Analysis of immune-related adverse events caused by immune checkpoint inhibitors using the Japanese Adverse Drug Event Report database

Shiori Hasegawa¹,² | Hiroaki Ikesue¹ | Satoshi Nakao² | Kazuyo Shimada² |
Ririka Mukai² | Mizuki Tanaka² | Kiyoka Matsumoto² | Misaki Inoue² |
Riko Satake² | Yu Yoshida² | Fumiya Goto² | Tohru Hashida¹ |
Mitsuhiro Nakamura²

¹Department of Pharmacy, Kobe City Medical Center General Hospital, Kobe, Hyogo, Japan
²Laboratory of Drug Informatics, Gifu Pharmaceutical University, Gifu, Gifu, Japan

Abstract

Purpose: The aim of our study was to characterize the clinical features of immune-related adverse events (irAEs) associated with immune checkpoint inhibitors (ICIs) in a real-world setting using the Japanese Adverse Drug Event Report (JADER) database.

Methods: The irAEs were defined using the preferred terms of the Medical Dictionary for Regulatory Activities. irAEs were categorized as follows: adrenal insufficiency, colitis, eye diseases, hematological disorder, hepatitis, hyperthyroidism, hypopituitarism, hypothyroidism, myasthenia gravis, myocarditis, nephritis/renal dysfunction, pneumonitis, rash, and type 1 diabetes mellitus. We used several indices such as reporting odds ratio (ROR) to assess disproportionality in pharmacovigilance data, time-to-onset analysis using Weibull shape parameters, and the association rule mining technique to evaluate possible risk factors between variables in the spontaneous reporting system database.

Results: The JADER database contained 534,688 reports from April 2004 to June 2018. The RORs of pneumonitis including interstitial lung disease for nivolumab, pembrolizumab, and ipilimumab were 7.02 (95% confidence interval: 6.55-7.52), 9.08 (8.28-9.97), and 1.74 (1.27-2.38), respectively. The median onsets (quartiles, 25-75%) of myocarditis caused by nivolumab and pembrolizumab were 28.0 (15.5-60.5) and 18.0 (13.0-44.5) days, respectively. Co-therapy with nivolumab and ipilimumab may be associated with irAEs in several categories as per the association rule mining analysis.

Conclusion: Our results demonstrated a potential risk of irAEs associated with ICIs, based on RORs and time-to-onset analysis. Furthermore, our findings indicated that
patients receiving nivolumab and ipilimumab as co-therapy should be carefully monitored.

KEYWORDS
adverse events report, immune checkpoint inhibitor, immune-related adverse event, JADER, pharmacoepidemiology

1 | INTRODUCTION

Immune checkpoints are involved in maintaining immune response homeostasis and are closely involved in the development of peripheral immune tolerance to self-antigens and autoimmune diseases. Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that act against cytotoxic T lymphocyte antigen-4 (CTLA-4), programmed cell death protein (PD-1), and its ligand PD-L1 to eliminate cancer cells and restore immune control. ICIs are one of the most important breakthroughs in cancer treatment, but are associated with a spectrum of drug-related autoimmune disorders and inflammatory diseases known as immune-related adverse events (irAEs). These irAEs represent a serious clinical problem during treatment with ICIs. In patients treated with anti-PD-1 antibodies, the rate of overall irAEs is approximately 64% and 13% for any and severe grades, whereas in patients treated with ipilimumab, the rate of irAEs is 72% and 24%, respectively. Thus, all potential irAEs should be brought to the attention of healthcare professionals in a timely manner because early intervention can prevent progression and permanent damage.

The symptoms and progression of irAEs are different from those of adverse events (AEs) caused by conventional anticancer agents. irAEs may affect any organ or system such as the colon (colitis), eye disease, hematological disorder, liver (hepatitis), nervous system (myasthenia gravis), heart (myocarditis), kidneys (renal dysfunction), lungs (pneumonitis), skin (rash), and endocrine system (adrenal insufficiency, hypopituitarism, thyroiditis, diabetes mellitus). Such irAEs are mostly transient and mild and can lead to the discontinuation of therapy with ICIs or immunosuppressive agents. Although fatal toxic effects associated with ICIs are uncommon and compare favorably with fatal toxic effects that occur with other oncologic interventions, they do occur, at a rate of 0.3-1.3%. Healthcare professionals should be aware of potential irAEs since occasional fatalities have also been observed.

The spontaneous reporting system (SRS) has been used for pharmacovigilance assessments that reflect the realities of clinical practice. The US Food and Drug Administration (FDA) has developed the FDA Adverse Event Reporting System (FAERS), and based on this data, the irAE profiles of ICIs and the risk factors of associated myocarditis have been reported. The Pharmaceuticals and Medical Devices Agency (PMDA), a regulatory authority in Japan, has developed the Japanese Adverse Drug Event Report (JADER) database. Neurological and related AEs of ICIs have been reported using the reporting odds ratio (ROR) and median onset of AEs, based on the JADER database.

The detailed time-to-onset profiles of irAEs in many organs are not clear in clinical settings; therefore, we focused on this aspect in our present study. Furthermore, association rule mining has been proposed as a novel analytical technique to identify undetected relationships such as possible risk factors between variables in the SRS database. Two widely used SRS databases are the JADER and FAERS databases. In this study, we conducted a retrospective analysis of the JADER database to address irAEs in patients receiving ICI therapy and to primarily identify the time-to-onset profiles of irAEs in a real-world setting. Additionally, we reviewed current studies to determine appropriate steps in patient evaluation for the prompt diagnosis of irAEs. We also determined suitable strategies for optimizing patient outcomes to prevent fatalities.

2 | METHODS

2.1 | Data source

Healthcare professionals, marketing approval holders, patients, and consumers voluntarily send AE reports to the PMDA. The JADER data...
from April 2004 to June 2018 are publicly available and can be downloaded from the PMDA website (www.pmda.go.jp). All reported AE data are fully anonymized by the PMDA before inclusion in the JADER database. This database has four tables: patient demographic information containing the sex, age, and reporting year (demo); drug information, including drug name, purpose of administration, its association with AEs, routes of drug administration, and the start and end date of administration (drug); information of AEs indicating outcome and onset dates (reac); and medical history, describing patient history (hist). The “drug” column assigns a code to each drug, namely, suspected, concomitant, or interacting. In this study, the analyses were restricted to reports where drugs were coded as “suspected.”

2.2 Target drugs and irAEs

Between the years 2014 and early 2018, five ICIs were available in Japan: the anti-PD-1 antibodies nivolumab and pembrolizumab; the anti-PD-L1 antibodies atezolizumab and avelumab; and the anti-CTLA-4 antibody ipilimumab.

The AEs in the JADER database are coded according to the terminology preferred by the Medical Dictionary for Regulatory Activities/Japanese (MedDRA/J) version 19.0 (www.pmrj.jp/jmo/php/indexj.php). Several studies on irAEs have been reported; however, we could not find a gold standard for the classification and selection of preferred terms (PTs) in each category. For example, the clinical guidelines of the Japanese Endocrine Society indicate the classifications of irAE in the endocrine region. Other reviews and papers listed other irAEs such as colitis, hyperthyroidism, and hypothyroidism. Furthermore, the research using the SRS database focuses on myasthenia gravis and myocarditis. Using the FAERS database, Ji et al. comprehensively evaluated AE profiles, including irAEs using Standardized MedDRA Queries that consist of PTs grouped according to the level that relates to a defined medical condition. Based on previous reports, we categorized irAEs into the following 14 groups: adrenal insufficiency, colitis, eye disease, hematological disorder, hepatitis, hyperthyroidism, hypopituitarism, hypothyroidism, myasthenia gravis, myocarditis, nephritis/renal dysfunction, pneumonitis, rash, and type 1 diabetes mellitus and selected PTs for each category (Table 1).

2.3 ROR

The ROR is the odds of reporting a specific AE caused by a particular drug, divided by the odds of the same AE caused by all other drugs. The ROR is a disproportionality measure that detects signals of specific AEs not associated with the drug. Therefore, varying rates of AEs over time may indicate a drug-AE relationship. The Weibull shape parameter test is used for the statistical analysis of time-to-onset data, and it describes the non-constant incidence rates of AEs (ie, changes in risk over time). The scale parameter \( \alpha \) determines the scale of the distribution function, while the shape parameter \( \beta \) determines the shape of the distribution function. A larger \( \alpha \) value shows stretch distribution, whereas a smaller value indicates shrinkage. The hazard function for the Weibull model increases over time if \( \beta > 1 \) (wear-out failure type), decreases if \( \beta < 1 \) (initial failure type), and remains if \( \beta = 1 \), where it reduces to the exponential distribution.

