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Immune Checkpoint Inhibitor-Associated Autoimmune Hemolytic Anemia and Immune Thrombocytopenia: Cross-Database Consistency in FAERS and JADER

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Abstract

Background/Objectives: Autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP) are uncommon hematologic immune-related adverse events of immune checkpoint inhibitors (ICIs). We evaluated whether strict reporting signals were consistent across two national spontaneous-reporting systems and whether this consistency persisted after reviewer-requested harmonization analyses. **Methods:** We performed a cross-database disproportionality study using cumulative FAERS data through 2025 Q3 and JADER 202608. MedDRA 29.0 preferred-term phenotype definitions and analytic rules were defined before final analysis. Primary analyses used primary/secondary-suspect ICI reports in FAERS and suspected-drug reports in JADER, with oncology-restricted, role-harmonized, common-calendar, interaction, and time-to-onset sensitivity analyses. **Results:** FAERS contained 207,459 ICI-exposed reports, including 338 AIHA reports (ROR 8.13, 95% CI 7.26–9.09) and 602 ITP reports (ROR 6.38, 95% CI 5.87–6.93). JADER contained 86,270 ICI-exposed reports, including 128 AIHA reports (ROR 4.27, 95% CI 3.48–5.24) and 410 ITP reports (ROR 3.56, 95% CI 3.18–3.98). Among 20 adequately supported shared comparisons, all were directionally concordant and 19 were positive in both databases. Role-harmonized analysis yielded 18/18 positive comparisons and a common 2025 Q3 cutoff yielded 19/19. Exact-day time to onset was available for 43.8% of JADER AIHA and 51.0% of ITP reports and was sensitive to drug-event interval selection, particularly for AIHA. **Conclusions:** Strict ICI-associated AIHA and ITP definitions show robust cross-database directional consistency. These data quantify reporting disproportionality, rather than incidence or clinical risk; cancer-context and temporal findings remain exploratory.

Keywords: immune checkpoint inhibitors; autoimmune hemolytic anemia; immune thrombocytopenia; pharmacovigilance; FAERS; JADER

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1. Introduction

Immune checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte antigen 4 (CTLA-4) have transformed treatment across multiple solid and hematologic malignancies. By disrupting inhibitory immune signaling, these agents can also produce immune-related adverse events affecting almost any organ system [1–3].

Hematologic immune-related adverse events are less common than endocrine, dermatologic, gastrointestinal, or pulmonary toxicities, but they can be rapidly progressive and clinically consequential. Autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP) are among the best-described immune cytopenias associated with checkpoint

blockade. Their diagnosis is challenging in patients with cancer because anemia and thrombocytopenia also arise from marrow infiltration, infection, bleeding, cytotoxic therapy, nutritional deficiency, disseminated intravascular coagulation, and other drugs [4].

Published evidence has established that both AIHA and ITP can occur during checkpoint blockade, but the available studies have addressed different questions. Early VigiBase and Food and Drug Administration (FDA) case-based analyses established the clinical signal [5,6]. French registries and multicenter series added clinical adjudication, laboratory findings, and treatment outcomes [7–9]. Several recent FDA Adverse Event Reporting System (FAERS) studies focused specifically on ITP signal detection and time-to-onset [10–12]. A 2026 FAERS study broadened the field further, by screening hematologic and thrombotic toxicities across ICI classes [13]. Collectively, these studies support a genuine safety concern, but they do not establish whether strict AIHA and ITP reporting signals show directional consistency across national spontaneous-reporting systems, remain detectable against an oncology-only comparator background, or show formal cancer-indication effect modification under sparse-data safeguards and multiplicity control.

Recent denominator-based studies provide complementary clinical context. A 2026 multicenter cohort identified clinically adjudicated ICI-associated ITP in 214 of 86,467 ICI-treated patients (0.25%), while a 2026 Japanese cohort identified 40 hematologic immune-related adverse events among 3371 ICI-treated patients (1.2%), with ITP the most common phenotype. These estimates cannot be converted directly into fold increases from spontaneous-report RORs because the denominators, observation periods, and ascertainment methods differ.

We therefore performed a phenotype-focused cross-database analysis of ICI-associated AIHA and ITP using FAERS and Japanese Adverse Drug Event Report (JADER) databases. Phenotype definitions, exposure sets, and analytic rules were defined before final analysis. The primary objective was to test whether strict all-ICI reporting signals and their direction were consistent across databases. Secondary and exploratory analyses examined oncology-restricted backgrounds, checkpoint classes, individual agents, cancer-context heterogeneity, report-level outcomes, and JADER time-to-onset. We anticipated that signal direction could transport across systems, even when absolute ROR magnitude differed, because spontaneous-reporting systems capture different populations, drug uptake, indications, and reporting processes.

2. Materials and Methods

2.1. Data Sources and Reporting Framework

FAERS was analyzed using the cumulative DiAna 25 Q3 release, with report deduplication and standardized active-ingredient mapping [14,15]. JADER was analyzed using the Pharmaceuticals and Medical Devices Agency (PMDA) 202,608 cumulative release. The study was designed and reported with reference to contemporary guidance for FAERS interpretation and the READUS-PV recommendations for disproportionality analyses [16].

The primary FAERS universe comprised 15,488,744 deduplicated reports. Primary ICI exposure required a primary-suspect or secondary-suspect drug role. The standardized JADER DEMO table contained 1,049,684 unique report identifiers and 1,049,684 unique report identifier-plus-version case keys, with no duplicated report identifiers or case keys remaining after case construction. JADER ICI exposure required the suspected-drug role. All analyses were performed at report level. A reviewer-requested sensitivity analysis truncated JADER through 2025 Q3 to match the FAERS calendar endpoint. The analysis hierarchy was explicitly defined as primary strict all-ICI endpoints, secondary/supportive checkpoint-class and oncology-restricted analyses, and exploratory individual-agent, interaction, demographic, broad-phenotype, multiple-ICI, outcome, and TTO sensitivity

analyses. Study-defined phenotype tiers are summarized in Supplementary Table S1, the ICI exposure set in Supplementary Table S2, canonical cancer categories in Supplementary Table S3, and the complete revised analysis hierarchy and quality-control framework in Supplementary Table S12.

2.2. ICI Exposure Definitions

The FAERS exposure set included 12 PD-1, PD-L1, or CTLA-4 inhibitors represented through 2025 Q3: nivolumab, pembrolizumab, cemiplimab, tislelizumab, dostarlimab, toripalimab, retifanlimab, atezolizumab, durvalumab, avelumab, ipilimumab, and tremelimumab. Generic and brand-name aliases were defined before final analysis. JADER contained nine directly comparable agents: nivolumab, pembrolizumab, cemiplimab, tislelizumab, atezolizumab, durvalumab, avelumab, ipilimumab, and tremelimumab. Analyses were conducted for all ICIs, checkpoint classes, and individual agents where report support was adequate.

