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Incidence of severe adverse events in cancer patients after treatment with immune-checkpoint inhibitors during the COVID- 19 pandemic

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Abstract

Immune-checkpoint inhibitors (ICIs) can cause inflammation and immune-related adverse events (irAEs). Although irAEs may be caused by dysregulation of cytokines, the impact of various COVID- 19-related factors on expression of ICI-related AEs remains unclear. Assessment of AEs following ICI administration during the COVID- 19 pandemic may provide valuable insights that enable optimization of patient selection, thereby maximizing the benefits of ICI therapy. The aim of this study was to investigate the actual occurrence of severe AEs after ICI administration during the COVID- 19 pandemic. The medical records of patients who received ICI at Saga University Hospital were examined retrospectively. The primary endpoint was the incidence of all AEs ≥ Grade 3 that occurred after ICI administration. The survey period, from Jan 2020 to Dec 2022, was divided into an earlier (Jan 2020–March 2021) and a later (April 2021–Dec 2022) period. AEs with a clear cause other than ICI were excluded from the analysis. A total of 527 patients were included in the analysis, with a median follow-up of 422 days. During the COVID- 19 pandemic, the incidence of AEs ≥ Grade 3 after ICI administration was 52.8%. The incidence of AEs ≥ Grade 3 AEs after ICI administration was significantly higher during the later period [23.4% (57/244) in the earlier period and 49.8% (236/474) in the later period; mixed effect model $p < 0.0001$, odds ratio, 3.37 (95% CI: 2.32–4.89)]. Overall survival was significantly worse in the group with AEs ≥ Grade 3 than in the group without AEs ≥ Grade 3 [HR (95% CI) = 0.48 (0.36–0.65), $p = 0.0001$]. During the COVID- 19 pandemic, it became clear that the incidence of severe AEs (including irAEs) increased after ICI administration, particularly during the later period of the disease. Various factors may be associated with occurrence of severe AEs after ICI administration, and long-term careful observation and prospective multicenter clinical studies are required.

Keywords Immune-checkpoint inhibitor, Adverse events, COVID- 19 pandemic

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Introduction

Recently, antibodies specific for cytotoxic T lymphocyte-associated antigen- 4 (CTLA- 4), programmed cell death-1 (PD- 1), and programmed cell death ligand- 1 (PD-L1) were introduced into clinical practice as cancer chemotherapy. Immune-checkpoint inhibitors (ICIs) trigger strong activation of anticancer immune responses; however, there is a risk that they also activate an immune response against autologous tissues. Injury to autologous tissues via this type of immune response is referred to as an immune-related adverse event (irAE), and it can occur in various organs of cancer patients due to an adverse reaction to cancer immunotherapy. The history of cancer treatment, encompassing cytotoxic agents, molecularly-targeted therapies, and combination regimens, has deepened our understanding of irAEs and continues to inform future therapeutic strategies [1].

Infection with coronavirus SARS-CoV2 (COVID- 19 disease) remains a threat worldwide, and cancer patients are at particularly high risk for severe COVID- 19-related illness, respiratory failure, and death [2–4]. Furthermore, the COVID- 19 pandemic limited access to medical care, resulting in delays in treatment and an increased risk of cancer progression and other complications [5, 6]. Such delays may have a decisive impact on prognosis, especially for patients who require time-critical treatments such as surgery and chemotherapy. Furthermore, the impact of the virus on immunomodulation may pose significant risks. Cancer patients are at particularly high risk of becoming infected with COVID- 19 due to their weakened immune systems; therefore, they were prioritized for COVID- 19 vaccination [6]. There was a concern that the COVID- 19 vaccine itself may cause cytokine release syndrome during ICI treatment; however, the effects of particular COVID- 19 variants on occurrence of AEs after ICI are not clear [7].

Although irAEs may be caused by dysregulation of cytokines, the impact of various COVID- 19-related factors on expression of ICI-related AEs remains unclear. The combination of COVID- 19 vaccination and ICIs in cancer patients has the potential to enhance immunological stimulation, possibly yielding reciprocal benefits; however, given the distinct immunomodulatory effects of both interventions, concerns have been raised regarding the potential for increased irAEs and other unintended interactions [8]. Assessment of AEs following ICI administration during the COVID- 19 pandemic may provide valuable insights that enable optimization of patient selection, thereby increasing the proportion of individuals who will benefit from ICI therapy [1].

The aim of the present study was to investigate the real incidence of severe AEs after ICI administration from January 1, 2020, to December 31, 2022, during the COVID- 19 pandemic. We attempted to collect data regarding all AEs that occurred in patients after ICI administration over time, and so did not adhere to the strict definition of irAEs.

Patients and methods

Patients

The present study involved a retrospective review of the medical records of 539 patients who received any ICIs at Saga University Hospital from January 2020 to December 2022. ICIs included ipilimumab, nivolumab, pembrolizumab, atezolizumab, durvalumab, and avelumab. The following patients who could not be evaluated for AEs after ICI administration were excluded: 11 patients who were transferred to another hospital after two or fewer ICI doses, and one patient who suddenly stopped attending the hospital (reason unknown) (Fig. 1).