2.5 Association rule mining

Association rule mining is a useful technique for inferring relationships between drugs and possible risk factors. An association rule is a pair of a set of attributes (X, Y) that can be expressed as the antecedent X (left-hand-side, lhs) of the rule) leading to the consequent Y
### Table 1  Preferred terms (PTs) associated with immune-related adverse events (irAEs) in MedDRA

| Categories | PT | PT code | Categories | PT | PT code |
|------------|----|---------|------------|----|---------|
| **Adrenal insufficiency** | Addison's disease (1 case) | – | Hypopituitarism | Hypophysitis (67 cases) | – |
| | Adrenal androgen deficiency (0 case) | – | Hypopituitarism | Hypophysitis (128 cases) | – |
| | Adrenal atrophy (4 cases) | – | Hypothyroidism | Autoimmune hypothyroidism (0 case) | 10076644 |
| | Adrenal insufficiency (602 cases) | – | Hypothyroidic goitre (3 cases) | 10059844 |
| | Adrenal suppression (23 cases) | – | Hypothyroidism (662 cases) | 10021114 |
| | Acute adrenal cortex dysfunction (67 cases) | – | Premature transient hypothyroxinosis (0 case) | – |
| | Glucocorticoid deficiency (1 case) | – | Primary hypothyroidism (7 cases) | 10036697 |
| | Hypoaldosteronism (4 cases) | – | Secondary hypothyroidism (9 cases) | 10039840 |
| | Mineralcorticoid deficiency (0 case) | – | Tertiary hypothyroidism (0 case) | 10043289 |
| | Primary adrenal insufficiency (6 cases) | – | Thyroid atrophy (0 case) | 10043693 |
| | Secondary adrenal cortex dysfunction (102 cases) | – | Viscous edema (0 case) | – |
| | Steroid withdrawal syndrome (29 cases) | 10042028 | Myasthenia gravis | Myasthenia gravis (201 cases) | – |
| **Colitis** | Acute haemorrhagic ulcerative colitis (1 case) | 10075634 | Myocarditis | Autoimmune myocarditis (1 case) | 10064539 |
| | Allergic colitis (3 cases) | 10059447 | Eosinophilic myocarditis (25 cases) | 10014961 |
| | Autoimmune colitis (22 cases) | – | Lupus myocarditis (0 case) | 10066391 |
| | Colitis (760 cases) | 10009887 | Myocarditis (203 cases) | 10028606 |
| | Colitis erosive (7 cases) | 10058358 | Radiation myocarditis (0 case) | 10076389 |
| | Colitis ischaemic (707 cases) | 10009895 | Nephritis/renal dysfunction | Acute renal failure (0 case) | – |
| | Colitis microscopic (465 cases) | 10056979 | Autoimmune nephritis (7 cases) | 10077087 |
| | Colitis psychogenic (0 case) | 10053397 | Lupus nephritis (44 cases) | 10025140 |
| | Colitis ulcerative (342 cases) | 10009900 | Nephritis (162 cases) | 10029117 |
| | Crohn’s disease (64 cases) | 10011401 | Nephritis haemorrhagic (2 cases) | 10029132 |
| | Diarrhoea (7532 cases) | 10012735 | Perinephritis (162 cases) | – |
| | Diarrhoea haemorrhagic (38 cases) | 10012741 | Renal failure (2220 cases) | 10038435 |
| | Diarrhoea neonatal (0 case) | 10012743 | Renal impairment (8050 cases) | 10062237 |
| | Enterocolitis (1023 cases) | 10014893 | Tubulointerstitial nephritis (1533 cases) | 10048302 |
| | Enterocolitis haemorrhagic (741 cases) | 10014896 | Tubulointerstitial nephritis and uveitis syndrome (44 cases) | 10069034 |
| | Eosinophilic colitis (4 cases) | 10057271 | Pneumonitis | Acute interstitial pneumonitis (13 cases) | 10066728 |
| | Inflammatory bowel disease (11 cases) | 10021972 | Interstitial lung disease (24 123 cases) | 10022611 |
| | Necrotising colitis (82 cases) | 10051606 | Pneumonitis (967 cases) | 10035742 |
| | Neutropenic colitis (19 cases) | 10062959 | Pneumonitis (967 cases) | 10035742 |
| | Pseudopolyposis (1 case) | – | Erythema (2350 cases) | 10001510 |
| | Eye disease | Uveitis (275 cases) | 10046851 | Pruritus (1463 cases) | 10037087 |
| | Hematological disorder | Autoimmune hemolytic anemia (205 cases) | 10073785 | Pruritus allergic (1 case) | 10063438 |
| | Immune thrombocytopenic purpura (733 cases) | 10074667 | Pruritus generalised (276 cases) | 10052576 |
| | Hepatitis | Abnormal liver function test (0 case) | – | Rash (6302 cases) | 10037844 |
| | | Acute hepatic failure (332 cases) | 10000804 | Rash erythematous (223 cases) | 10037855 |
The Apriori algorithm was used to find association rules, which are a set of rules that can identify population at a high risk of developing a particular disease. Support, confidence, and lift were the measures of statistical significance used as indicators to decide the relative strength of the rules, and these parameters were calculated as follows:

\[
\text{Support} = \frac{|X \cap Y|}{|D|}
\]

\[
\text{Confidence} = \frac{|X \cap Y|}{|X|}
\]

\[
\text{Lift} = \frac{|X \cap Y|}{|X|/|Y|}
\]

where, D is the total number of transactions. Support in an itemset is defined as the proportion of transactions and shows how frequently the rule appears in the transaction. Confidence is the proportion of cases covered by the lhs of the rule that was covered by the rhs and provides an estimate of the conditional probability \( P(Y | X) \). Lift is a measure of the importance of the association, and it is independent of coverage, which is a measure of how often the rule can be applied. It is the confidence divided by the proportion of all cases that are covered by the rhs. In other words, lift is the ratio between the confidence of the rule and the support of the itemset in the consequent of the rule. It is evaluated as follows:

\[
\text{Chi-squared} = \frac{D(\text{lift} - 1)^2}{(\text{Confidence} - \text{Support}) \times (\text{Lift} - \text{Confidence})}
\]

The association rule mining was performed using the Apriori function of arules library in the arules package of R version 3.3.3 software. In the first step, the Apriori algorithm searched for itemsets in the database that had more than minimum support as applied by the user. In the second step, rules were generated by selecting the

---

**TABLE 1** (Continued)

| Categories | PT | Categories | PT | Categories | PT |
|------------|----|------------|----|------------|----|
| Alanine aminotransferase increased (2772 cases) | 10001551 | Rash generalised (2194 cases) | 10037858 |
| Aspartate aminotransferase increased (2537 cases) | 10003481 | Rash macular (22 cases) | 10037867 |
| Autoimmune hepatitis (283 cases) | 10003827 | Rash maculo-papular (157 cases) | 10037868 |
| Hepatic enzyme increased (627 cases) | 10060795 | Rash papular (124 cases) | 10037876 |
| Hepatic failure (1084 cases) | 10019663 | Rash pruritic (114 cases) | 10037884 |
| Hepatitis (465 cases) | 10019717 | Type 1 diabetes mellitus | Diabetic ketoacidosis (482 cases) | 10012671 |
| Hepatitis acute (893 cases) | 10019727 | Fulminant type 1 diabetes mellitus (136 cases) | 10072628 |
| Hepatotoxicity (102 cases) | 10019851 | Latent autoimmune diabetes in adults (9 cases) | 10066389 |
| Liver disorder (9664 cases) | 10024670 | Type 1 diabetes mellitus (549 cases) | 10067584 |
| Liver injury (84 cases) | 10067125 |
| Transaminases increased (137 cases) | 10054889 |
| Hyperthyroidism Basedow's disease (145 cases) | 10004161 |
| Hyperthyroidism (857 cases) | 10020850 |
| Marine Lenhart syndrome (0 case) | 10068828 |
| Primary hyperthyroidism (0 case) | 10075899 |
| Secondary hyperthyroidism (1 case) | 10053260 |
| Thyroid dermatopathy (1 case) | 10069771 |
| Thyrotoxic crisis (38 cases) | 10043786 |
| Thyrotoxic periodic paralysis (3 cases) | 10043788 |
| Toxic goitre (0 case) | 10075050 |
| Toxic nodular goitre (1 case) | 10044242 |

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term.
itemsets from the first step and applying minimum confidence. Because all possible rules were extracted from this large database, the first step was to narrow these down. In order to extract association rules efficiently, thresholds for minimum support and confidence were defined based on factors such as data size and the number of items. For the whole data set, we defined the minimum support and confidence thresholds at 0.00001 and 0.0001, respectively. Furthermore, the maximum length of the itemset per rule (maxlen), a parameter in the arules package, was restricted to 3. For the subset data, we applied the minimum support and confidence thresholds, 0.00007 and 0.001, respectively, and maxlen was restricted to 3.