2.3. Outcome Definitions

AIHA and ITP were defined using MedDRA 29.0 preferred-term (PT)-level phenotype sets curated within institutional licensed-terminology environments. The strict definition used one highly specific PT for each phenotype; sensitivity definitions broadened AIHA to 3 PTs and ITP to 2 PTs, and a broader exploratory AIHA definition comprised 5 PTs. English and Japanese implementations were harmonized at the same hierarchy level. Generic thrombocytopenia and platelet-count-decrease concepts were excluded from the primary ITP phenotype because the objective was immune thrombocytopenia, rather than nonspecific platelet reduction. Exact licensed PT names, codes, and bilingual mappings are not redistributed because of MedDRA licensing restrictions; this is acknowledged as a reproducibility limitation.

2.4. Disproportionality and Sensitivity Analyses

For each exposure-endpoint pair, a 2 × 2 reporting table was constructed and the reporting odds ratio (ROR) with 95% confidence interval (CI), proportional reporting ratio (PRR), Fisher exact test, chi-square statistic, and an unshrunk observed-to-expected information component were calculated. The ROR was the primary effect measure. A conventional positive signal required at least 3 exposed endpoint reports and an ROR lower 95% confidence bound greater than 1. Continuity correction was used only when a 2 × 2 cell was zero. RORs quantify reporting disproportionality, and were not interpreted as incidence, absolute-risk, or causal treatment effects [17].

Sensitivity analyses in FAERS used primary-suspect exposure only, broader endpoint definitions, healthcare-professional- and consumer-reporter strata, sex and age strata, and an oncology-restricted background. JADER sensitivity analyses included spontaneous reports, endpoint expansions, oncology restriction, reporter/sex/age strata, and a common calendar cutoff through 2025 Q3. A role-harmonized cross-database sensitivity compared FAERS primary-suspect-only exposure directly with JADER suspected-drug exposure in the shared nine-agent set. Complete FAERS primary and sensitivity disproportionality outputs are provided in Supplementary Table S4A–E; the role-harmonized and common-calendar cross-database sensitivities are summarized in Supplementary Table S14A,B.

2.5. Cancer-Indication Interaction Models

Fifteen canonical cancer-indication groups were defined before final analysis, and harmonized across databases. Within the broad oncology universe, we modeled the strict endpoint as a function of ICI exposure, cancer-indication membership, their interaction,

sex, age group, and report year. A model was fitted only when each of the four exposure-by-indication cells contained at least 3 endpoint events and at least 3 non-events. Grouped maximum-likelihood logistic regression was used when stable; separation or boundary behavior was handled with bias-reduced logistic regression. BH correction was applied across estimable interaction terms within each database. Interaction estimates were interpreted only as exploratory heterogeneity in reporting disproportionality, not clinical risk modification. For revision, a sensitivity analysis required cancer-category membership among ICI-exposed reports to be linked specifically to the suspect ICI drug row (FAERS: PRIMARYID plus DRUG_SEQ; JADER: indication on the suspected-ICI row), while preserving the original report-level category definition for non-ICI comparator reports. Complete original interaction models are reported in Supplementary Tables S5 and S8, and the indication-linkage QC and linked-indication sensitivity are reported in Supplementary Table S16A,B.

2.6. Cross-Database Consistency and Heterogeneity

For direct cross-database comparison, FAERS was restricted to the nine-agent ICI set shared with JADER. Eligibility required at least 3 exposed endpoint reports in both databases; low- or zero-event rows remained visible in the complete supplementary table but were labeled descriptive only, and excluded from the denominator. Directional consistency required ROR estimates on the same side of 1, and a positive signal in both databases required the predefined minimum-event and lower-confidence-bound criteria in each system. Magnitude heterogeneity was quantified as the FAERS:JADER ratio of RORs with 95% CIs derived from log-ROR standard errors and BH-adjusted heterogeneity tests. Because only two databases were compared, ratio-of-ROR was preferred to I-squared. These analyses characterize transportability of reporting measures and not biological differences between countries [18].

2.7. Time-to-Onset and Reported Outcomes

JADER time-to-onset (TTO) analysis required day-precision drug-start and adverse-event onset dates. The primary analysis selected the earliest plausible non-negative case-level interval from 0 to 3650 days when multiple eligible intervals existed. Reviewer-requested sensitivity restricted the analysis to reports with one eligible ICI-event interval. Exact-day coverage was reported, relative to all ICI-associated endpoint reports. Weibull distributions were fitted when at least 10 exact-day observations were available. A beta below 1 was described as an observed onset distribution weighted toward earlier treatment periods, rather than a patient-level hazard. No same-day observations were present in the overall AIHA or ITP exact-day subsets, so day-0 exclusion did not alter the overall fits; primary timing summaries are reported in Supplementary Table S10A,B and Supplementary Figure S2, while reviewer-requested coverage and interval-selection sensitivities are reported in Supplementary Table S15A–C and Supplementary Figure S5 [19].

FAERS seriousness fields and JADER reaction outcomes were summarized descriptively. Reviewer-requested exploratory comparisons contrasted non-overlapping AIHA-only and ITP-only FAERS reports for report-level seriousness designations. Because these fields apply to spontaneous safety reports, rather than adjudicated endpoint-specific outcomes, percentages were not interpreted as case-fatality or clinical severity rates. Co-reporting of multiple ICI products was explored, but was not equated with confirmed concurrent combination therapy. Primary descriptive outcome and multiple-ICI analyses are provided in Supplementary Table S11A–D and Supplementary Figures S3 and S4; reviewer-requested exclusive-group seriousness and AIHA/ITP overlap analyses are provided in Supplementary Table S17A,B and Supplementary Figure S6.

2.8. Ethics and Data Sources

The study used de-identified, publicly available pharmacovigilance reports without patient contact or attempted re-identification. Per local legislation, this work is considered exempt from institutional ethics committee review. Source FAERS and JADER data are available from the FDA and PMDA, respectively. In accordance with the JADER terms of use, PMDA was notified in advance of the planned publication of results derived from the Japanese Adverse Drug Event Report database. Derived aggregate tables used in this analysis are supplied as Supplementary Materials. Analysis code and additional aggregate outputs are available from the corresponding author, upon reasonable request.

2.9. Generative AI Assistance

OpenAI ChatGPT (version 5.6 Sol) was used for language editing, manuscript organization, and assistance with drafting and debugging R code. All analytic specifications, code execution, numerical outputs, and scientific interpretations were reviewed and verified by the author.

3. Results

3.1. Study Populations and Primary Reporting Signals

FAERS contained 207,459 primary- or secondary-suspect ICI-exposed reports. Strict AIHA was reported in 338 ICI-exposed reports (ROR 8.13, 95% CI 7.26–9.09) and strict ITP in 602 (ROR 6.38, 95% CI 5.87–6.93). Positive signals were present across PD-1, PD-L1, and CTLA-4 classes (Figure 1). For AIHA, class RORs were 8.24 for PD-1, 7.61 for PD-L1, and 11.12 for CTLA-4; corresponding ITP RORs were 6.46, 6.02, and 5.92. Major individual agents also showed positive signals when sufficient events were available (Supplementary Table S4A).

