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ORIGINAL REPORT

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

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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.[1] 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.[1-3]

ICIs are one of the most important breakthroughs in cancer treatment,[4] but are associated with a spectrum of drug-related autoimmune disorders and inflammatory diseases known as immune-related adverse events (irAEs).[5,6] 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,[7] whereas in patients treated with ipilimumab, the rate of irAEs is 72% and 24%, respectively.[8] 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.[3,9]

The symptoms and progression of irAEs are different from those of adverse events (AEs) caused by conventional anticancer agents.[6] 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).[2,9,10] Such irAEs are mostly transient and mild and can lead to the discontinuation of therapy with ICIs or immunosuppressive agents.[11] 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%.[2] Healthcare professionals should be aware of potential irAEs since occasional fatalities have also been observed.[11]

The spontaneous reporting system (SRS) has been used for pharmacovigilance assessments that reflect the realities of clinical practice.[12] 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[10] and the risk factors of associated myocarditis[13] 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.[14]

KEY POINTS

1. We used a spontaneous reporting system (SRS), the Japanese Adverse Drug Event Report (JADER) database, as a data source to analyze immune-related adverse events (irAEs) in a real-world scenario.
2. Despite the inherent limitations associated with SRS, we demonstrated the potential risks of irAEs associated with immune checkpoint inhibitors (ICIs) based on disproportionality and time-to-onset analyses.
3. Our results, based on the evaluation of JADER, are consistent with those of previous studies and represent a valuable contribution to improve the understanding of ICI-induced irAEs.
4. Patients administered nivolumab and ipilimumab as co-therapy regimens require close monitoring for irAEs.
5. Our comparative safety study indicated the importance of comparing safety profiles of ICIs using post-marketing real-world data.

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.[15-18] 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 Japan Endocrine Society indicate the classifications of irAE in the endocrine region.[19] Other reviews and papers[3,6,9,11] listed other irAEs such as colitis, hyperthyroidism, and hypothyroidism. Furthermore, the research using the SRS database focuses on myasthenia gravis,[14] and myocarditis.[13] Using the FAERS database, Ji et al[10] comprehensively evaluated AE profiles, including irAEs using Standardized MedDRA Queries[20] that consist of PTs grouped according to the level that relates to a defined medical condition. Based on previous reports,[3,6,9-11,13,14,19,21] 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 present in the database.[12,22] This ratio assesses disproportionality in pharmacovigilance data and evaluated the association between the drugs of interest and a specific AE. We calculated RORs using a two-by-two contingency table to detect potential associations between ICIs and irAEs. A signal was considered positive when the lower limit of 95% confidence interval (CI) of the ROR was greater than 1.[22] Two or more cases were required to define a signal.[22,23]

The data subsetting strategy may help mitigate indication bias on signal detection by limiting the analysis to a population of patients that are thought to share common risk factors and diseases.[24-27] We defined a patient subset with anticancer therapies from the whole JADER data and evaluated the intra-class RORs of this subset. We extracted the purpose of administration from the cases that were administered ICIs as listed in the "drug" table of the JADER database. Patients receiving anticancer therapies similar to therapy with ICIs were subsetted by the term of the medical history as indicated in the supplemental material (S1 Table). If the indication field in the "hist" table was incomplete, that particular record was excluded from the subset data. Since the JADER database does not contain information on the severity of disease, this parameter was not considered in our analyses.

2.4 | Time-to-onset analysis

The JADER database includes the date of first administration of each individual drug and the onset date of each individual AE, whereas the FAERS database lacks this dated information for each drug recorded in its databases. Using the JADER database, we calculated the time span between the date of first administration of the drug and the date of first occurrence of the AE. We excluded reports that lacked complete AE occurrences and prescription start dates. If the same drug was prescribed in the report, duplicate prescriptions were also excluded from the analysis. To evaluate the onset profiles of AEs, we used median onset, quartile, and Weibull shape parameter tests.[28-30] The ROR is a disproportionality measure that detects signals of specific AEs in excessive frequencies over other AEs. Recently, time-to-onset analysis has been proposed as a method to detect signals for AEs in the SRS. The rate of AEs after prescription is thought to depend on a causal mechanism and often varies over time. In contrast, AEs not associated with the drug will occur at a constant background rate. 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).[29,31,32] The scale parameter α determines the scale of the distribution function, while the shape parameter β determines the shape of the distribution function. A larger α 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.[31]

2.5 | Association rule mining

Association rule mining is a useful technique for inferring relationships between drugs and possible risk factors.[15,18,33,34] 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 (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	Rash	Erythema (2350 cases)	10015150
	Pseudopolyposis (1 case)	–		Pemphigoid (1052 cases)	10034277
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

TABLE 1 (Continued)

Categories	PT	PT code	Categories	PT	PT code
	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.

