapolation to the broader CRC population addressed within limitations and conclusions.
	12b	Discuss the potential relevance of results in clinical practice.	Sections 4.1 & 5: organ-prioritized monitoring implications for clinical and pharmacy practice.
	12c	Propose further study designs if applicable.	Sections 4.4 & 5: time-to-onset analysis, triangulation with registry or claims data, and prospective surveillance proposed (external database validation now performed in JADER and VigiAccess, Sections 2.8 & 3.6).
Discussion — Limitations	13	Present general limitations, making clear that disproportionality analysis alone cannot prove causation or measure incidence, and specific limitations, including confounding and reporting bias and efforts to mitigate them.	Section 4.3: general limitations (underreporting, notoriety bias/Weber effect; no incidence, no causality) and specific limitations (indication misclassification, deduplication asymmetry, concomitant medications, ipilimumab co-reporting (20.2%) with within-drug attenuation, Q1-2026 coverage) with mitigation efforts; Section 4.3 (validation addendum): modest JADER

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			cohort (587 reports), imprecise rare-event estimates, nephritis not assessable, MedDRA/J mapping uncertainty with sensitivity analysis, VigiAccess drug-level aggregation only; Section 4.4: no public preregistration, registry-data triangulation still absent, no case-by-case analysis.
Declarations	14a	Provide the source of funding/sponsorship and the role of the funders/sponsors for the present study and for any original study on which the present article is based.	Declarations — Funding: no specific funding from any public, commercial, or non-profit agency.
	14b	Clearly identify potential commercial and intellectual conflicts of interest (e.g., link to any drug/event investigated, whether financial, legal action, or software used).	Declarations — Competing interests: none declared.
	14c	Declare any institutional approval needed or granted in the investigation.	Declarations — Ethics approval and consent to participate: publicly available, de-identified FAERS data; institutional review board approval not required.
	14d	Include a statement on data availability, code availability (including the version of the statistical software used), and protocol registration.	Section 2.7: Python 3.12 with pandas and matplotlib; Declarations — Availability of data and materials: raw FAERS data via openFDA API; JADER publicly available from the PMDA portal (version pmdacasereport202608, downloaded 13 September 2026); VigiAccess publicly accessible; analytic dataset and

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			scripts on reasonable request; complete 382-PT screening results (with FDR q-values) in Supplementary Data File S1 (see also Declarations — Supplementary Information); Section 4.4: analysis plan specified a priori, not publicly preregistered.

Table 2. READUS-PV checklist for abstracts

Section and topic	Item #	Checklist item	Location in abstract / notes
Background	1a	State the aim/rationale for performing the study.	Abstract — Background: no colorectal cancer-specific pharmacovigilance analysis exists; aim stated at the end of the Background paragraph, including external validation in an independent national database.
	1b	Specify the adverse event(s) and/or the drug(s) under study, when applicable.	Abstract — Background/Methods: irAEs; pembrolizumab and nivolumab.
	1c	Specify the specific population or setting, when applicable.	Abstract: patients with colorectal cancer.
Methods	2a	Identify the study as a “disproportionality analysis” and specify the type of data used.	Abstract — Methods: “This disproportionality analysis queried FAERS...” (individual case safety reports).
	2b	Specify the name of the database(s) used and the type of access.	Abstract — Background/Methods: “US FDA Adverse Event Reporting System (FAERS) ... via the openFDA interface”; “External validation used the Japanese Adverse Drug Event Report database (JADER...) ... plus drug-level corroboration in VigiAccess”.
	2c	Specify the timeframe and geographical region, when applicable.	Abstract — Results: “(August 2014–March 2026)”; US FDA database with international reports; JADER

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Results			validation cohort 2018Q4–2026Q1, Japanese national reports.
	2d	Specify the disproportionality measure(s) used and their statistical significance threshold(s).	Abstract — Methods: “proportional reporting ratio, reporting odds ratio (ROR), and information component, requiring concordance of all three”.
	2e	Specify if a case-by-case analysis is performed.	Abstract — Methods: “No case-by-case analysis was performed.”
	3	Report main findings including their precision (e.g., 95% confidence intervals), together with a short summary of the case-by-case analysis.	Abstract — Results: all seven signal estimates reported with 95% CIs; comparator-reversal results; six of seven signals replicated in JADER under both comparators with the diarrhea reversal qualitatively replicated; no case-by-case analysis performed.
Conclusion	4a	Clearly report key conclusions.	Abstract — Conclusions: organ-prioritized, cross-database-validated toxicity pattern; disease-matched comparators methodologically necessary.
	4b	Acknowledge that the disproportionality analysis is a hypothesis generating or refinement approach.	Abstract — Results: exploratory findings explicitly “all hypothesis-generating”.
	4c	State the implications and clinical relevance of the findings.	Abstract — Conclusions: “an organ-prioritized, cross-database-validated pattern warranting targeted monitoring”.