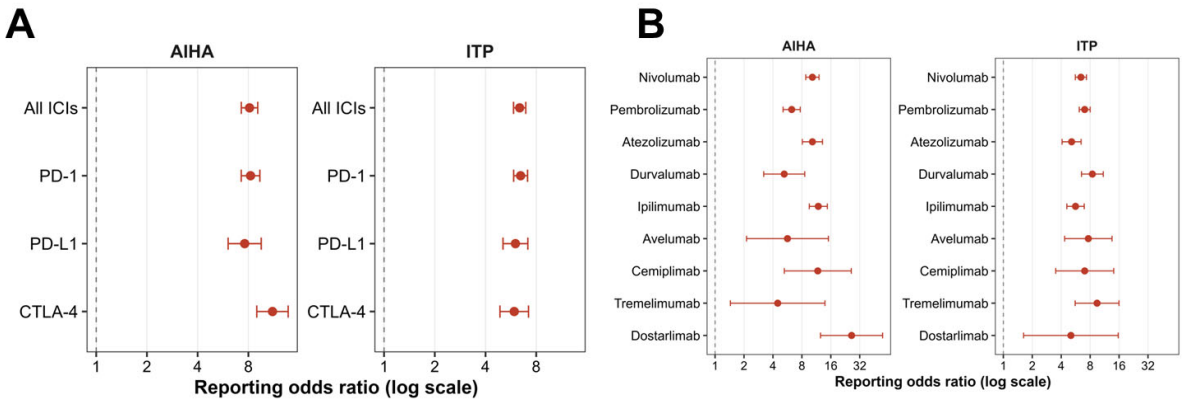


Figure 1. Primary FAERS reporting signals for ICI-associated autoimmune hemolytic anemia and immune thrombocytopenia. (**A**) Checkpoint-class analysis. The left facet shows strict AIHA and the right facet strict ITP. Within each facet, points and horizontal bars represent the reporting odds ratio (ROR) and 95% confidence interval for all ICIs combined and for the PD-1, PD-L1, and CTLA-4 classes. (**B**) Individual-agent analysis. Strict AIHA (left facet) and strict ITP (right facet) are shown for individual ICIs with adequate report support. Primary FAERS exposure required the ICI to be recorded as a primary- or secondary-suspect drug. The vertical dashed line at ROR = 1 is the null value; estimates to the right indicate disproportionate reporting, relative to the remainder of the FAERS comparison universe. The x axes are logarithmic. RORs describe reporting disproportionality, and must not be interpreted as incidence, relative risk, or causal effect. AIHA, autoimmune hemolytic anemia; CI, confidence interval; CTLA-4, cytotoxic T-lymphocyte antigen 4; FAERS, FDA Adverse Event Reporting System; ICI, immune checkpoint inhibitor; ITP, immune thrombocytopenia; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; ROR, reporting odds ratio.

JADER contained 86,270 suspected-drug ICI-exposed reports. AIHA was reported in 128 ICI-exposed reports (ROR 4.27, 95% CI 3.48–5.24) and ITP in 410 (ROR 3.56, 95% CI 3.18–3.98). Positive signals were again present for PD-1, PD-L1, and CTLA-4 classes. Overall and class-level results for the nine-agent shared-exposure set are shown in Table 1. At class level, JADER RORs for AIHA were 3.85 for PD-1, 3.99 for PD-L1, and 3.27 for CTLA-4; corresponding ITP RORs were 3.17, 3.66, and 3.22. Among shared agents with adequate event support, nivolumab, pembrolizumab, ipilimumab, atezolizumab, durvalumab, and tremelimumab generally showed positive signals, although estimates for less frequently reported agents were less precise.

Table 1. Cross-database primary strict reporting signals for the shared ICI exposure set. The FAERS comparison uses the nine ICI agents shared with JADER. A positive signal required at least 3 exposed endpoint reports and a lower 95% ROR confidence bound >1. AIHA, autoimmune hemolytic anemia; CI, confidence interval; FAERS, FDA Adverse Event Reporting System; ICI, immune checkpoint inhibitor; ITP, immune thrombocytopenia; JADER, Japanese Adverse Drug Event Report; ROR, reporting odds ratio.

Exposure	Endpoint	FAERS Event Reports	FAERS Exposed Reports	FAERS ROR (95% CI)	JADER Event Reports	JADER Exposed Reports	JADER ROR (95% CI)
All ICIs	AIHA	332	204,918	8.07 (7.20–9.03)	128	86,270	4.27 (3.48–5.24)
All ICIs	ITP	600	204,918	6.43 (5.92–6.99)	410	86,270	3.56 (3.18–3.98)
PD-1	AIHA	251	149,557	8.17 (7.19–9.29)	96	66,776	3.85 (3.08–4.83)
PD-1	ITP	453	149,557	6.54 (5.95–7.20)	301	66,776	3.17 (2.80–3.60)
PD-L1	AIHA	77	47,021	7.61 (6.07–9.54)	32	19,190	3.99 (2.79–5.72)
PD-L1	ITP	136	47,021	6.02 (5.08–7.14)	108	19,190	3.66 (3.01–4.44)
CTLA-4	AIHA	86	36,066	11.12 (8.98–13.78)	29	21,061	3.27 (2.24–4.76)
CTLA-4	ITP	103	36,066	5.92 (4.87–7.20)	105	21,061	3.22 (2.65–3.93)

3.2. Robustness to Alternative Backgrounds and Definitions

Restricting FAERS to an oncology-only comparator background attenuated the AIHA signal, but it remained clearly positive (315 events; ROR 4.21, 95% CI 3.69–4.81); the ITP signal remained strong (559 events; ROR 5.37, 95% CI 4.84–5.95) (Figure 2A). Corresponding JADER oncology-restricted estimates were also positive: ROR 4.49 (95% CI 3.38–5.95) for AIHA and 6.29 (95% CI 5.28–7.49) for ITP.

FAERS primary-suspect-only estimates were 7.86 (95% CI 6.93–8.91) for AIHA and 6.31 (95% CI 5.75–6.92) for ITP. Expanding to sensitivity endpoint definitions yielded RORs of 7.65 and 5.68, respectively. Broadening AIHA to include nonspecific hemolytic anemia attenuated the ROR to 4.03 in FAERS and 1.32 in JADER, supporting the importance of phenotype specificity. Healthcare-professional-only analyses remained positive in both databases. Full FAERS reporter-, sex-, and age-stratified results are provided in Supplementary Table S6 and visualized in Supplementary Figure S1. JADER results are provided individually as the primary strict analysis (Supplementary Table S7A), spontaneous-report sensitivity analysis (Supplementary Table S7B), phenotype-sensitivity analysis (Supplementary Table S7C), broad exploratory-phenotype analysis (Supplementary Table S7D), and oncology-restricted strict analysis (Supplementary Table S7E). In FAERS, healthcare-professional-only RORs were 5.52 for AIHA and 4.79 for ITP, whereas consumer-only estimates were 13.62 and 6.40, respectively. Adult age strata remained positive for both endpoints; these stratum-specific

analyses were used to assess robustness, and were not interpreted as formal demographic-effect modification.