3RESULTS

The JADER database contained 534,688 reports from April 2004 to June 2018. The reported number of irAEs of nivolumab, pembrolizumab, ipilimumab, atezolizumab, and avelumab were 4419, 2148, 545, 41, and 5, respectively (Table 2). The RORs of whole data with nivolumab, pembrolizumab, ipilimumab, and atezolizumab in pneumonitis including interstitial lung disease were 7.02 (95% CI: 6.55-7.52), 9.08 (8.28-9.97), 1.74 (1.27-2.38), and 5.71 (2.73-11.97), respectively. The RORs of subset data with nivolumab, pembrolizumab, ipilimumab, and atezolizumab in pneumonitis were 2.18 (95% CI: 2.03-2.35), 2.79 (2.54-3.07), 0.51 (0.38-0.70), and 1.70 (0.81-3.56), respectively. The RORs of whole data for type 1 diabetes mellitus with nivolumab, pembrolizumab, and ipilimumab were 20.13 (16.77-24.15), 308.92 (196.82-484.87), and 16.62 (10.07-27.45), respectively, while values for subset data for type 1 diabetes mellitus caused by nivolumab, pembrolizumab, and ipilimumab were 31.58 (22.76-43.82), 177.53 (110.62-284.90), and 9.15 (5.45-15.39), respectively. The RORs of whole data for myasthenia gravis caused by nivolumab and pembrolizumab were 37.68 (26.62-53.34) and 41.25 (26.96-63.10), respectively, and the values of subset data for myasthenia gravis caused by nivolumab and pembrolizumab were 13.55 (8.61-21.32) and 11.61 (7.18-18.77), respectively.

The median onsets (quartiles, 25%-75%) of adenral insufficiency caused by nivolumab, pembrolizumab, and ipilimumab were 156.0 (98.0-214.0), 118.0 (75.3-168.3), and 60.0 (27.5-84.5) days, respectively (Figure 1). The median onsets (quartiles, 25%-75%) of pneumonitis caused by nivolumab, pembrolizumab, ipilimumab, and atezolizumab were 56.0 (19.0-133.0), 41.0 (13.0-80.5), 38.0 (22.0-76.0), and 13.0 (7.5-31.5) days, respectively, whereas median onsets (quartiles, 25%-75%) for colitis caused by nivolumab, pembrolizumab, and ipilimumab were 74.0 (35.0-141.0), 62.0 (25.5-105.5), and 32.5 (16.3-55.0) days, respectively (Figure 1). The median onsets (quartiles, 25%-75%) for type 1 diabetes mellitus caused by nivolumab, pembrolizumab, and ipilimumab were 190.0 (109.0-328.0), 129.0 (81.0-180.0), and 46.0 (26.0-64.5) days, respectively, and the corresponding values for myasthenia gravis caused by nivolumab and pembrolizumab were 28.0 (15.5-60.5) and 18.0 (13.0-44.5) days, respectively. The Weibull shape parameter $\beta$ for nivolumab and pembrolizumab in pneumonitis was determined to be 0.89 (0.85-0.94) and 0.90 (0.84-0.96), respectively, while the $\beta$ value for nivolumab and ipilimumab in colitis was 1.12 (1.02-1.21) and 1.21 (1.03-1.40), respectively. In type 1 diabetes mellitus, the Weibull shape parameter for nivolumab and pembrolizumab was determined to be 1.34 (1.14-1.55) and 1.72 (1.19-2.37), respectively.

We used a mosaic plot to summarize the outcome profiles of irAEs encompassed by the 14 categories (Table 3 and Figure 2). The plot indicated that nivolumab, pembrolizumab, and ipilimumab showed improvement or recovery in more than 40% of cases in each category, except in the case of eye disease related to ipilimumab, hematological disorder and myocarditis related to pembrolizumab, and type 1 diabetes mellitus related to nivolumab and ipilimumab. The reporting ratios of outcomes for colitis to all AEs for nivolumab, pembrolizumab, and ipilimumab were 14.64% (387/2643 cases), 12.34% (161/1305 cases), and 24.78% (115/464 cases), respectively. For colitis, the ratios of AEs that were assigned a status of unimproved, with sequelae, or death due to nivolumab, pembrolizumab, and ipilimumab were 10.34% (40/387), 20.50% (33/161), and 8.70% (10/115), respectively. The reporting ratio for pneumonitis caused by nivolumab, pembrolizumab, and ipilimumab were 41.73% (1103/2643 cases), 50.04% (653/1305 cases), and 9.27% (43/464 cases), respectively. For pneumonitis, the ratios of AEs designated as unimproved, with sequelae, or death due to nivolumab, pembrolizumab, and ipilimumab in pneumonitis were 25.75% (284/1103), 26.34% (172/653), and 9.30% (4/43), respectively.

Next, we evaluated the possible association between irAEs and demographic data in the whole data set. The mining algorithm identified the following rule between each irAE and co-therapy of nivolumab and ipilimumab (supplemental materials: S2-S15 Table): adrenal insufficiency (S2 Table [nivolumab: id [6]], colitis (S3 Table [nivolumab: id [15]]), eye disease (S4 Table [nivolumab: id [5]]), hematological disorder (S5 Table [nivolumab: id [1]]), hepatitis (S6 Table [nivolumab: id [10]]), hyperthyroidism (S7 Table [nivolumab: id [6]]), hypopituitarism (S8 Table [nivolumab: id [2]]), hypothyroidism (S9 Table [nivolumab: id [28]]), nephritis/renal dysfunction (S12 Table [nivolumab: id [34]]), pneumonitis (S13 Table [nivolumab: id [237]]), rash (S14 Table [nivolumab: id [20]]), and type 1 diabetes mellitus (S15 Table [nivolumab: id [8]]). According to the predefined minimum support and confidence thresholds, no association rules between co-therapy of nivolumab and ipilimumab for myasthenia gravis and myocarditis were detected (S10 and S11 Tables).

Furthermore, we evaluated the possible association between irAEs and co-therapy of nivolumab and ipilimumab in the subset data. The following rules were observed between each irAE and co-therapy of nivolumab and ipilimumab (supplemental materials: S16-S27 Table, S1-S12 Figure): [hypopituitarism, nivolumab+ipilimumab] = > [adrenal insufficiency] (S16 Table: id [1]), [adrenal insufficiency, nivolumab+ipilimumab] = > [hypopituitarism] (S22 Table: id [1]), [hypothyroidism, nivolumab+ipilimumab] = > [hypopituitarism] (S22 Table: id [2]), and [hypopituitarism, nivolumab+ipilimumab] = > [hypothyroidism] (S23 Table: id [7]).
### Table 2
Reporting odds ratios (RORs) of immune-related adverse events (irAEs)

|                | Nivolumab | Pembrolizumab | Ipilimumab | Atezolizumab | Averumab |
|----------------|-----------|---------------|------------|--------------|----------|
|                | Whole data | Subset data   | Whole data | Subset data  | Whole data | Subset data |
| **Whole data** |            |               |            |              |           |             |
| **Case (n)**   | Nivolumab | Pembrolizumab | Ipilimumab | Atezolizumab | Averumab  |
| **Case ROR (95% CI)** |            |               |            |              |           |             |
| **Adrenal insufficiency** | 4.50 (3.48-6.47) | 1.85 (1.65-2.07) | 1.49 (1.26-1.75) | 12.49 (10.16-15.36) | 4.98 (4.04-6.14) |
| **Colitis**    | 2.60 (1.71-4.00) | 1.85 (1.65-2.07) | 1.49 (1.26-1.75) | 12.49 (10.16-15.36) | 4.98 (4.04-6.14) |
| **Hematological disorder** | 3.73 (2.56-5.45) | 9.57 (5.65-15.91) | 2.15 (1.27-3.62) | 6.41 (4.04-10.55) | 2.27 (1.05-4.93) |
| **Hepatitis**  | 1.40 (1.21-1.62) | 1.26 (1.08-1.47) | 0.56 (0.41-0.78) | 6.56 (5.25-8.20) | 6.04 (4.81-7.58) |
| **Hyperthyroidism** | 17.32 (14.34-20.92) | 9.83 (7.72-12.52) | 31.76 (25.96-38.87) | 22.40 (14.56-36.48) | 8.80 (6.64-13.73) |
| **Hypopituitarism** | 153.30 (115.06-204.24) | 13.87 (10.41-18.48) | 37.77 (24.75-57.63) | 22.40 (14.56-36.48) | 74.97 (53.82-104.43) |
| **Hypothyroidism** | 11.09 (8.44-14.57) | 6.89 (4.94-9.60) | 10.76 (7.35-15.74) | 21.09 (12.34-36.05) | 10.19 (6.84-17.79) |
| **Myasthenia gravis** | 14.12 (9.24-21.57) | 12.49 (9.65-22.45) | 17.49 (10.35-29.58) | 22.40 (14.56-36.48) | 74.97 (53.82-104.43) |
| **Myocarditis**  | 20.00 (16.37-24.00) | 19.17 (15.28-24.00) | 27.96 (22.17-35.25) | 20.96 (15.45-28.45) | 10.19 (6.84-17.79) |
| **Nephritis/renal dysfunction** | 0.90 (0.73-1.11) | 1.35 (1.10-1.65) | 1.34 (1.07-1.59) | 1.39 (1.06-1.84) | 1.50 (1.25-1.81) |
| **Pneumonitis**  | 2.11 (1.21-3.67) | 1.35 (1.10-1.65) | 1.34 (1.07-1.59) | 1.39 (1.06-1.84) | 1.50 (1.25-1.81) |
| **Rash**        | 0.90 (0.73-1.11) | 0.96 (0.78-1.19) | 1.21 (0.94-1.57) | 1.31 (1.01-1.71) | 1.61 (1.02-2.56) |