[(right-hand-side, rhs) of the rule], where X and Y are mutually exclusive sets of items.[35,36] It can be represented as X = > Y. 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:

$$\begin{aligned} support &= P(X \cap Y) = \{X \cap Y\}/\{D\} \\ confidence &= P(X \cap Y)/P(X) \\ lift &= P(X \cap Y)/P(X)\,P(Y) \end{aligned} \quad (1)$$

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.[36] *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).[16,17,36,37] It is important for a rule to have high *confidence* because it accurately predicts the association between the items in the rule. The *lift* of an association rule is the frequency used to gauge the interestingness of a rule and represents the ratio of probability. Since P (Y) appears in the denominator of the *lift* equation, the *lift* can be expressed as the *confidence* divided by P (Y). *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: *lift* = 1, > 1, or < 1 if X and Y are independent, positively correlated, or negatively correlated, respectively. Furthermore, we calculated the chi-squared values to evaluate the association rules:[17]

$$Chi-squared = D(lift-1)^2 \frac{Support * Confidence}{(Confidence - Support) * (Lift - Confidence)}$$

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.[16,38] In the second step, rules were generated by selecting the

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.

3 | RESULTS

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 adrenal 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 myocarditis 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 β 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 β 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		
	Case (n)		Case	ROR (95% CI)		Case	ROR (95% CI)		Case	ROR (95% CI)		Case	ROR (95% CI)		Case	ROR (95% CI)	
	Whole data	Subset data	(for irAE, n)	Whole data	Subset data	(for irAE, n)	Whole data	Subset data	(for irAE, n)	Whole data	Subset data	(for irAE, n)	Whole data	Subset data	(for irAE, n)	Whole data	Subset data
	534 688[a]	52 474[a]	4419[a]			2148[a]			545[a]			41[a]			5[a]		
Adrenal insufficiency	837	325	204	40.50 (34.48-47.55)	19.17 (15.28-24.06)	82	27.96 (22.17-35.25)	8.18 (6.34-10.55)	54	74.92 (56.08-100.08)	20.96 (15.45-28.45)	0	–[b]	–[b]	0	–[b]	–[b]
Colitis	11 311	2762	387	4.56 (4.10-5.07)	1.85 (1.65-2.07)	161	3.79 (3.22-4.45)	1.49 (1.26-1.75)	115	12.49 (10.16-15.36)	4.98 (4.04-6.14)	1	–[c]	–[c]	0	–[b]	–[b]
Eye disease	275	71	40	20.60 (14.71-28.85)	14.15 (8.84-22.64)	14	13.38 (7.80-22.95)	5.79 (3.22-10.40)	8	29.79 (14.67-60.49)	12.26 (5.85-25.72)	0	–[b]	–[b]	0	–[b]	–[b]
Hematological disorder	932	60	28	3.73 (2.56-5.45)	9.57 (5.76-15.91)	8	2.15 (1.07-4.32)	3.61 (1.71-7.62)	6	6.41 (2.86-14.37)	10.69 (4.58-24.96)	0	–[b]	–[b]	0	–[b]	–[b]
Hepatitis	16 545	1827	188	1.40 (1.21-1.62)	1.26 (1.08-1.47)	38	0.56 (0.41-0.78)	0.49 (0.35-0.68)	94	6.56 (5.25-8.20)	6.04 (4.81-7.58)	0	–[b]	–[b]	0	–[b]	–[b]
Hyperthyroidism	1023	269	126	17.32 (14.34-20.92)	9.83 (7.72-12.52)	111	31.76 (25.96-38.87)	17.30 (13.52-22.14)	22	22.40 (14.56-34.48)	8.80 (5.64-13.73)	0	–[b]	–[b]	1	–[b]	–[b]
Hypopituitarism	191	191	106	153.30 (115.06-204.24)	13.87 (10.41-18.48)	25	37.77 (24.75-57.63)	3.56 (2.33-5.43)	64	559.48 (408.93-765.47)	74.97 (53.82-104.43)	0	–[b]	–[b]	0	–[b]	–[b]
Hypothyroidism	681	148	57	11.09 (8.44-14.57)	6.89 (4.94-9.60)	28	10.76 (7.35-15.74)	5.53 (3.65-8.36)	14	21.09 (12.34-36.05)	10.19 (5.84-17.79)	0	–[b]	–[b]	0	–[b]	–[b]