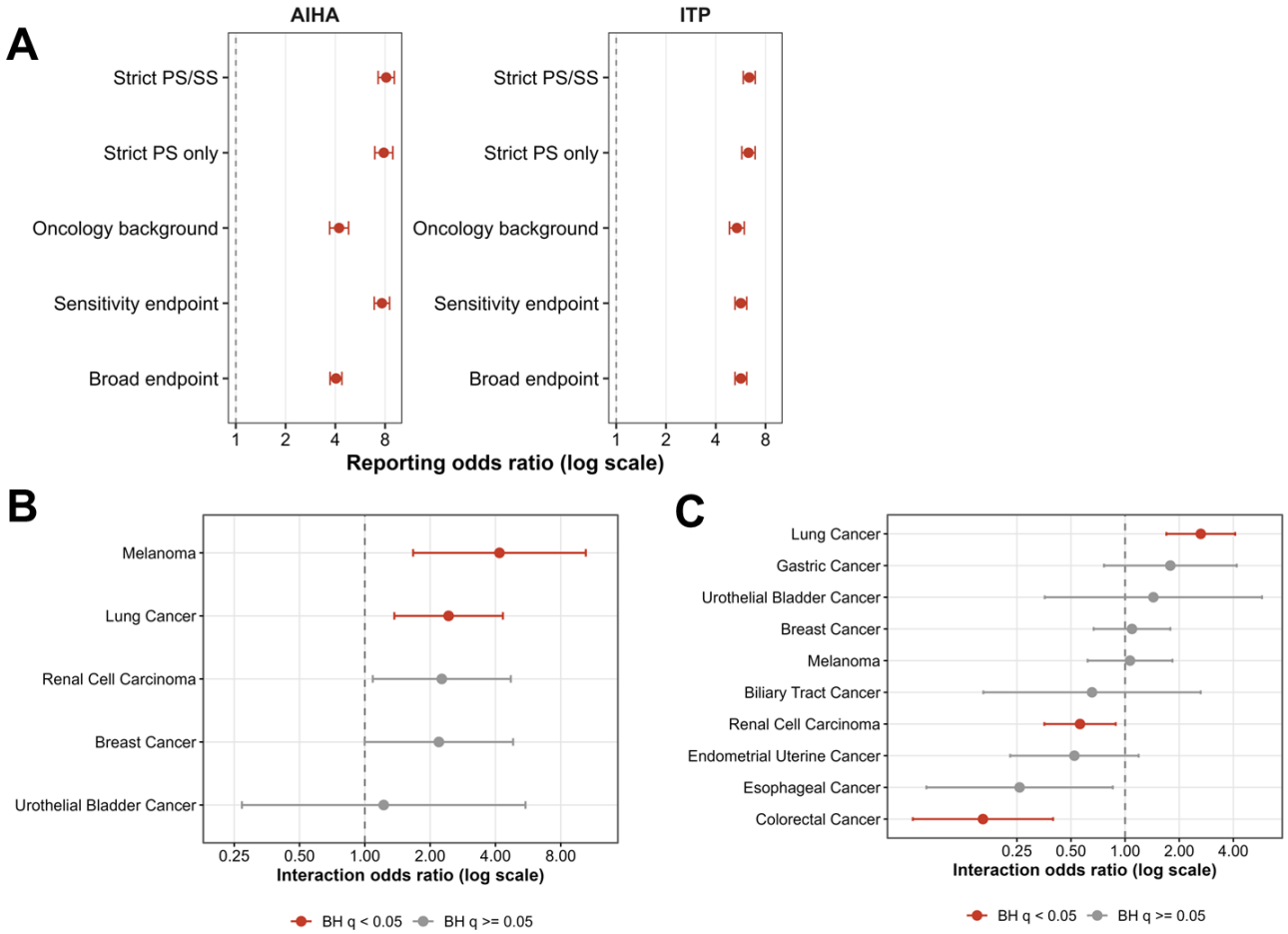


Figure 2. Robustness of the FAERS signal and exploratory cancer-indication heterogeneity. (**A**) Overall FAERS sensitivity analyses for AIHA and ITP, including the primary primary-/secondary-suspect analysis, primary-suspect-only exposure, oncology-background restriction, sensitivity phenotype definitions, and broader exploratory phenotype definitions. (**B**) AIHA ICI-linked cancer-indication interaction analysis. (**C**) ITP ICI-linked cancer-indication interaction analysis. In panels B-C, cancer-category membership among ICI-exposed reports was required to be linked specifically to the suspect ICI drug row, while non-ICI comparator reports retained report-level category membership. Points and horizontal bars show adjusted interaction ORs and 95% CIs. Red estimates remained significant after BH correction, and gray estimates did not. Interaction OR > 1 indicates stronger relative reporting disproportionality within the cancer category and OR < 1 relative attenuation. Models were adjusted for sex, age group, and report year, and were fitted only when all four exposure-by-category cells met the support criterion. Interaction estimates are exploratory, and are not clinical risk-modification estimates. AIHA, autoimmune hemolytic anemia; BH, Benjamini–Hochberg; CI, confidence interval; FAERS, FDA Adverse Event Reporting System; ICI, immune checkpoint inhibitor; ITP, immune thrombocytopenia; OR, odds ratio.

3.3. Exploratory Cancer-Indication Heterogeneity

In the original FAERS report-level cancer-category analysis, 15 of 30 endpoint-by-category models met the support criterion and six interaction terms remained significant after BH correction: AIHA with lung cancer, melanoma, and breast cancer; and ITP with lung cancer, renal cell carcinoma, and colorectal cancer (Table 2; Supplementary Table S5). When cancer-category membership among ICI-exposed reports was restricted to indications linked specifically to the suspect ICI, five of these six retained BH significance with pre-

served direction (Figure 2B,C; Table 2; Supplementary Table S16A,B). AIHA-breast cancer attenuated from OR 3.85 (95% CI 2.02–7.33; BH q < 0.001) to OR 2.19 (95% CI 1.00–4.82; BH q = 0.095). The linked sensitivity retained AIHA-lung cancer (OR 2.43; BH q = 0.009), AIHA-melanoma (OR 4.17; BH q = 0.009), ITP-lung cancer (OR 2.64; BH q < 0.001), ITP-colorectal cancer (OR 0.16; BH q < 0.001), and ITP-renal cell carcinoma (OR 0.56; BH q = 0.040).