Abbreviations: ROR: reporting odds ratio; CI: confidence interval.

*The number of irAE reports from whole data in the "demo" table.

Non-case was not reported.

Number of cases < 2.
4 | DISCUSSION

Due to limitations of the SRS, disproportionality measures such as RORs neither quantify risk nor does not demonstrate causality, but merely offer an estimate of the signal strength and thus only relevant to the hypothesis being studied. ROR is an indicator of an increased risk in AE reporting, but does not indicate the risk of AE occurrence in absolute terms. Therefore, careful attention has to be paid while interpreting these values. Since the lower limits of the 95% CI of RORs of the whole data for all irAE categories except hepatitis, nephritis/renal dysfunction, and rash were more than 1, an association between ICIs and most irAEs may be suggested. The irAE profiles of the anti-PD-1 antibodies nivolumab and pembrolizumab were remarkably similar.

To better understand the detailed time-to-onset profiles of irAEs in clinical settings, we used the time-to-onset analysis and validated the results. As anti-PD-1 antibodies, nivolumab and pembrolizumab had similar median onset times and Weibull shape parameter \( \beta \) in our study, the timing of an intervention for the irAEs of these two drugs will be similar. In contrast, the onset profiles of irAEs with ipilimumab were different from those exhibited by the anti-PD-1 antibody.

Many irAEs of ipilimumab occur earlier than those of nivolumab. In our results, almost all irAEs occurred faster in ipilimumab than in anti-PD1 antibodies, except hyperthyroidism. A precise explanation for these observed time-to-onset results is unknown. The PD-1 pathway in T-cells is involved with the tumor microenvironment. CTLA-4 is expressed by activated T-cells. The CTLA-4 pathway predominantly acts in lymph nodes. These different mechanisms and targets of anti-PD-1 and anti-CTLA-4 antibodies might, in part, explain the differences in time-to-onset profiles between them.

The irAEs of the endocrine system include primary adrenal insufficiency, hypopituitarism, thyroid dysfunction, and type 1 diabetes mellitus. Primary adrenal insufficiency and type 1 diabetes mellitus are rare, but can lead to life-threatening consequences if not promptly recognized and treated. A systematic review reports that the rate of primary adrenal insufficiency was 0.7%, of which 0.2% was graded 3 or higher. A case report shows that primary adrenal insufficiency developed 8 weeks after initiation of nivolumab treatment and 16 weeks after initiation of ipilimumab. The median onset time of adrenal insufficiency was shorter for ipilimumab than that for the anti-PD-1 antibody. In either case, monitoring adrenal insufficiency is required for several months, if detected.

Thyroid dysfunction following treatment with anti-PD-1 antibodies is reported to be 5% to 10%, which is higher than the outcome with anti-CTLA-4 antibody therapy, which is reported to be 0% to 5%. Thyroiditis induced by ICIs usually causes transient hyperthyroidism and develops 2 to 6 weeks after administration in most cases. Hyperthyroidism is often followed by the subsequent development of hypothyroidism. The median onset date of hyperthyroidism induced by nivolumab and pembrolizumab was closer than that of hypothyroidism in our results.

Hypopituitarism induced by the anti-PD-1 antibody and ipilimumab was <1% and 10% to 17%, respectively. Hypopituitarism induced by ICIs can develop even after drug withdrawal. Hypopituitarism was observed approximately 10 weeks after commencement of anti-CTLA-4 antibody therapy and up to several months after the initiation of anti-PD-1 antibody therapy. The median onset time of ipilimumab was shorter than that of the anti-PD-1 antibodies for hypopituitarism. Our results are consistent with these reported findings.

The rate of type 1 diabetes mellitus in patients treated with ICIs was 0.2% and the rate was higher with anti-PD-1 antibody therapy than with anti-CTLA-4 antibody therapy. Type 1 diabetes mellitus developed within 3 months commencement of anti-PD-1 or PD-L1 antibody therapy. Another study reports a mean duration of type 1 diabetes mellitus as 22 weeks with a range from 2 to 72 weeks. Our results showed a median duration of approximately 18 to 27 weeks and 7 weeks, for the anti-PD-1 antibody and ipilimumab therapies, respectively. The median onset time of ipilimumab was shorter than that of the anti-PD-1 antibodies for type 1 diabetes mellitus.

All grades of colitis were more frequent with anti-CTLA-4 antibody therapy. The rate of colitis induced by nivolumab and ipilimumab was 1% and 8% to 22%, respectively. Life-threatening diarrhea and colitis occurred with anti-PD-1 therapy (1%–4%) and in co-therapy with ipilimumab and nivolumab (15%). Nivolumab and pembrolizumab had a lower reporting ratio for colitis than ipilimumab did (Table 3). Diarrhea and colitis have been reported to occur within 6 to 18 weeks after initiating anti-PD-1 antibody therapy, and within 6 to 7 weeks in patients treated with ipilimumab.

Hypothyroidism induced by the anti-PD-1 antibody and ipilimumab was <1% and 10% to 17%, respectively. Hypopituitarism induced by ICIs can develop even after drug withdrawal. Hypopituitarism was observed approximately 10 weeks after commencement of anti-CTLA-4 antibody therapy and up to several months after the initiation of anti-PD-1 antibody therapy. The median onset time of ipilimumab was shorter than that of the anti-PD-1 antibodies for hypopituitarism. Our results are consistent with these reported findings.

The rate of type 1 diabetes mellitus in patients treated with ICIs was 0.2% and the rate was higher with anti-PD-1 antibody therapy than with anti-CTLA-4 antibody therapy. Type 1 diabetes mellitus developed within 3 months commencement of anti-PD-1 or PD-L1 antibody therapy. Another study reports a mean duration of type 1 diabetes mellitus as 22 weeks with a range from 2 to 72 weeks. Our results showed a median duration of approximately 18 to 27 weeks and 7 weeks, for the anti-PD-1 antibody and ipilimumab therapies, respectively. The median onset time of ipilimumab was shorter than that of the anti-PD-1 antibodies for type 1 diabetes mellitus.

All grades of colitis were more frequent with anti-CTLA-4 antibody therapy. The rate of colitis induced by nivolumab and ipilimumab was 1% and 8% to 22%, respectively. Life-threatening diarrhea and colitis occurred with anti-PD-1 therapy (1%–4%) and in co-therapy with ipilimumab and nivolumab (15%). Nivolumab and pembrolizumab had a lower reporting ratio for colitis than ipilimumab did (Table 3). Diarrhea and colitis have been reported to occur within 6 to 18 weeks after initiating anti-PD-1 antibody therapy, and within 6 to 7 weeks in patients treated with ipilimumab.

The median onset time for the development of colitis with anti-PD-1 antibody therapy was approximately 9 to 11 weeks, whereas that for ipilimumab was 5 weeks. Our results are consistent with these previous reports.

In the FAERS database, ROR signals for autoimmune hemolytic anemia and immune thrombocytopenic purpura are detected in nivolumab and ipilimumab therapies. We observed similar results; however, the number of reports was small, and further research is required.