To enable a longitudinal comparison, including data from non-COVID- 19 periods, an additional analysis was conducted on patients from 2019 who met the study inclusion criteria.

Data collection and outcome assessment

The primary endpoint was the incidence of all ≥Grade 3 AEs that occurred after ICI administration. The end of the follow-up period was December 31, 2023. Data extracted from the medical records of eligible patients included age, sex, diagnosis, cancer type, complications, treatment history, medication history, and AEs.

AEs were defined as any medical event occurring in patients who received an ICI, including unintended signs, symptoms, illnesses, or abnormal test results, regardless of causality. AEs with a clearly documented causal relationship unrelated to ICI in the medical record were excluded. The following events were excluded: AEs of

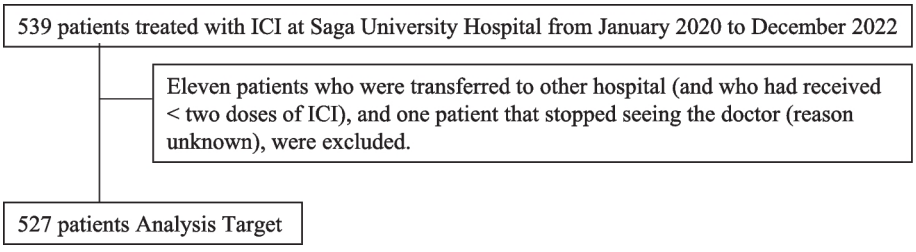

Fig. 1 Flow chart outlining the study. COVID-19 era (Jun.2020-Dec.2022)

non-ICI drugs, including hematologic toxicity and other complications from antineoplastic agents administered after the ICI (when explicitly documented in the medical record); complications definitively associated with the underlying disease, such as tumor progression and post-surgical complications; events with an explicitly documented alternative cause in the medical record; and non-emergency hospital admissions, including those for scheduled surgery, radiotherapy, or palliative care for symptoms with a clear etiology. Collected AEs were categorized based on their clinical significance and impact according to the Common Terminology Criteria for Adverse Events (CTCAE) and guidelines for irAEs [9–11]. The affected organ systems included the neuromuscular, cardiac and vascular, respiratory, gastrointestinal, hepatobiliary, renal, skin, endocrine, blood and lymphatic system, and others. The severity of AEs was assessed according to the CTCAE version 5.0, and guidelines for irAE [9–11]. The definitions, exclusion criteria, categorization, and assessment criteria for AEs are presented in Supplementary Table 1.

The present study was approved by the Clinical Research Ethics Review Committee of Saga University Hospital (Saga University Clinical Research Review Board; Approval No.: 2023-12-02), and was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki. The need for informed consent was waived owing to the retrospective nature of the study. The official website of the institution was used to allow patients to opt out from participation.

Statistical methods

Kaplan–Meier analysis was used to estimate the cumulative incidence of ≥ Grade 3 AEs after ICI administration from January 2020 to December 2022. In Japan, the number of COVID- 19 cases peaked in 2022, and the COVID- 19 vaccination program was initiated in April 2021. Therefore, the incidence of all AEs ≥ Grade 3 that occurred after ICI administration were analyzed separately during the earlier (from January 1, 2020 to March 31, 2021) and later (from April 1, 2021 to December 31, 2022) periods. A mixed-effects model was used for group comparisons when two groups of nonidentical patients and two groups of identical patients were mixed. The $\chi 2$ test (Fisher's exact test for expected frequencies of 5 or less) was used to assess differences in the incidence of ≥ Grade 3 AEs between the earlier and later periods; this test was used to compare data from two groups that did not contain the same patients. The McNemar test was used to compare two groups that did contain the same patients. Survival probability was estimated using the Kaplan–Meier method, and hazard ratios (HR) with 95% confidence intervals (CI) were estimated using a Cox proportional hazards model. Statistical analysis was performed using JMP (17.2), and a P value <0.05 was deemed significant.

Results

Patient characteristics

Overall, 527 patients were included in the analysis, with a median follow-up of 422 days (1–1455 days). The median age was 70 years (17–90), and 72.3% of the cohort were male. The most common primary tumor was respiratory, followed by head and neck, and gastrointestinal tract. The background of the eligible patients, including their ICI regimens, is shown in Table 1.