Myasthenia gravis	177	76	42	37.68 (26.62–53.34)	13.55 (8.61–21.32)	25	41.25 (26.96–63.10)	11.61 (7.18–18.77)	0	–[b]	–[b]	0	–[b]	–[b]	0	–[b]	–[b]
Myocarditis	229	45	24	14.12 (9.24-21.57)	12.49 (6.95-22.45)	15	17.49 (10.35-29.58)	11.79 (6.33-21.95)	0	–[b]	–[b]	0	–[b]	–[b]	0	–[b]	–[b]
Nephritis/renal dysfunction	11 823	968	106	1.09 (0.90-1.32)	1.35 (1.10-1.65)	54	1.14 (0.87-1.50)	1.39 (1.06-1.84)	9	0.74 (0.38-1.43)	0.89 (0.46-1.73)	2	2.27 (0.55-9.39)	2.73 (0.66-11.33)	0	–[b]	–[b]
Pneumonitis	25 090	7456	1103	7.02 (6.55–7.52)	2.18 (2.03–2.35)	653	9.08 (8.28–9.97)	2.79 (2.54–3.07)	43	1.74 (1.27–2.38)	0.51 (0.38–0.70)	9	5.71 (2.73–11.97)	1.70 (0.81–3.56)	0	–[b]	–[b]
Rash	12 596	1157	94	0.90 (0.73-1.11)	0.96 (0.78-1.19)	61	1.21 (0.94-1.57)	1.31 (1.01-1.71)	19	1.50 (0.95-2.37)	1.61 (1.02-2.56)	0	–[b]	–[b]	0	–[b]	–[b]
Type 1 diabetes mellitus	986	187	138	20.13 (16.77–24.15)	31.58 (22.76–43.82)	30	308.92 (196.82–484.87)	177.53 (110.62–284.90)	16	16.62 (10.07–27.45)	9.15 (5.45–15.39)	0	–[b]	–[b]	0	–[b]	–[b]

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

[a]The number of irAE reports from whole data in the "demo" table.

[b]Non-case was not reported.

[c]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.[22] ROR is an indicator of an increased risk in AE reporting, but does not indicate the risk of AE occurrence in absolute terms.[39] 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.[40]

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 β 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.[6,19,41,42] 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.[43] CTLA-4 is expressed by activated T-cells. The CTLA-4 pathway predominantly acts in lymph nodes.[44] 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.[19,45] Primary adrenal insufficiency and type 1 diabetes mellitus are rare, but can lead to life-threatening consequences if not promptly recognized and treated.[19] A systematic review reports that the rate of primary adrenal insufficiency was 0.7%, of which 0.2% was graded 3 or higher.[46] A case report shows that primary adrenal insufficiency developed 8 weeks after initiation of nivolumab treatment[47] and 16 weeks after initiation of ipilimumab.[19,48] 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%.[19,42,46,49,50] Thyroiditis induced by ICIs usually causes transient hyperthyroidism[9,51] and develops 2 to 6 weeks after administration in most cases. Hyperthyroidism is often followed by the subsequent development of hypothyroidism.[50] 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.[19,42,46,49,52] Hypopituitarism induced by ICIs can develop even after drug withdrawal.[19] Hypopituitarism was observed approximately 10 weeks after commencement of anti-CTLA-4 antibody therapy[52] and up to several months after the initiation of anti-PD-1 antibody therapy.[53,54] 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%,[46] and the rate was higher with anti-PD-1 antibody therapy than with anti-CTLA-4 antibody therapy.[19] Type 1 diabetes mellitus developed within 3 months commencement of anti-PD-1 or PD-L1 antibody therapy.[55] Another study reports a mean duration of type 1 diabetes mellitus as 22 weeks with a range from 2 to 72 weeks.[19,56] 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.[57] The rate of colitis induced by nivolumab and ipilimumab was 1%[6] and 8% to 22%,[58,59] respectively. Life-threatening diarrhea and colitis occurred with anti-PD-1 therapy (1%-4%) and in co-therapy with ipilimumab and nivolumab (15%).[9,51,59] 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.[41,60,61]