Table 2. Exploratory cancer-indication interaction findings: original FAERS estimates, reviewer-requested ICI-linked indication sensitivity, and corresponding ICI-linked JADER estimates. BH q values are within-database multiplicity-adjusted values. None of the linked JADER interaction terms survived BH correction. These estimates describe heterogeneity in reporting disproportionality, rather than clinical risk modification. BH, Benjamini–Hochberg; CI, confidence interval; OR, odds ratio.

Endpoint	Cancer	Original FAERS	ICI-Linked FAERS	ICI-Linked JADER	Direction	Status
AIHA	Breast Cancer	3.85 (2.02–7.33); q = 0.000297	2.19 (1.00–4.82); q = 0.095	4.30 (1.27–14.56); q = 0.080	Yes	Attenuated; not BH-significant
AIHA	Lung Cancer	2.54 (1.43–4.52); q = 0.00545	2.43 (1.37–4.33); q = 0.009	1.13 (0.54–2.36); q = 0.843	Yes	Robust
AIHA	Melanoma	4.14 (1.66–10.35); q = 0.00714	4.17 (1.67–10.43); q = 0.009	Not estimable	Yes	Robust
ITP	Lung Cancer	2.63 (1.69–4.09); q = 0.000251	2.64 (1.70–4.09); q = 0.000	1.90 (1.10–3.29); q = 0.080	Yes	Robust
ITP	Colorectal Cancer	0.16 (0.06–0.39); q = 0.000297	0.16 (0.07–0.40); q = 0.001	0.26 (0.08–0.86); q = 0.080	Yes	Robust
ITP	Renal Cell Carcinoma	0.51 (0.32–0.80); q = 0.00911	0.56 (0.36–0.89); q = 0.040	0.59 (0.26–1.33); q = 0.387	Yes	Robust

JADER supported 9 of 30 original interaction models, and none survived BH correction (Supplementary Table S8). None of the ICI-linked JADER interaction terms survived BH correction, either (Supplementary Table S16B). Nominal unadjusted JADER *p* values were, therefore, not considered corroborative evidence. All interaction findings were treated as exploratory reporting heterogeneity, rather than tumor-specific modification of clinical toxicity risk.

3.4. Cross-Database Directional Consistency

Among 20 exposure-endpoint comparisons with at least three exposed endpoint reports in both databases, all 20 (100%) had concordant ROR direction and 19 (95%) met the positive-signal definition in both FAERS and JADER (Figure 3; revised Supplementary Table S9). AIHA was positive in both databases for 9 of 10 eligible comparisons and ITP for all 10. The only eligible comparison not positive in both systems was tremelimumab-AIHA; both point estimates remained above 1, but the JADER 95% CI included 1. Low- or zero-event rows visible in Supplementary Table S9 were descriptive only, and did not enter these denominators.

Reviewer-requested harmonization analyses strengthened the directional-consistency result. With FAERS restricted to primary-suspect exposure and JADER to suspected-drug exposure, 18/18 eligible comparisons were directionally concordant and positive in both databases (Supplementary Table S14A). When both databases were restricted through 2025 Q3, 19/19 eligible comparisons were directionally concordant and positive in both; tremelimumab-AIHA no longer met the event-support threshold under the common cutoff and was excluded, rather than counted as negative (Supplementary Table S14B). Absolute ROR magnitude, nevertheless, differed substantially: 18 of 20 eligible primary comparisons

had BH-significant magnitude heterogeneity, emphasizing that direction transported more consistently than effect size (Supplementary Table S9).