A meta-analysis shows that hepatitis develops in 5% to 10% of patients when nivolumab, pembrolizumab, or ipilimumab is used as monotherapy. Hepatitis begins to develop approximately 4 to 10 weeks after ipilimumab administration, of which 1% to 2% cases are grade 3. Severe autoimmune hepatitis occurred in 20% of patients who were co-administered nivolumab and ipilimumab. It is reported that the ROR signals of nivolumab, pembrolizumab, and ipilimumab were detected in the FAERS database, whereas the signal of pembrolizumab was not detected in the JADER database. Conflicts between reporters and reported AE terms, discrepancies in reported drugs, reported AEs, reporter type, anomalies between reporting systems across countries as a result of country-specific regulation, etc., are well-known. Such possibilities should not be overlooked when comparing different SRSs.
A study has reported that 0.1% to 0.2% of patients treated with ICIs develop myasthenia gravis with an onset of 2 to 3 weeks after the commencement of therapy, whereas another study reports an onset range of 2 to 12 weeks. In our study, the median onset of myocarditis was 3 to 4 weeks following the commencement of individual drugs was difficult. Nevertheless, our results obtained for the FAERS data set complement the results obtained for the JADER data set, in which the same AE is connected with other drugs. This is referred to as the masking or cloaking effect, and considered to be one reason for a lack of signal.

FIGURE 1
Box plot and Weibull shape parameter (β) of immune-related adverse events (irAEs) of immune checkpoint inhibitors (ICIs) using the JADER database, which is consistent with our results. Approximately 4 weeks. Sato et al reported this value as 4 weeks. A wide range of renal dysfunction symptoms were often observed for rash and nephritis/renal dysfunction. Atezolizumab 2 70.0 (29.5–200.0) 129.7 (85.9–191.1) 1.11 (0.78–1.50) 4 42.0 (21.5–41.0) 27.5 (4.2–162.3) 1.07 (0.31–2.63) 148 74.0 (20.0–184.3) 111.9 (91.7–135.9) 0.86 (0.77–0.96) 25 33.0 (19.0–55.5) 34.0 (22.7–51.7) 1.07 (0.77–1.40) 79 34.0 (21.0–50.0) 43.0 (37.6–48.6) 1.90 (1.50–2.25) 108 29.5 (21.0–42.8) 57.8 (35.0–72.1) 0.91 (0.75–1.10) 90 32.5 (21.0–42.5) 43.0 (30.2–52.5) 1.24 (1.00–1.50) 11 124.0 (54.0–152.0) 129.4 (74.6–216.5) 1.37 (0.87–2.12) 70 154.0 (85.0–229.0) 171.6 (146.3–208.0) 1.38 (1.06–1.78) 17 147.0 (86.5–215.0) 115.6 (97.6–171.5) 1.97 (0.99–3.87) 53 62.0 (26.5–79.0) 77.6 (53.7–105.0) 0.96 (0.79–1.19) 48 80.5 (44.8–133.3) 106.0 (63.4–135.6) 1.27 (1.02–1.55) 24 63.5 (39.5–90.0) 96.0 (67.5–118.0) 1.84 (1.31–2.40) 12 36.0 (26.5–62.8) 51.1 (32.7–77.8) 1.57 (0.96–2.31) 34 28.0 (20.0–40.0) 27.2 (19.2–36.0) 1.10 (0.84–1.40) 22 28.5 (21.0–49.0) 47.9 (36.4–66.9) 1.31 (0.96–1.71) 21 28.0 (15.8–50.0) 52.2 (27.5–103.6) 0.70 (0.49–0.96) 13 18.0 (13.0–44.0) 35.9 (21.6–57.9) 1.32 (0.82–2.00) 86 56.0 (23.5–135.0) 94.3 (73.3–135.9) 0.95 (0.80–1.15) 42 63.0 (21.0–114.0) 66.5 (42.3–118.6) 1.02 (0.80–1.30) 4 30.0 (27.0–173.0) 38.5 (1.6–84.1) 0.54 (0.18–1.16) 2 70.0 (11.0–129.0) 69.9 (34.6–119.2) 0.97 (0.21–2.10) 916 56.0 (19.0–133.0) 90.1 (83.3–199.7) 0.89 (0.69–0.96) 577 41.0 (13.0–90.0) 59.9 (32.9–94.1) 0.93 (0.64–0.96) 35 38.0 (22.0–45.0) 59.3 (42.0–82.8) 1.16 (0.88–1.47) 5 13.0 (7.3–21.5) 23.0 (8.0–48.3) 1.74 (0.71–3.98) 5 72.0 (13.0–161.0) 69.1 (65.5–130.4) 0.92 (0.69–0.96) 43 45.0 (12.0–90.0) 62.0 (42.0–90.0) 0.86 (0.67–1.09) 18 9.6 (6.0–15.5) 19.6 (10.9–34.7) 0.97 (0.65–1.54) 105 190.0 (109.0–328.0) 230.4 (177.5–287.8) 1.34 (1.14–1.55) 23 129.0 (81.0–180.0) 116.0 (86.4–151.0) 1.72 (1.10–2.77) 13 46.0 (26.4–64.5) 40.5 (21.9–72.3) 1.09 (0.67–1.59)
| Outcome                | Adrenal insufficiency | Colitis | Eye disease | Hematological disorder | Hepatitis | Hyperthyroidism | Hypopituitarism | Myasthenia gravis | Myelodysplasia | Nephritis/renal dysfunc. | Pneumonitis | Rash | Type 1 diabetes | NIVH * | Total * |
|------------------------|-----------------------|--------|-------------|------------------------|-----------|----------------|---------------|-----------------|---------------|-------------------------|-------------|------|-----------------|--------|---------|
| **Nivolumab**          |                       |        |             |                        |           |                |               |                 |               |                         |             |      |                 |        |         |
| Recovered              | 17.16% (35/204)       | 47.03%| 45.00%      | 46.43%                 | 36.17%    | 53.97%         | 23.58%        | 14.04%          | 23.81%        | 29.17%                  | 20.75%      | 23.75%| 45.74%          | 11.59% | 29.40% |
| Improved               | 44.61% (91/204)       | 36.43%| 14.00%      | 28.57%                 | 29.26%    | 19.05%         | 37.74%        | 43.86%          | 40.48%        | 20.83%                  | 29.25%      | 41.70%| 42.49%          | 24.64% | 36.93% |
| Unimproved             | 17.65% (36/204)       | 7.49% | 22.50%      | 17.68%                 | 17.55%    | 10.32%         | 21.70%        | 33.33%          | 14.29%        | 4.17%                   | 22.64%      | 9.52% | 8.51%           | 40.58% | 13.89% |
| With sequelae          | 24.53% (5/204)        | 0.52% | 7.50%       | 0.00%                  | 1.06%     | 4.76%          | 2.83%         | 1.75%           | 2.38%         | 1.47%                   | 2.83%       | 2.27% | 0.00%           | 9.42%  | 2.46%  |
| Death                  | 14.77% (3/204)        | 2.33% | 0.00%       | 7.14%                  | 6.91%     | 0.00%          | 1.89%         | 0.00%           | 9.52%         | 4.17%                   | 7.55%       | 13.94%| 0.00%           | 0.72%  | 7.79%  |
| Uncertain              | 16.67% (34/204)       | 6.20% | 10.00%      | 0.00%                  | 9.04%     | 11.90%         | 12.26%        | 7.02%           | 9.52%         | 0.00%                   | 16.98%      | 8.79% | 4.26%           | 13.04% | 9.53%  |
| **Total**              | 7.72% (204/2643)      | 14.64%| 1.51%       | 1.06%                  | 7.11%     | 4.77%          | 4.01%         | 2.16%           | 1.59%         | 0.91%                   | 4.01%       | 41.73%| 3.56%           | 5.22%  | 26.43% |
| **Pembrolizumab**      |                       |        |             |                        |           |                |               |                 |               |                         |             |      |                 |        |         |
| Recovered              | 17.07% (17/99)        | 36.65%| 28.57%      | 12.50%                 | 26.32%    | 44.14%         | 24.00%        | 17.86%          | 12.00%        | 20.00%                  | 27.78%      | 22.97%| 27.87%          | 16.67% | 26.13% |
| Improved               | 40.21% (32/82)        | 38.51%| 50.00%      | 25.00%                 | 36.50%    | 23.42%         | 40.00%        | 25.00%          | 36.00%        | 6.67%                   | 24.07%      | 44.41%| 29.51%          | 43.33% | 38.70% |
| Unimproved             | 24.39% (20/82)        | 16.15%| 7.14%       | 37.50%                 | 15.79%    | 18.92%         | 24.00%        | 46.43%          | 20.00%        | 6.67%                   | 27.78%      | 10.72%| 14.75%          | 23.33% | 15.56% |
| With sequelae          | 6.10% (5/82)          | 0.00% | 0.00%       | 0.00%                  | 1.80%     | 4.00%          | 4.00%         | 4.00%           | 6.67%         | 0.00%                   | 0.00%       | 6.67% | 1.23%           |        |         |
| Death                  | 0.00% (0/82)          | 4.35% | 0.00%       | 0.00%                  | 2.65%     | 0.00%          | 0.00%         | 12.00%          | 26.67%        | 5.56%                   | 15.01%      | 4.92% | 3.33%           | 9.20%  | 2.90%  |
| Uncertain              | 12.00% (10/82)        | 4.35% | 14.29%      | 25.00%                 | 18.42%    | 11.71%         | 8.00%         | 10.71%          | 16.00%        | 33.33%                  | 14.81%      | 6.28% | 22.95%          | 6.67%  | 9.20%  |
| **Total**              | 6.28% (82/1305)       | 12.34%| 1.07%       | 0.61%                  | 2.91%     | 8.51%          | 1.92%         | 2.15%           | 1.92%         | 1.15%                   | 4.14%       | 50.04%| 4.67%           | 2.30%  | 13.05% |
| **Ipilimumab**         |                       |        |             |                        |           |                |               |                 |               |                         |             |      |                 |        |         |
| Recovered              | 7.41% (4/54)          | 52.17%| 25.00%      | 3.33%                  | 43.62%    | 68.18%         | 15.63%        | 14.29%          | -             | -                       | 22.22%      | 44.19%| 42.11%          | 6.25%  | 35.78% |
| Improved               | 44.44% (24/54)        | 32.17%| 12.50%      | 3.33%                  | 31.91%    | 9.09%          | 42.19%        | 35.71%          | -             | -                       | 44.44%      | 39.53%| 25.63%          | 25.00% | 35.13% |
| Unimproved             | 29.63% (16/54)        | 8.70% | 50.00%      | 3.33%                  | 15.96%    | 9.09%          | 26.56%        | 42.86%          | -             | -                       | 22.22%      | 2.33% | 0.00%           | 50.00% | 17.89% |
| With sequelae          | 5.56% (3/54)          | 0.00% | 0.00%       | 0.00%                  | 0.00%     | 3.13%          | 0.00%         | 0.00%           | 0.00%         | 4.65%                   | 0.00%       | 0.00% | 12.50%          | 1.94%  | 9.46%  |
| Death                  | 0.00% (0/54)          | 0.00% | 0.00%       | 7.45%                  | 0.00%     | 0.00%          | 0.00%         | 0.00%           | 0.00%         | 0.00%                   | 0.00%       | 0.00% | 0.00%           | 0.00%  | 1.72%  |
The ROR signal of nivolumab and pembrolizumab for nephritis/renal dysfunction was detected from the subset data, but not from the whole data. This difference may be owing to a different risk among groups or an inconsistent reporting rate of nephritis in the whole data set vs subset data. Disproportionality by therapeutic area may provide an intra-class analysis from a clinical perspective and help reduce indication bias by selecting a data set where only AEs reported with ICIs are represented. Subsetting strategy may be applied in the evaluation of AE associations in disproportionality analyses using the ROR, if these values are suspected to be affected by the cloaking effect. However, the data subsetting strategy does not account for channeling bias, which arises when drugs are prescribed differently based on the disease severity\textsuperscript{22} or on the basis of their alternative use as first-, second-, and third-line therapies. Since we could not obtain detailed information on disease severity using therapy with ICIs from the JADER database, our results may be biased. In addition to this channeling bias, other sources of bias are inherently and inadvertently included in the SRS data. These biases can potentially be overcome by considering various clinical settings during calculations.