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.[10] 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.[62] Hepatitis begins to develop approximately 4 to 10 weeks after ipilimumab administration, of which 1% to 2% cases are grade 3.[63,64] Severe autoimmune hepatitis occurred in 20% of patients who were co-administered nivolumab and ipilimumab.[9,62] It is reported that the ROR signals of nivolumab, pembrolizumab, and ipilimumab were detected in the FAERS database,[10] 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.[65] Such possibilities should not be overlooked when comparing different SRSs.

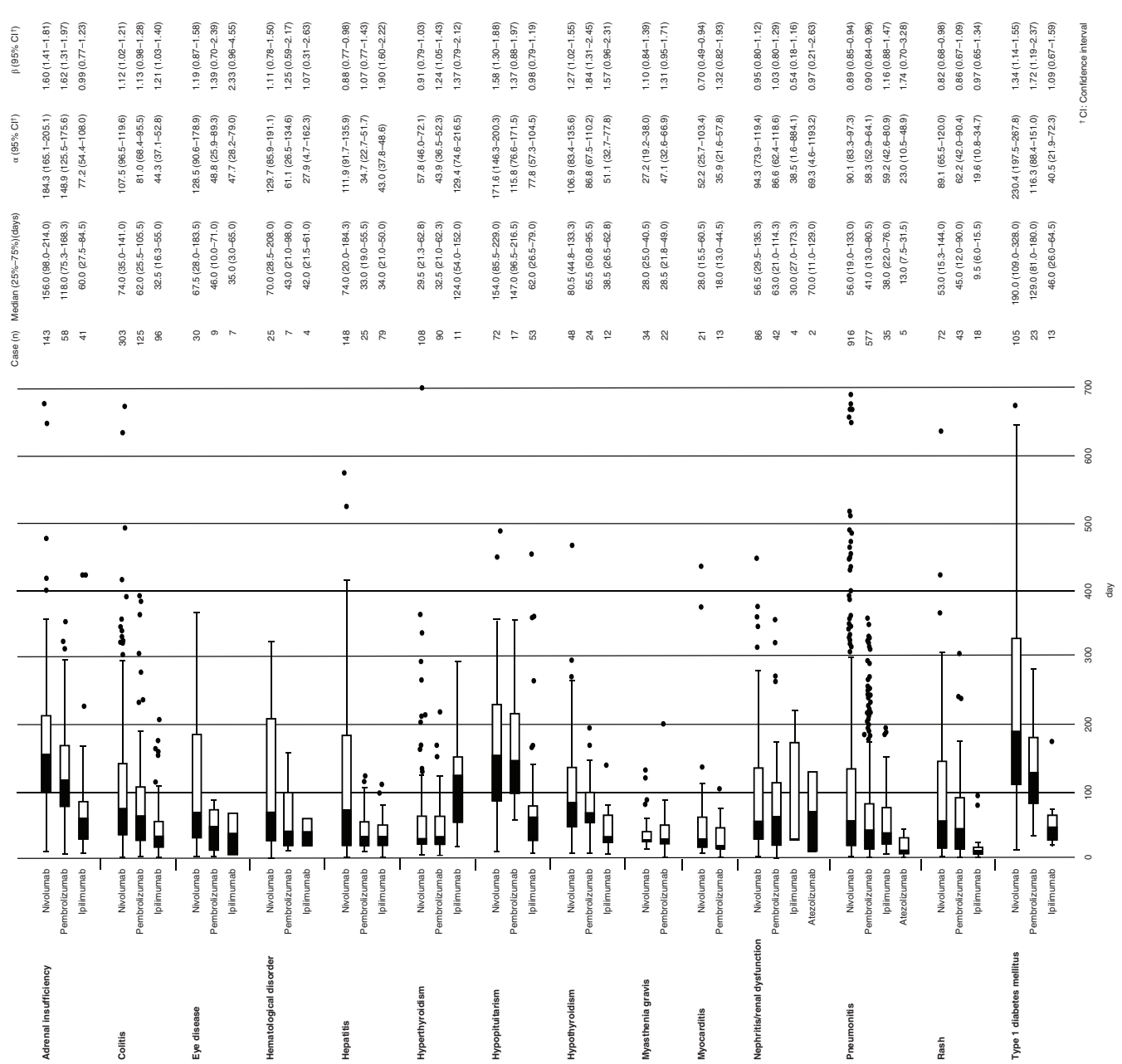

FIGURE 1 Box plot and Weibull shape parameter (β) of immune-related adverse events (irAEs) of immune checkpoint inhibitors (ICIs)

A study has reported that 0.1% to 0.2% of patients treated with ICIs develop myasthenia gravis[3] with an onset of 2 to 3 weeks after the commencement of therapy,[3] whereas another study reports an onset range of 2 to 12 weeks.[66] In our study, the median onset of myasthenia gravis induced by anti-PD-1 antibody therapy was approximately 4 weeks. Sato et al reported this value as 4 weeks using the JADER database,[14] which is consistent with our results.

Myocarditis can follow a lethal course.[67] Several studies based on the FAERS database have reported ROR signals for myocarditis.[10,13] We conducted a time-to-onset analysis of the JADER data set and found that the median onset of myocarditis was 3 to 4 weeks following a treatment with anti-PD-1 antibodies. In the FAERS database, information including the date of therapy commencement was not recorded; consequently, matching the date of onset of AEs and treatment initiation of individual drugs was difficult. Nevertheless, our results obtained for the JADER data set complement the results obtained for the FAERS data set.

A wide range of renal dysfunction symptoms were often observed with the anti-PD-1 antibody.[3,9,10] Rash was a common dermatological AE induced by anti-PD-1 antibodies and the anti-CTLA-4 antibody, ipilimumab.[5,10,68-70] In our study, the ROR signals of the whole data for rash and nephritis/renal dysfunction were not detected. ROR signals can be suppressed in a large number of reports in which the same AE is connected with other drugs. This is referred to as the masking or cloaking effect,[71] and considered to be one reason for a lack of signal.

TABLE 3 Outcomes of the immune-related adverse events (irAEs) by immune checkpoint inhibitors (ICIs)