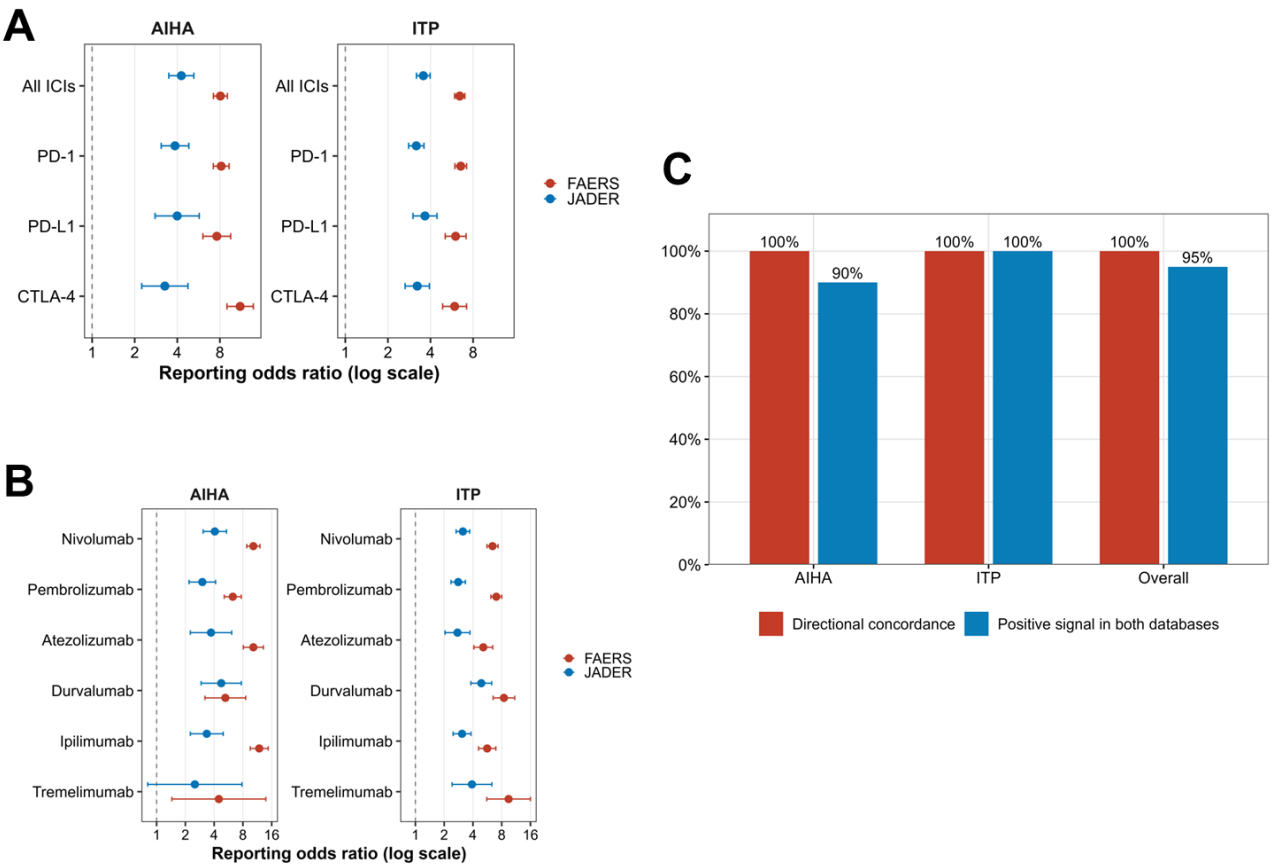


Figure 3. Cross-database directional consistency of strict AIHA and ITP reporting signals in FAERS and JADER. (**A**) Overall and checkpoint-class paired estimates for the nine ICI agents shared between databases. (**B**) Individual-agent paired FAERS and JADER RORs for adequately supported comparisons. (**C**) Summary of the percentage of eligible comparisons with concordant ROR direction and with a positive signal in both databases. Eligibility required at least three exposed endpoint reports in both databases. Direction was concordant for 10/10 AIHA, 10/10 ITP, and 20/20 overall eligible comparisons; positive reporting signals were present in both databases for 9/10 AIHA, 10/10 ITP, and 19/20 overall comparisons. Low- or zero-event rows in Supplementary Table S9 are descriptive only, and do not enter these denominators. The dashed vertical line in panels A and B denotes ROR = 1; x axes are logarithmic. Differences in ROR magnitude are quantified separately, and are not interpreted as differences in clinical risk. AIHA, autoimmune hemolytic anemia; CI, confidence interval; CTLA-4, cytotoxic T-lymphocyte antigen 4; FAERS, FDA Adverse Event Reporting System; ICI, immune checkpoint inhibitor; ITP, immune thrombocytopenia; JADER, Japanese Adverse Drug Event Report database; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; ROR, reporting odds ratio.

3.5. Temporal Characteristics and Descriptive Outcomes

Exact-day JADER TTO was available for 56 of 128 ICI-associated AIHA reports (43.8%) and 209 of 410 ITP reports (51.0%). Under the primary earliest-plausible-interval rule, median TTO was 76.5 days (IQR 27.75–295.5) for AIHA and 48 days (IQR 17–146) for ITP. Restricting to reports with one eligible interval increased the AIHA median to 139.5 days (n = 38; IQR 40.5–387.25) and the ITP median to 59 days (n = 158; IQR 21–160.75). Unique-interval Weibull beta remained below 1 (AIHA 0.798, 95% CI 0.599–0.998; ITP 0.784, 95% CI 0.693–0.875), consistent with an earlier-weighted reported-onset distribution, but showing greater sensitivity for AIHA. No day-0 observations were present, so day-0 exclusion did

not alter the fits (Figure 4; Supplementary Tables S10A,B and S15A–C; Supplementary Figures S2 and S5).

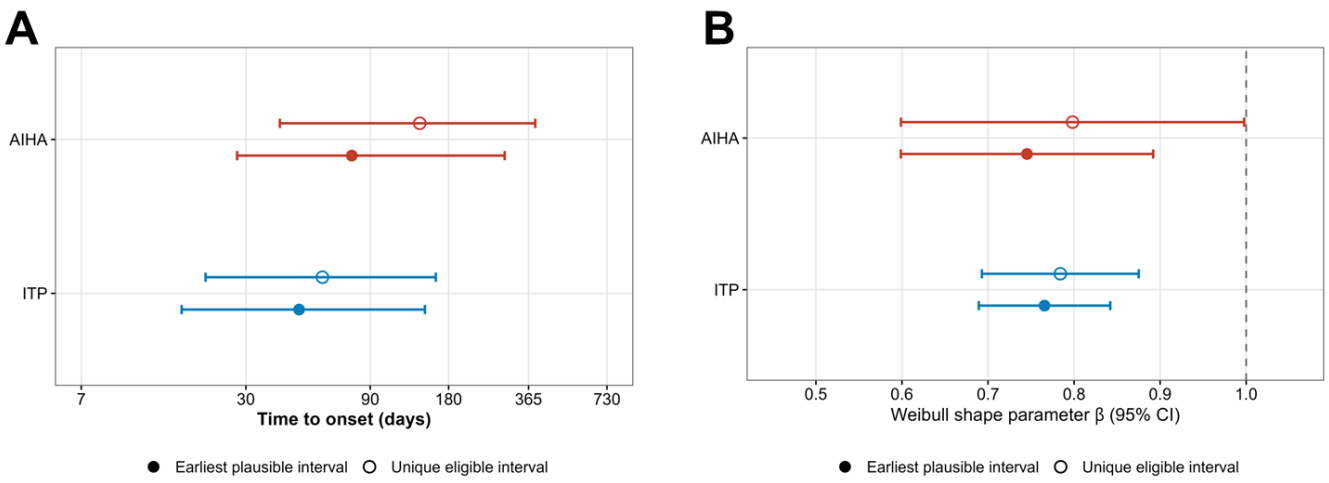


Figure 4. Reviewer-requested sensitivity of JADER time-to-onset characterization to drug-event interval selection. (**A**) Median TTO and IQR for the primary earliest-plausible-interval approach (filled circles) and the sensitivity restricted to reports with one eligible ICI-event interval (open circles). AIHA is shown in red and ITP in blue. Exact-day TTO was available for 56 of 128 ICI-associated AIHA reports (43.8%) and 209 of 410 ITP reports (51.0%). Median TTO shifted from 76.5 to 139.5 days for AIHA and from 48 to 59 days for ITP, under the unique-interval sensitivity. (**B**) Weibull shape parameter beta with 95% CI for the same interval-selection approaches. The dashed vertical line at beta = 1 is the reference value. Beta below 1 describes a reported-onset distribution weighted toward earlier treatment periods, and is not a patient-level hazard. No day-0 observations were present in the overall endpoint subsets. These analyses characterize timing among reports with valid exact-day dates, and do not estimate cumulative incidence. AIHA, autoimmune hemolytic anemia; CI, confidence interval; ICI, immune checkpoint inhibitor; IQR, interquartile range; ITP, immune thrombocytopenia; JADER, Japanese Adverse Drug Event Report database; TTO, time to onset.

Report-level seriousness descriptors in FAERS and reaction outcomes in JADER remained descriptive supplementary analyses. In exploratory comparisons restricted to non-overlapping AIHA-only and ITP-only FAERS reports, only the life-threatening designation remained different after descriptive multiplicity adjustment (11.2% vs. 23.1%; OR for AIHA vs ITP 0.42, 95% CI 0.28–0.63; BH-adjusted $p < 0.001$). FAERS contained 17 strict AIHA + ITP co-reports and 28 explicit Evans-syndrome reports; JADER contained 8 and 18, respectively. These are report-level fractions, not prevalence estimates (Supplementary Tables S11A–D and S17A,B; Supplementary Figures S3, S4 and S6).

4. Discussion

This cross-database study demonstrates robust directional consistency of reporting disproportionality for strict ICI-associated AIHA and ITP across FAERS and JADER. The principal signal was not dependent on one comparator background, checkpoint class, or database. Reviewer-requested role-harmonized and common-calendar analyses strengthened, rather than weakened, the conclusion. These findings support reproducibility of signal direction under alternative data-construction choices, but they should not be interpreted as independent biological confirmation, equality of effect magnitude, incidence, or patient-level risk.