Pneumonitis in patients treated with anti-PD-1 antibodies was approximately 3\textpercent.\textsuperscript{8} The median time-to-onset for the anti-PD-1 antibodies categorized as initial failure type was approximately 6 to 8 weeks, whereas that for ipilimumab was approximately 5 weeks. The rate of occurrence of AEs after commencing drug therapy depends on the causal mechanism and often varies with time. A non-constant rate (initial failure type) over time may indicate a drug-AE association. The median onset time of pneumonitis induced by anti-PD-1/PD-L1 was reported to be 4.5 weeks.\textsuperscript{72} Immune-related pneumonitis was observed 8 to 14 weeks after the first dose of ipilimumab.\textsuperscript{11}

Eye disease caused by ICIs are rare but clinically important; they manifest as uveitis, conjunctivitis, and keratitis. The occurrence rate of uveitis ranged from 0.3 to 6\textpercent following treatment with ICIs.\textsuperscript{73} We found a disproportionality in signals in the PT of uveitis.

The treatment regimens were classified as PD-1 or CTLA-4 inhibitor treatment when the agents were administered as monotherapy, or as co-therapy when ipilimumab and nivolumab were administered concurrently.\textsuperscript{14,46,74} We observed association rules with nivolumab and ipilimumab co-therapy in most related categories of irAEs. Many studies have reported that the use of a combination of nivolumab and ipilimumab poses a high risk for irAEs.\textsuperscript{10,46,59} Therefore, healthcare professionals should pay attention to the risk of irAEs in patients administered ICIs as a co-therapy. Optimized interventions such as corticosteroid administration to treat irAEs should be introduced.\textsuperscript{64,72} The \textit{Apriori} algorithm can generate many rules that meet minimum support and confidence criteria. However, some of the rules can be redundant, and this is a drawback of the algorithm. We should be mindful of this problem and accordingly scrutinize several rules in order to find meaningful rules.\textsuperscript{17}

We evaluated the association rules between irAEs and co-therapy of nivolumab and ipilimumab in the subset data (S16-S27 Table, S1-S12 Figure). The pituitary, thyroid, and adrenal glands are endocrine
organs that are typically affected by ICIs. High incidences of hypothyroidism (17%), hypophysitis (13%), and hyperthyroidism (10%) of any grade have been reported with the co-therapy of nivolumab and ipilimumab. Hypophysitis, which can result in hypopituitarism, is associated with hypothyroidism and adrenal insufficiency in most cases of ipilimumab therapy. The precise mechanism by which ICIs

![Mosaic plot of outcomes of immune-related adverse events (irAEs) by immune checkpoint inhibitors (ICIs). A mosaic plot is divided into rectangles where each vertical length represents the proportion of each level of the Y variable within each level of the X variable.](image-url)
leads to endocrinopathies remains unknown. We observed the association rules between hypopituitarism and adrenal insufficiency and between hypopituitarism and hypothyroidism. The objection will no doubt be raised that the results from association rule mining do not prove causality; however, the detected association rules in the co-therapy of nivolumab and ipilimumab are thought-provoking observations.

Some limitations of our present analysis using the SRS JADER database should be noted. The choice of PTs should be made in accordance with the purpose of the study; the calculated RORs may vary significantly depending on the selection of PTs. The JADER database does not contain detailed information such as clinical background, types and stages of cancers, and chemotherapy regimens. Furthermore, SRSs are subject to either over- or under-reporting, confounding factors, and a lack of a control population or reference group. The intervention of regulatory authorities may influence the JADER database reporting based on the year of reporting. However, we did not evaluate the subsets as before/after the PMDA regulation. Multivariate regression analyses may be an approach to deal with confounders that affect the reliability of the results. We suggest that they should be assessed in a structured manner and include more complex interactions of the possible confounders. The use of propensity scores to reduce bias by equating groups based on covariates or other appropriate parameters would be a useful assessment approach. We consider the results of the JADER database analysis to be valid owing to appropriate methods of analyses and believe that the evaluation of subsets are valuable in disproportionality analysis. The results of analysis using SRSs should be cautiously interpreted, while keeping in mind the existing clinical outcomes.

5 | CONCLUSIONS

Despite the inherent limitations associated with SRS data, we demonstrated the potential risks of irAEs associated with ICIs based on RORs and time-to-onset analysis. Our findings indicated that patients who are co-administered nivolumab and ipilimumab should be carefully monitored. Our results, based on the evaluation of JADER, are consistent with those previously reported and represent a valuable contribution in improving the understanding of ICI-induced irAEs. These data may be particularly beneficial to medical practitioners and could contribute to improving the management of irAEs. Finally, our comparative safety study indicated the importance of comparing safety profiles of ICIs using post-marketing real-world data.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

ACKNOWLEDGEMENTS

This research was partially supported by the Japan Society for the Promotion of Science JSPS (grant no. 17K08452).