	Outcome	Adrenal insufficiency [a]	Colitis [a]	Eye disease [a]	Hematological disorder [a]	Hepatitis [a]	Hyperthyroidism [a]	Hypopituitarism [a]	Hypothyroidism [a]	Myasthenia gravis [a]	Myocarditis [a]	Nephritis/renal dysfunction [a]	Pneumonitis [a]	Rash [a]	Type 1 diabetes mellitus [a]	Total [a]
Nivolumab	Recovered	17.16% (35/204)	47.03% (182/387)	45.00% (18/40)	46.43% (13/28)	36.17% (68/188)	53.97% (68/126)	23.58% (25/106)	14.04% (8/57)	23.81% (10/42)	29.17% (7/24)	20.75% (22/106)	23.75% (262/1103)	45.74% (43/94)	11.59% (16/138)	29.40% (777/2643)
	Improved	44.61% (91/204)	36.43% (141/387)	14.00% (6/40)	28.57% (8/28)	29.26% (55/188)	19.05% (24/126)	37.74% (40/106)	43.86% (25/57)	40.48% (17/42)	20.83% (5/24)	29.25% (31/106)	41.70% (460/1103)	42.49% (39/94)	24.64% (34/138)	36.93% (976/2643)
	Unimproved	17.65% (36/204)	7.49% (29/387)	22.50% (9/40)	17.86% (5/28)	17.55% (33/188)	10.32% (13/126)	21.70% (23/106)	33.33% (19/57)	14.29% (6/42)	4.17% (1/24)	22.64% (24/106)	9.52% (105/1103)	8.51% (8/94)	40.58% (56/138)	13.89% (367/2643)
	With sequelae	2.45% (5/204)	0.52% (2/387)	7.50% (3/40)	0.00% (0/28)	1.06% (2/188)	4.76% (6/126)	2.83% (3/106)	1.75% (1/57)	2.38% (1/42)	4.17% (1/24)	2.83% (3/106)	2.27% (25/1103)	0.00% (0/94)	9.42% (13/138)	2.46% (65/2643)
	Death	1.47% (3/204)	2.33% (9/387)	0.00% (0/40)	7.14% (2/28)	6.91% (13/188)	0.00% (0/126)	1.89% (2/106)	0.00% (0/57)	9.52% (4/42)	41.67% (10/24)	7.55% (8/106)	13.96% (154/1103)	0.00% (0/94)	0.72% (1/138)	7.79% (206/2643)
	Uncertain	16.67% (34/204)	6.20% (24/387)	10.00% (4/40)	0.00% (0/28)	9.04% (17/188)	11.90% (15/126)	12.26% (13/106)	7.02% (4/57)	9.52% (4/42)	0.00% (0/24)	16.98% (18/106)	8.79% (97/1103)	4.26% (4/94)	13.04% (18/138)	9.53% (252/2643)
	Total	7.72% (204/2643)	14.64% (387/2643)	1.51% (40/2643)	1.06% (28/2643)	7.11% (188/2643)	4.77% (126/2643)	4.01% (106/2643)	2.16% (57/2643)	1.59% (42/2643)	0.91% (24/2643)	4.01% (106/2643)	41.73% (1103/2643)	3.56% (94/2643)	5.22% (138/2643)	2643
Pembrolizumab	Recovered	17.07% (14/82)	36.65% (59/161)	28.57% (4/14)	12.50% (1/8)	26.32% (10/38)	44.14% (49/111)	24.00% (6/25)	17.86% (5/28)	12.00% (3/25)	20.00% (3/15)	27.78% (15/54)	22.97% (150/653)	27.87% (17/61)	16.67% (5/30)	26.13% (341/1305)