The study builds directly on, but differs materially from, the earlier work that established hematologic immune-related adverse events as a recognizable complication of checkpoint blockade. Davis and colleagues used VigiBase through March 2018 to identify 168 hematologic toxicities, of which immune thrombocytopenia (n = 68) and hemolytic anemia (n = 57) were the most common; their landmark report characterized tumor types, timing, recovery, and fatal outcomes, but did not perform endpoint-specific cross-database consistency assessment or an oncology-background disproportionality analysis [5]. Delanoy et al. clinically adjudicated 35 grade 2 or higher hematologic immune-related adverse events from French registries, including nine AIHA and nine ITP cases, and estimated a frequency of approximately 0.5% in the prospective REISAMIC cohort [7]. That design provided clinical certainty and severity grading unavailable in spontaneous-reporting systems, but it was restricted to anti-PD-1/PD-L1 therapy and selected clinically recognized events, rather than population-scale signal transportability. Tanios et al. subsequently assembled 68 FDA AIHA cases and a literature review, establishing AIHA as a serious ICI-associated event, but without an oncology comparator, formal interaction modeling, or cross-database comparison [6]. A structured comparison of key prior studies and the present design is provided in Supplementary Table S13.

The distinction from the recent ITP-focused FAERS literature is similarly important. Moore et al. combined FAERS pharmacovigilance with a systematic review and identified 329 PD-1/PD-L1-associated ITP reports through September 2022 [12]. Liu et al. analyzed 345 FAERS ITP reports from 2012–2022 using four signal algorithms, described indication distributions and onset patterns, and explored pan-cancer ROR variation, together with TCGA-derived biology [10]. Mo et al. extended FAERS through 2023, identified 404 ITP reports, used four signal-detection approaches, and performed time-to-onset and Weibull analyses [11]. These studies strongly support ITP as an ICI safety signal, but they are single-database analyses focused on ITP alone. The present study updates FAERS through 2025 Q3, analyzes AIHA and ITP in parallel, includes CTLA-4 and newer checkpoint exposures, makes the oncology-only comparator a core robustness analysis, and requires an explicit JADER cross-database consistency assessment for directly comparable exposure-endpoint pairs. Importantly, our temporal analysis is performed in JADER, rather than reused from FAERS, separating signal discovery from temporal characterization across separate reporting systems.

The 2026 study by Hou et al. is the closest contemporary broad pharmacovigilance comparator, but its scientific objective was different [13]. That work surveyed a wide landscape of hematologic toxicities and thrombosis in FAERS from 2014–2024, using disproportionality methods to compare classes, regimens, clinical characteristics, time-to-onset, and outcomes [13]. Such breadth is valuable for mapping the overall hematologic safety spectrum, but it necessarily places immune cytopenias alongside nonspecific anemia, thrombocytopenia, neutropenia, myelosuppression, thrombosis, and disseminated intravascular coagulation. Our study deliberately takes the opposite approach: two biologically coherent autoimmune cytopenias were defined before final analysis, strict and sensitivity phenotype tiers were separated, nonspecific platelet reduction was excluded from the primary ITP phenotype, and the analyses were optimized for robustness and cross-database consistency, rather than signal inventory. Hou et al. did not perform a cross-database JADER comparison, an oncology-background disproportionality analysis, or formal ICI-by-cancer-indication interaction modeling [13]. The studies are therefore complementary, rather than duplicative: one maps breadth, whereas ours tests cross-database consistency and context dependence for two specific immune-mediated phenotypes.

The indication-interaction analysis provides an additional distinction from prior work. Earlier ITP studies described underlying cancer distributions or calculated cancer-specific

RORs. For example, Liu et al. found that lung and skin cancers accounted for a large fraction of ITP reports, and explored pan-cancer ROR variation [10]. Such analyses are informative descriptively, but a high ROR within one cancer type is not, in itself, a formal test for whether cancer type modifies the ICI association. We therefore modeled an explicit ICI-by-indication interaction within a broad oncology universe, adjusted for sex, age group, and report year, required minimum event and non-event support in all four interaction cells, and controlled the false-discovery rate across estimable models. Six original FAERS interactions survived BH correction; after requiring the cancer indication in ICI-exposed reports to be linked specifically to the suspect ICI, five remained BH-significant and all six preserved direction. The AIHA-breast cancer interaction attenuated, and no longer survived multiplicity correction. No JADER interaction survived BH correction in either the original or linked-indication analysis. These patterns should therefore be treated as hypothesis-generating reporting heterogeneity, rather than evidence that tumor biology causally modifies toxicity. Potential explanations include regimen mix, prior cytotoxic or targeted therapy, co-medication, tumor-associated immune dysregulation, calendar-time uptake, and differential reporting intensity.

Cross-database directional consistency is a major methodological contribution of this work over prior single-database FAERS analyses. JADER was not used simply as a descriptive adjunct: FAERS was restricted to the nine ICI agents available in both systems, eligibility was explicitly defined, and direction and magnitude were evaluated separately. The reviewer-requested role-harmonized and common-calendar analyses further tested whether concordance depended on exposure-role or calendar differences. These results support consistency of signal direction under a common analytic framework, not independent biological confirmation or equality of clinical effect size [15,17,18].

The temporal analysis uses JADER for timing characterization and explicitly reports exact-day coverage and interval-selection sensitivity. Under the primary earliest-interval rule, the 48-day ITP median remained close to prior FAERS estimates [11]. AIHA timing, however, was more sensitive to interval selection. In the unique-interval sensitivity, Weibull beta remained below 1 for both endpoints, consistent with an observed reported-onset distribution weighted toward earlier treatment periods. These analyses describe timing among selected reports with exact-day data, and do not estimate patient-level hazard, cumulative incidence, or a recommended monitoring interval.

The biological plausibility of both phenotypes is consistent with checkpoint biology, but cannot be resolved from spontaneous-reporting data. PD-1/PD-L1 and CTLA-4 pathways are central to peripheral tolerance; their blockade can amplify autoreactive T-cell responses, alter regulatory T-cell restraint, and indirectly promote B-cell activation and autoantibody-mediated blood-cell clearance [4,7,8]. AIHA and ITP may, therefore, represent different hematologic manifestations of a broader loss of immune tolerance, rather than drug-specific off-target toxicity. The positive signals across PD-1, PD-L1, and CTLA-4 classes are compatible with this interpretation, but the database design cannot identify the operative mechanism in individual cases or distinguish antibody-mediated from predominantly cellular immune injury.

The distinction between signal direction and magnitude is important. FAERS RORs were generally larger than JADER RORs, and 18 of 20 eligible primary comparisons showed BH-significant magnitude heterogeneity. National reporting systems differ in reporter composition, drug uptake, indication mix, regulatory pathways, and coding practice. The revised ratio-of-ROR analysis therefore makes magnitude heterogeneity explicit, while supporting the narrower conclusion of cross-database directional consistency.

The interaction analysis is now positioned uniformly as exploratory. No JADER interaction survived multiplicity correction, and nominal JADER p values are not considered

corroborative evidence. The ICI-linked indication sensitivity also showed why caution is appropriate: five of six original FAERS BH-significant interactions remained significant, whereas AIHA-breast cancer attenuated, and no longer survived BH correction. These patterns may generate hypotheses, but they do not establish tumor-specific modification of clinical toxicity risk.