ORCID

Shiori Hasegawa https://orcid.org/0000-0003-0444-7945
Hiroaki Ikesue https://orcid.org/0000-0002-8499-131X
Tohru Hashida https://orcid.org/0000-0002-5702-5124
Mitsuhiro Nakamura https://orcid.org/0000-0002-5062-5522

REFERENCE

1. Haanen JBAG, van TH, Blank CU. Toxicity patterns with immunomodulating antibodies and their combinations. Semin Oncol. 2015;42:423-428. https://doi.org/10.1053/J.SEMINONCOL.2015.02.011.
2. Wang DY, Salem JE, Cohen JV, et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. JAMA Oncol. 2018;4:1721-1728. https://doi.org/10.1001/jamaoncol.2018.3923.
3. Connolly C, Bambahania K, Naidoo J. Immune-related adverse events: a case-based approach. Front Oncol. 2019;9:530. https://doi.org/10.3389/fonc.2019.00530.
4. Xu C, Chen YP, Du XJ, et al. Comparative safety of immune checkpoint inhibitors in cancer: systematic review and network meta-analysis. BMJ. 2018;363:k4226. https://doi.org/10.1136/bmj.k4226.
5. Postow MA. Managing immune checkpoint-blocking antibody side effects. Am Soc Clin Oncol Educ B. 2015;35:76-83. https://doi.org/10.14694/edbook.am.2015.35.76.
6. Kadono T. Immune-related adverse events by immune checkpoint inhibitors. Japanese J Clin Immunol. 2017;40:83-89. https://doi.org/10.2177/jsci.40.83.
7. Pillai RN, Behera M, Owonikoko TK, et al. Comparison of the toxicity profile of PD-1 versus PD-L1 inhibitors in non-small cell lung cancer: a systematic analysis of the literature. Cancer. 2018;124:271-277. https://doi.org/10.1002/cncr.31043.
8. Wang PF, Chen Y, Song SY, et al. Immune-related adverse events associated with anti-PD-1/PD-L1 treatment for malignancies: a meta-analysis. Front Pharmacol. 2017;8:730. https://doi.org/10.3389/fphar.2017.00730.
9. Heinzerling L, de Toni EN, Schett G, Hundorfean G, Zimmer L. Checkpoint inhibitors. Dtsch Arztebl Int. 2019;116:119-126. https://doi.org/10.3238/arztebl.2019.0119.
10. Ji H, Tang X, Dong Z, Song L, Jia Y. Adverse event profiles of anti-CTLA-4 and anti-PD-1 monoclonal antibodies alone or in combination: analysis of spontaneous reports submitted to FAERS. Clin Drug Invest. 2019;39:319-330. https://doi.org/10.1007/s40261-018-0735-0.
11. Kumar V, Chaudhary N, Garg M, Floudas CS, Soni P, Chandra AB. Current diagnosis and management of immune related adverse events (irAEs) induced by immune checkpoint inhibitor therapy. Front Pharmacol. 2017;8:49. https://doi.org/10.3389/fphar.2017.00049.
12. Bate A, Evans SJW. Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiol Drug Saf. 2009;18:427-436. https://doi.org/10.1002/pds.1742.
13. Zamani Y, Niimura T, Okada N, et al. Factors associated with immune checkpoint inhibitor-related myocarditis. JAMA Oncol. 2019;5:1635-1637. https://doi.org/10.1001/jamaoncol.2019.3113.
14. Sato K, Mano T, Iwata A, Toda T. Neurological and related adverse events in immune checkpoint inhibitors: a pharmacovigilance study from the Japanese Adverse Drug Event Report database. J Neurooncol. 2019;145:1-9. https://doi.org/10.1007/s11060-019-03273-1.
15. Fujiwara M, Kawasaki Y, Yamada H. A pharmacovigilance approach for post-marketing in Japan using the Japanese Adverse Drug Event Report (JADER) database and association analysis. PLoS One. 2016;11:e0154425. https://doi.org/10.1371/journal.pone.0154425.

16. Harpaz R, Chase HS, Friedman C. Mining multi-item drug adverse effect associations in spontaneous reporting systems. BMC Bioinformatics. 2010;11:S7. https://doi.org/10.1186/1471-2105-11-S7.

17. Yıldırım P. Association patterns in open data to explore ciprofloxacin adverse events. Appl Clin Inform. 2015;6:728-747. https://doi.org/10.4338/ACI-2015-06-RA-0076.

18. Tanaka M, Hasegawa S, Nakao S, et al. Analysis of drug-induced hearing loss by using a spontaneous reporting system database. PLoS One. 2019;14:e0217951. https://doi.org/10.1371/journal.pone.0217951.

19. Arima H, Iwama S, Inaba H, et al. Management of immune-related adverse events in endocrine organs induced by immune checkpoint inhibitors: clinical guidelines of the Japan endocrine society. Endocr J. 2019;66:581-586. https://doi.org/10.1507/endocrj.EJ19-0163.

20. MedDRA MSSO. Introductory guide for Standardised MedDRA Queries (SMQs) version 19.0. 2016. http://www.meddra.org/sites/default/files/guidance/file/smq_intguide_19_0_english.pdf. Accessed May 27, 2020.

21. Abdel-Wahab N, Shah M, Suarez-Almazor ME. Adverse events associated with immune checkpoint blockade in patients with cancer: a systematic review of case reports. PLoS One. 2016;11:e0160221. https://doi.org/10.1371/journal.pone.0160221.

22. Poluzzi E, Raschi E, Piccinni C, De F. Data mining techniques in pharmacovigilance: analysis of the publicly accessible FDA Adverse Event Reporting System (AERS). Data Mining Applications in Engineering and Medicine. London: InTech; 2012:265-302. https://doi.org/10.5772/50095.

23. van Puijenbroek EP, Bate A, Leufkens HGM, Lindquist M, Orre R, Egberts ACG. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. Pharmacoepidemiol Drug Saf. 2002;11:3-10. https://doi.org/10.1002/pds.668.

24. Almenoff JS, Pattishall EN, Gibbs TG, DuMouchel W, Evans SJW, Vuen N. Novel statistical tools for monitoring the safety of marketed drugs. Clin Pharmcoul Ther. 2007;82:157-166. https://doi.org/10.1038/sj.cpt.640258.

25. Raschi E, Piccinni C, Poluzzi E, Marchesini G, De Ponti F. The association of pancreatitis with antidiabetic drug use: gaining insight through the FDA pharmacovigilance database. Acta Diabetol. 2013;50:569-577. https://doi.org/10.1007/s00592-011-0340-7.

26. Grégoire F, Pariente A, Fourrier-Reglat A, Haramburu F, Bégaud B, Moore N. A signal of increased risk of hypoglycaemia with angiotensin receptor blockers caused by confounding. Br J Clin Pharmacol. 2008;66:142-145. https://doi.org/10.1111/j.1365-2125.2008.03176.x.

27. Umetsu R, Abe J, Ueda N, et al. Association between selective serotonin reuptake inhibitor therapy and suicidality: analysis of U.S. Food and Drug Administration Adverse Event Reporting System data. Biol Pharm Bull. 2015;38:1689-1699. https://doi.org/10.1248/bpb.b15-00243.

28. Hatahira H, Abe J, Hane Y, et al. Drug-induced gingival hyperplasia: a retrospective study using spontaneous reporting system databases. J Pharm Heal Care Sci. 2017;3:19. https://doi.org/10.1186/s40780-017-0088-5.

29. Nakamura M, Umetsu R, Abe J, et al. Analysis of the time-to-onset of osteonecrosis of jaw with bisphosphonate treatment using the data from a spontaneous reporting system of adverse drug events. J Pharm Heal Care Sci. 2015;1:34. https://doi.org/10.1186/s40780-015-0035-2.

30. Sasaoka S, Matsui T, Hane Y, et al. Time-to-onset analysis of drug-induced long QT syndrome based on a spontaneous reporting system for adverse drug events. PLoS One. 2016;11:e0164309. https://doi.org/10.1371/journal.pone.0164309.

31. Sauzet O, Carvajal A, Escudero A, Molokhia M, Cornelius VR. Illustration of the weibull shape parameter signal detection tool using electronic healthcare record data. Drug Saf. 2013;36:995-1006. https://doi.org/10.1007/s40264-013-0061-7.

32. Yamada M, Hanada J. Comparison of the onset time profile among the interferon formulations in adverse drug reaction of suicide- or diabetes-related. Japanese J Pharmacoepidemiol. 2014;19:23-30. https://doi.org/10.3820/jjpe.19.23.

33. Wright A, Chen ES, Maloney FL. An automated technique for identifying associations between medications, laboratory results and problems. J Biomed Inform. 2010;43:891-901. https://doi.org/10.1016/j.jbi.2010.09.009.

34. Shirakami Y, Okamoto K, Kawashita N, Yasunaga T, Takagi T. Signal detection of drug complications applying association rule learning for Stevens-Johnson syndrome. J Comput Aided Chem. 2009;10:118-127. https://doi.org/10.2751/jcac.10.118.