	Improved	40.24% (33/82)	38.51% (62/161)	50.00% (7/14)	25.00% (2/8)	36.84% (14/38)	23.42% (26/111)	40.00% (10/25)	25.00% (7/28)	36.00% (9/25)	6.67% (1/15)	24.07% (13/54)	44.41% (290/653)	29.51% (18/61)	43.33% (13/30)	38.70% (505/1305)
	Unimproved	24.39% (20/82)	16.15% (26/161)	7.14% (1/14)	37.50% (3/8)	15.79% (6/38)	18.92% (21/111)	24.00% (6/25)	46.43% (13/28)	20.00% (5/25)	6.67% (1/15)	27.78% (15/54)	10.72% (70/653)	14.75% (9/61)	23.33% (7/30)	15.56% (203/1305)
	With sequelae	6.10% (5/82)	0.00% (0/161)	0.00% (0/14)	0.00% (0/8)	0.00% (0/38)	1.80% (2/111)	4.00% (1/25)	0.00% (0/28)	4.00% (1/25)	6.67% (1/15)	0.00% (0/54)	0.61% (4/653)	0.00% (0/61)	6.67% (2/30)	1.23% (16/1305)
	Death	0.00% (0/82)	4.35% (7/161)	0.00% (0/14)	0.00% (0/8)	2.63% (1/38)	0.00% (0/111)	0.00% (0/25)	0.00% (0/28)	12.00% (3/25)	26.67% (4/15)	5.56% (3/54)	15.01% (98/653)	4.92% (3/61)	3.33% (1/30)	9.20% (120/1305)
	Uncertain	12.20% (10/82)	4.35% (7/161)	14.29% (2/14)	25.00% (2/8)	18.42% (7/38)	11.71% (13/111)	8.00% (2/25)	10.71% (3/28)	16.00% (4/25)	33.33% (5/15)	14.81% (8/54)	6.28% (41/653)	22.95% (14/61)	6.67% (2/30)	9.20% (120/1305)
	Total	6.28% (82/1305)	12.34% (161/1305)	1.07% (14/1305)	0.61% (8/1305)	2.91% (38/1305)	8.51% (111/1305)	1.92% (25/1305)	2.15% (28/1305)	1.92% (25/1305)	1.15% (15/1305)	4.14% (54/1305)	50.04% (653/1305)	4.67% (61/1305)	2.30% (30/1305)	1305
Ipilimumab	Recovered	7.41% (4/54)	52.17% (60/115)	25.00% (2/8)	33.33% (2/6)	43.62% (41/94)	68.18% (15/22)	15.63% (10/64)	14.29% (2/14)	-	-	22.22% (2/9)	44.19% (19/43)	42.11% (8/19)	6.25% (1/16)	35.78% (166/464)
	Improved	44.44% (24/54)	32.17% (37/115)	12.50% (1/8)	33.33% (2/6)	31.91% (30/94)	9.09% (2/22)	42.19% (27/64)	35.71% (5/14)	-	-	44.44% (4/9)	39.53% (17/43)	52.63% (10/19)	25.00% (4/16)	35.13% (163/464)
	Unimproved	29.63% (16/54)	8.70% (10/115)	50.00% (4/8)	33.33% (2/6)	15.96% (15/94)	9.09% (2/22)	26.56% (17/64)	42.86% (6/14)	-	-	22.22% (2/9)	2.33% (1/43)	0.00% (0/19)	50.00% (8/16)	17.89% (83/464)
	With sequelae	5.56% (3/54)	0.00% (0/115)	0.00% (0/8)	0.00% (0/8)	0.00% (0/94)	0.00% (0/22)	3.13% (2/64)	0.00% (0/14)	-	-	0.00% (0/9)	4.65% (2/43)	0.00% (0/19)	12.50% (2/16)	1.94% (9/464)
	Death	0.00% (0/54)	0.00% (0/115)	0.00% (0/8)	0.00% (0/8)	7.45% (7/94)	0.00% (0/22)	0.00% (0/64)	0.00% (0/14)	-	-	0.00% (0/9)	2.33% (1/43)	0.00% (0/19)	0.00% (0/17)	1.72% (8/464)