Population-based epidemiology provides context, but not a conversion factor, for FAERS/JADER RORs. In Denmark, AIHA incidence was 1.77 per 100,000 person-years in 2008–2016, and prevalence was 17.01 per 100,000 persons in 2015 [20]. A French nationwide study estimated ITP incidence at 2.9 per 100,000 person-years [21]. In contrast, the 2026 multicenter ICI cohort identified adjudicated ICI-ITP in 0.25% of 86,467 treated patients [22], and a Japanese cohort identified any hematologic irAE in 1.2% of 3371 ICI-treated patients, with ITP the most common phenotype [23]. These denominator-based studies contextualize rarity and clinical relevance, but dividing them by annual population incidence or by spontaneous-report RORs would not yield a valid fold increase because populations, observation periods, and ascertainment methods are not comparable.

The greater number of ITP compared with AIHA reports should likewise not be interpreted as proof that ITP is more frequent after ICI therapy. AIHA had the larger ROR in both FAERS and JADER. Differences in report counts could reflect background disease frequency, recognition and coding, differential reporting, treatment setting, or true biological differences; this design cannot distinguish these mechanisms. Evans syndrome illustrates the same limitation: a Danish nationwide study estimated adult incidence at 1.8 per million person-years and prevalence at 21.3 per million persons [24], and clinical reviews estimate Evans syndrome in approximately 5–10% of adult warm AIHA and 2–5% of adult ITP [25]. The approximately 3% explicit Evans-syndrome reporting fraction in our AIHA/ITP union is therefore descriptive, and not directly comparable with population prevalence.

The limitations of this study include the following. FAERS and JADER are spontaneous-reporting systems subject to under-reporting, stimulated reporting, missing data, duplicate or follow-up records, confounding by indication, concomitant drugs, and lack of exposed-person denominators. RORs are measures of disproportional reporting, not incidence ratios or causal effects. Strict terminology-based phenotype definitions improve specificity, but cannot confirm laboratory criteria, direct antiglobulin testing, platelet nadirs, marrow findings, or exclusion of competing etiologies. This is precisely where clinically adjudicated series such as those reported so far remain indispensable [7–9]. Cancer indications were derived from report fields, and may be incomplete or overlapping; residual confounding remains possible, despite adjustment; and sparse-data restrictions reduced the number of JADER interaction models that could be estimated reliably. Report-level seriousness fields do not establish that AIHA or ITP caused hospitalization or death. Finally, the multiple-ICI analysis cannot distinguish confirmed concurrent combination therapy from sequential treatment or multiple suspect products in one report [14–16,18]. Exact licensed MedDRA PT names, codes, and bilingual mappings cannot be redistributed under the institutional terminology license, which limits independent reproducibility. Cancer indications may be incomplete or overlapping, despite the ICI-linked sensitivity analysis. Exact-day TTO was available only for selected subsets, and AIHA timing was sensitive to interval selection. Seriousness and death are report-level regulatory descriptors, rather than endpoint-attributable outcomes.

These limitations are balanced by features not combined in the earlier literature: strict- and sensitive-phenotype tiers defined before final analysis; transparent active-ingredient exposure definitions; parallel analysis of two autoimmune cytopenias; primary and oncology-restricted disproportionality analyses; formal but explicitly exploratory indication interactions; cross-database eligibility with role and calendar harmonization; quantitative magnitude heterogeneity; and exact-day temporal characterization with interval-selection sensi-

tivity. The resulting framework moves beyond isolated positive RORs toward a transparent assessment of signal consistency, while preserving the causal boundary appropriate for spontaneous-report data.

5. Conclusions

Strict ICI-associated AIHA and ITP definitions demonstrated strong cross-database directional consistency across FAERS and JADER, including under role-harmonized and common-calendar sensitivity analyses. The results should be interpreted as pharmacovigilance signal consistency, rather than clinical risk quantification. They support consideration of immune-mediated cytopenia in the differential diagnosis of otherwise unexplained anemia, hemolysis, or thrombocytopenia during ICI therapy, while emphasizing the need for denominator-based and clinically adjudicated studies to quantify absolute risk and validate cancer-context or temporal patterns.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/hemato7040041/s1. Table S1: Phenotype-construction framework; Table S2: ICI exposure set and cross-database availability; Table S3: Canonical cancer-indication categories; Table S4A–E: FAERS primary and sensitivity analyses; Table S5: Complete FAERS cancer-indication interaction models; Table S6: FAERS reporter-, sex-, and age-stratified analyses; Table S7A–E: JADER primary and sensitivity analyses; Table S8: Complete JADER cancer-indication interaction models; Table S9: Cross-database consistency and ROR-magnitude heterogeneity; Table S10A,B: JADER time-to-onset summaries; Table S11A–D: Report-level outcomes and multiple-ICI co-reporting analyses; Table S12: Revised analysis framework and quality control; Table S13: Design context of prior studies; Table S14A,B: Role-harmonized and common-calendar sensitivities; Table S15A–C: Exact-day TTO coverage and interval-selection/Weibull sensitivities; Table S16A,B: ICI-linked indication sensitivity analyses; Table S17A,B: Seriousness and Evans-syndrome/AIHA–ITP overlap analyses; Figure S1: FAERS stratified strict reporting signals; Figure S2: JADER exact-day TTO summaries; Figure S3: FAERS report-level seriousness descriptors; Figure S4: FAERS multiple-ICI co-reporting; Figure S5: TTO interval-selection sensitivity; Figure S6: AIHA-only versus ITP-only seriousness comparison.

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Institutional Review Board Statement: Not applicable. This study used deidentified, publicly available spontaneous-reporting data, and did not involve patient contact or attempted re-identification.

Informed Consent Statement: Not applicable.

Data Availability Statement: FAERS source data are publicly available from the US Food and Drug Administration, and JADER source data are publicly available from the Pharmaceuticals and Medical Devices Agency (PMDA), Japan. Derived non-licensed aggregate tables supporting this study are provided in the single Supplementary Material file. Official MedDRA terminology content and terminology-mapping dictionaries are not redistributed. Analysis code and additional aggregate outputs are available from the corresponding author upon reasonable request.

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Abbreviations

AIHA, autoimmune hemolytic anemia; BH, Benjamini–Hochberg; CI, confidence interval; CTLA-4, cytotoxic T-lymphocyte antigen 4; FAERS, FDA Adverse Event Reporting System; HCP, healthcare professional; ICI, immune checkpoint inhibitor; ITP, immune thrombocytopenia; JADER, Japanese Adverse Drug Event Report database; MedDRA, Medical Dictionary for Regulatory Activities; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PMDA, Pharmaceuticals and Medical Devices Agency; PRR, proportional reporting ratio; PT, preferred term; ROR, reporting odds ratio; TTO, time to onset.

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