35. Zhu A-L, Li J, Leong T-Y. Automated knowledge extraction for decision model construction: a data mining approach. Annu Symp Proceedings AMIA Symp. 2003;2003:758-762.

36. Hahsler M, Grün B, Hornik K. A computational environment for mining association rules and frequent item sets. J Stat Softw. 2005;14:1-25. Available at: http://www.jstatsoft.org/v014/i01/. Accessed May 27, 2020.

37. Shimada K, Hasegawa S, Nakao S, et al. Adverse event profiles of ifosfamide-induced encephalopathy analyzed using the Food and Drug Administration Adverse Event Reporting System and the Japanese Adverse Drug Event Report databases. Cancer Chemother Pharmacol. 2019;84:1097-1105. https://doi.org/10.1007/s00280-019-03949-5.

38. Agrawal R, Srikant R. Fast algorithms for mining association rules. Proceedings of the 20th International Conference on Very Large Data Bases; VLDB’94. United States: Very Large Data Bases Endowment Inc.; 1994:487-499. http://www.vldb.org/conf/1994/P487.PDF Accessed May 27, 2020.

39. Montastruc JL, Sommet A, Bagheri H, Lapeyre-Mestre M. Benefits and strengths of the disproportionality analysis for identification of adverse drug reactions in a pharmacovigilance database. Br J Clin Pharmacol. 2011;72:905-908. https://doi.org/10.1111/j.1365-2125.2011.04037.x.

40. Weber JS, Yang JC, Atkins MB, Disis ML. Toxicities of immunotherapy for the practitioner. J Clin Oncol. 2015;33:2092-2099. https://doi.org/10.1200/JCO.2014.60.0379.

41. Dine J, Gordon R, Shames Y, Kasler M, Barton-Burke M. Immune checkpoint inhibitors: an innovation in immunotherapy for the treatment and management of patients with cancer. Asia Pacific J Oncol Nuts. 2017;4:127-135. https://doi.org/10.4103/apjon.apjon_4_17.

42. González-Rodríguez E, Rodríguez-Abreu D. Immune checkpoint inhibitors: review and management of endocrine adverse events. Endocr Rev. 2015;27:3-10. https://doi.org/10.1210/endo-2014-0079.

43. Okazaki T, Honjo T. PD-1 and PD-1 ligands: from discovery to clinical application of the weibull shape parameter signal detection tool using electronic healthcare record data. J Pharm Heal Care Sci. 2015;1:34. https://doi.org/10.1186/s40780-015-0035-2.
55. Akturk HK, Higham CE, Trainer P, Lorigan P. Hypopatraemia secondary to nivolumab-induced primary adrenal failure. Endocrinol Diabetes Metab Case Reports. 2016;2016:16-0108. https://doi.org/10.1016/jedm.2016-0108.

56. Min I, Karamangil D, Tafra R, Hoffecker L, Murad MH, Eigentler TK, Hassel JC, Berking C, et al. Diagnosis, monitoring and resolution of immune-related adverse events of special interest with ipilimumab: detailed safety analysis from a phase 3 trial in patients with advanced melanoma. Cancer. 2013;119:1675-1682. https://doi.org/10.1002/cncr.27969.

57. Morita R, Igaku no Ayumi (Journal of clinical and experimental medicine). Adverse event caused immune-checkpoint inhibitor. 2017;263:104-108.

58. Nomura K, Takahashi K, Kiohara K, et al. Effect of database profile variation on drug safety assessment: an analysis of spontaneous adverse event reports of Japanese cases. Drug Des Devel Ther. 2015;9:3031-3041. https://doi.org/10.2147/DDDT.S81998.

59. Makarious D, Horwood K, Coward JIG. Myasthenia gravis: an emerging toxicity of immune checkpoint inhibitors. J Clin Oncol. 2017;35:1749-1755. https://doi.org/10.1200/JCO.2016.69.0924.

60. Makarious D, Horwood K, Coward JIG. Myasthenia gravis: an emerging toxicity of immune checkpoint inhibitors. J Clin Oncol. 2017;35:1749-1755. https://doi.org/10.1200/JCO.2016.69.0924.

61. Okano Y, Satoh T, Horiguchi K, et al. Nivolumab-induced hypophysitis in a patient with advanced malignant melanoma. Endocr J. 2016;63:905-912. https://doi.org/10.1507/endocrj.EJ16-0161.

62. Cho KY, Miyoshi H, Nakamura A, Kurita T, Atsumi T. Hyponatremia can be a powerful predictor of the development of isolated ACTH deficiency associated with nivolumab treatment. Endocr J. 2017;64:235-236. https://doi.org/10.1507/endocrj.EJ16-0596.

63. Akturk HK, Kahramangil D, Sarwal A, Hoffecker L, Murad MH, Michelis AW. Immune checkpoint inhibitor-induced type 1 diabetes: a systematic review and meta-analysis. Diabet Med. 2019;36:1075-1081. https://doi.org/10.1111/dme.14050.

64. Baden MY, Imagawa A, Abiru N, et al. Characteristics and clinical course of type 1 diabetes mellitus related to anti-programmed cell death-1 therapy. Diabetol Int. 2019;10:58-66. https://doi.org/10.1016/j.s13340-018-0362-2.

65. Khaja L, Day D, Wei-Wu Chen T, Siu L, Hansen A. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review - analysis of oncology. Ann Oncol. 2017;28:2377-2385. https://doi.org/10.1093/annonc/mdx286.

66. Gupta A, De Felice KM, Loftus EV, Khanna S. Systematic review: colitis associated with anti-CTLA-4 therapy. Aliment Pharmacol Ther. 2015;42:406-417. https://doi.org/10.1111/apt.13281.

67. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med. 2017;377:1345-1356. https://doi.org/10.1056/NEJMoa1709684.

68. Eigentler TK, Hassel JC, Berking C, et al. Diagnosis, monitoring and management of immune-related adverse drug reactions of anti-POD-1 antibody therapy. Cancer Treat Rev. 2016;45:7-18. https://doi.org/10.1016/j.ctrv.2016.02.003.

69. Yervoy. HIGHLIGHTS OF PRESCRIBING INFORMATION. New York: Bristol-Myers Squibb Company; 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125377s110bl.pdf.

70. Zhang X, Ran Y, Wang K, Zhu Y, Li J. Incidence and risk of hepatic toxicities with PD-1 inhibitors in cancer patients: a meta-analysis. Drug des Devel Ther. 2016;10:3153-3161. https://doi.org/10.2147/DDDT.S115493.

71. Weber JS, Dummer R, de Pril V, Lebbe C, Hodi FS. Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab: detailed safety analysis from a phase 3 trial in patients with advanced melanoma. Cancer. 2013;119:1675-1682. https://doi.org/10.1002/cncr.27969.
80. van Puijenbroek EP, Egberts ACG, Meyboom RHB, Leufkens HGM. Signalling possible drug-drug interactions in a spontaneous reporting system: delay of withdrawal bleeding during concomitant use of oral contraceptives and itraconazole. Br J Clin Pharmacol. 1999;47:689-693. https://doi.org/10.1046/j.1365-2125.1999.00957.x.

81. Wang X, Li L, Wang L, Feng W, Zhang P. Propensity score-adjusted three-component mixture model for drug-drug interaction data mining in FDA Adverse Event Reporting System. Stat Med. 2020;39:996-1010. https://doi.org/10.1002/sim.8457.

82. Akimoto H, Oshima S, Negishi A, et al. Assessment of the risk of suicide-related events induced by concomitant use of antidepressants in cases of smoking cessation treatment with varenicline and assessment of latent risk by the use of varenicline. PLoS One. 2016;11: e0163583. https://doi.org/10.1371/journal.pone.0163583.

83. Schuemie MJ, Ryan PB, Hripcsak G, Madigan D, Suchard MA. A systematic approach to improving the reliability and scale of evidence from health care data. New York: arVix; 2018. https://arxiv.org/pdf/1803.10791.pdf. Accessed May 27, 2020.

84. Hripcsak G, Ryan PB, Duke JD, et al. Characterizing treatment pathways at scale using the OHDSI network. Proc Natl Acad Sci U S A. 2016;113:7329-7336. https://doi.org/10.1073/pnas.1510502113.

85. Tian Y, Schuemie MJ, Suchard Marc A. Evaluating large-scale propensity score performance through real-world and synthetic data experiments. Int J Epidemiol. 2018;47:2005-2014. https://doi.org/10.1093/ije/dyy120.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Hasegawa S, Ikesue H, Nakao S, et al. Analysis of immune-related adverse events caused by immune checkpoint inhibitors using the Japanese Adverse Drug Event Report database. Pharmacoepidemiol Drug Saf, 2020;29:1279–1294. https://doi.org/10.1002/pds.5108