TABLE 3 (Continued)

Outcome	Adrenal insufficiency [a]	Colitis [a]	Eye disease [a]	Hematological disorder [a]	Hepatitis [a]	Hyperthyroidism [a]	Hypopituitarism [a]	Hypothyroidism [a]	Myasthenia gravis [a]	Myocarditis [a]	Nephritis/renal dysfunction [a]	Pneumonitis [a]	Rash [a]	Type 1 diabetes mellitus [a]	Total [a]
Uncertain	12.96% (7/54)	6.96% (8/115)	12.50% (1/8)	0.00% (0/8)	1.06% (1/94)	13.64% (3/22)	12.50% (8/64)	7.14% (1/14)	-	-	11.11% (1/9)	6.98% (3/43)	5.26% (1/19)	6.25% (1/16)	7.54% (35/464)
Total	11.64% (54/464)	24.78% (115/464)	1.72% (8/464)	1.29% (6/464)	20.26% (94/464)	4.74% (22/464)	13.79% (64/464)	3.02% (14/464)	-	-	1.94% (9/464)	9.27% (43/464)	4.09% (19/464)	3.45% (16/464)	464

[a]The number in parentheses the sum of outcomes from the 14 categories.

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[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%.[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.[72] Immune-related pneumonitis was observed 8 to 14 weeks after the first dose of ipilimumab.[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% following treatment with ICIs.[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.[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.[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.[64,72] The *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.[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

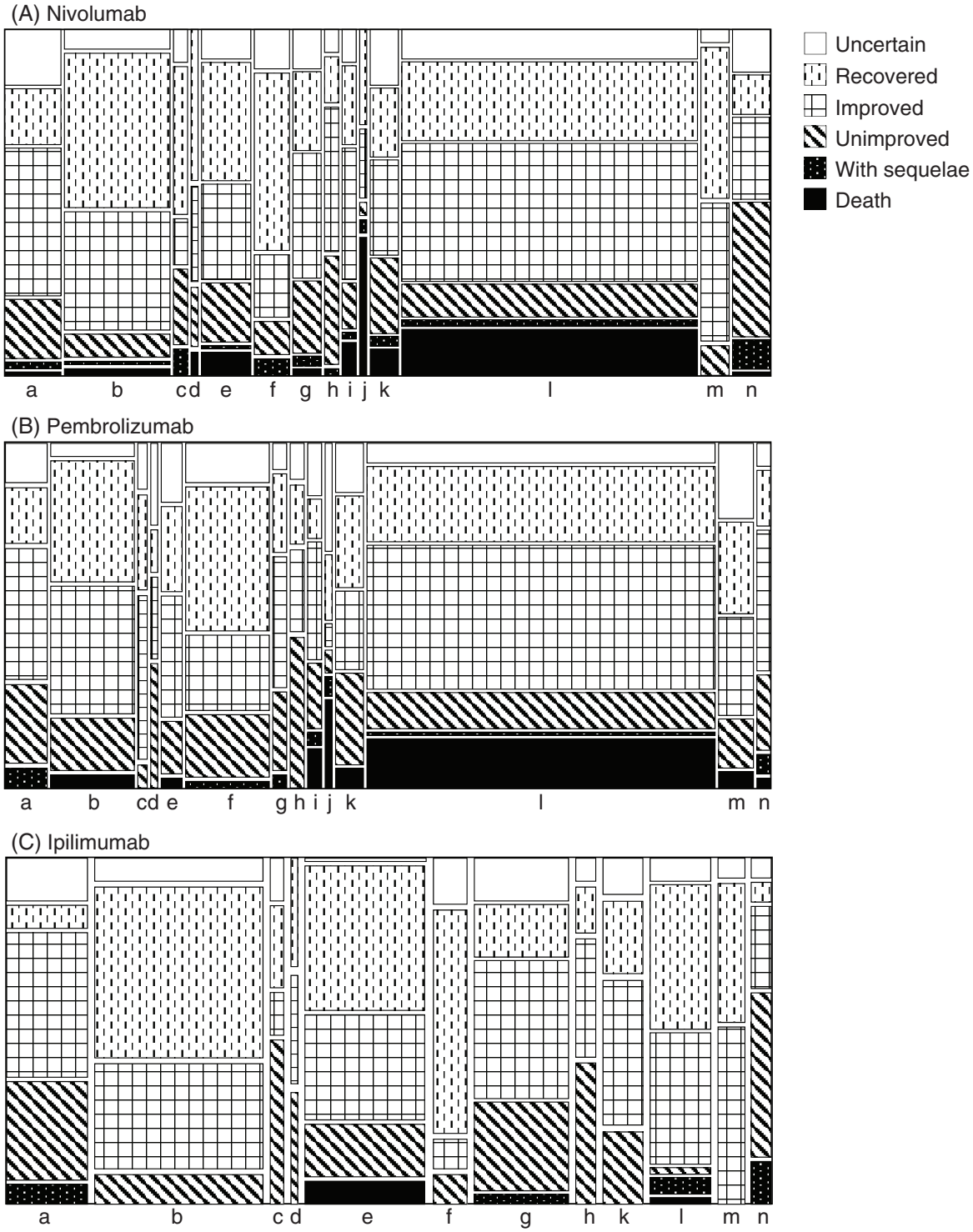

FIGURE 2 Mosaic plot of outcomes of immune-related adverse events (irAEs) by immune checkpoint inhibitors (ICIs). A mosaic plot is divided into rectangles where each vertical length represents the proportion of each level of the Y variable within each level of the X variable

organs that are typically affected by ICIs.[75] High incidences of hypothyroidism (17%), hypophysitis (13%), and hyperthyroidism (10%) of any grade have been reported with the co-therapy of nivolumab and ipilimumab.[76,77] Hypophysitis, which can result in hypopituitarism, is associated with hypothyroidism and adrenal insufficiency in most cases of ipilimumab therapy.[78] The precise mechanism by which ICIs

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.[23] 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 in this study. Multivariate regression analyses may be an approach to deal with confounders that affect the reliability of the results.[18,37,79,80] 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[81,82] to reduce bias by equating groups based on covariates or other appropriate parameters[83-85] 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.

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SUPPORTING INFORMATION

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

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