Table 1 Patient characteristics

Characteristics ($N=527$)	Value No. (%)
Sex	
Male/Female	381 (72.3)/146 (27.7)
Age at start of first ICI cycle (in years)	70 [17-90]
Primary tumor localization	
Respiratory tract/Head and neck/Digestive tract	214/88/70
Urinary tract/Hepatocellular, Biliary Tract/Female genital organs	67/35/24
Skin/Breast/Others	15/11/3
Comorbidities* (prior to the initiation of ICI therapy)	315 (59.8)
Immune-related comorbidities** (prior to initiation of ICI therapy)	62 (11.8)
ICI treatment line	
First or adjuvant	291 (55.2)
Second	151 (28.7)
Third or later	85 (16.2)
ICI agent	
Anti-PD-1 antibody (nivolumab/pembrolizumab)	216/204
Anti-PD-L1 antibody (atezolizumab/durvalumab/avelumab)	106/15/6
Anti-CTLA-4 antibody (ipilimumab)	56
ICI Combination regimen	
Anti-PD-(L)1 antibody Monotherapy	302
Anti-PD-(L)1 antibody and Chemotherapy	192
Anti-CTLA-4 antibody and Anti-PD-(L)1 antibody	56
Anti-CTLA-4 antibody and Anti-PD-(L)1 antibody and Chemotherapy	23
ICI Combination regimen; Chemotherapy	
Cytotoxic Drugs; platinum/taxane/5-FU pemetrexed/etoposide	137/37/30 46/30
Antiangiogenic Agents; bevacizumab/lenvatinib/axitinib	44/14/2

Comorbidities*; Diabetes mellitus, hypertension, ischemic heart disease (myocardial infarction, angina, myocardial ischemia), dyslipidemia (hypercholesterolemia), and chronic kidney disease

Immune-related comorbidities**; Rheumatoid arthritis, Graves' disease, hypothyroidism, Hashimoto's disease, Buerger's disease, Sjögren's syndrome, myasthenia gravis

The study design, in which the COVID- 19 pandemic period was divided into an earlier (from January 1, 2020 to March 31, 2021) and a later (from April 1, 2021 to December 31, 2022) period, is shown in Supplement Fig. 1. Of the total 527 patients included in the analysis, the earlier period group (244 patients) included 53 patients who could not be followed in the later period (after April 2021) due to death or transfer by March 31, 2021, and 191 patients who could be followed in the later period (121 of whom continued receiving ICI during the later period). The later period group (474 patients) included the 191 patients who were followed during both the earlier and the later periods, as well 283 patients who began taking ICI during the later period.

Incidence AEs ≥ Grade 3 after ICI administration

During the entire study period (from Jan 2020 to Dec 2022), 52.8% (278/527) of patients experienced at least one AE of ≥ Grade 3 after ICI administration. The incidence of AEs ≥ Grade 3 in the combined with ICI anti-CTLA- 4 antibody group was significantly higher than that in the uncombined anti-CTLA- 4 antibody group [66.1% (37/56) *vs.* 51.2% (241/471), respectively; χ^2 test $p = 0.0347$].

The trend in the incidence and number of ≥ Grade 3 AEs relative to the number of patients treated with ICI per month from January 2020 until December 2022 is shown in Fig. 2. Various differences were observed regarding the timing and number of AEs ≥ Grade 3 after administration of ICIs. For example, there were cases in which AEs ≥ Grade 3 occurred not only during the period of ICI administration, but also during several months after the end of ICI administration, as well as single patients in which multiple types and numbers of AEs ≥ Grade 3 occurred. AEs ≥ Grade 3after ICI administration included neuromuscular disorders (meningitis, myositis, seizures, neuropathy, weakness), cardiac and vascular disorders (stroke, heart failure, myocardial infarction, myocarditis, thrombosis), respiratory disorders (pneumonia, pleural effusion, respiratory distress), gastrointestinal disorders (gastrointestinal perforation, stomach/enteritis), hepatobiliary disorders, renal disorders, skin disorders, endocrine disorders (pituitary dysfunction, adrenocortical dysfunction, thyroid dysfunction, type 1 sugar diabetes), blood and lymphatic system disorders (thrombotic thrombocytopenic purpura, autoimmune anemia, lymphomatosis), and "other" disorders (i.e., various symptoms requiring hospitalization and treatment, including fatigue, or death within 1 month of ICI administration). The cumulative incidence curve for first-time AEs ≥ Grade 3 after administration of ICI from January 2020 until December 2022 is shown in Fig. 3. Overall, first-time AEs ≥ Grade 3 occurred in 265 patients from a population of 472 (excluding 55 patients who received an ICI prior to January 1, 2020, for whom the onset date of their first AE was unknown [527–55 = 472]). All AEs are shown in Fig. 3A, and the different AE categories are shown in Fig. 3B. Both panels show events occurring from January 2020 through December 2022, with a potential increase in incidence observed during the later period (after April 2021). Overall survival (OS) was significantly worse in the group with AEs ≥ Grade 3 than in the group without AEs ≥ Grade 3 [HR (95% CI) = 0.48 (0.36–0.65), $p = 0.0001$]; Fig. 4).

The incidence of AEs ≥ Grade 3 after ICI administration increased significantly during the later period; 23.4% (57/244) in the earlier period *vs.* 49.8% (236/474) in the later period [mixed-effects model, $p < 0.0001$; odds ratio, 3.37 (95% CI: 2.32–4.89); Fig. 5). Furthermore, analysis

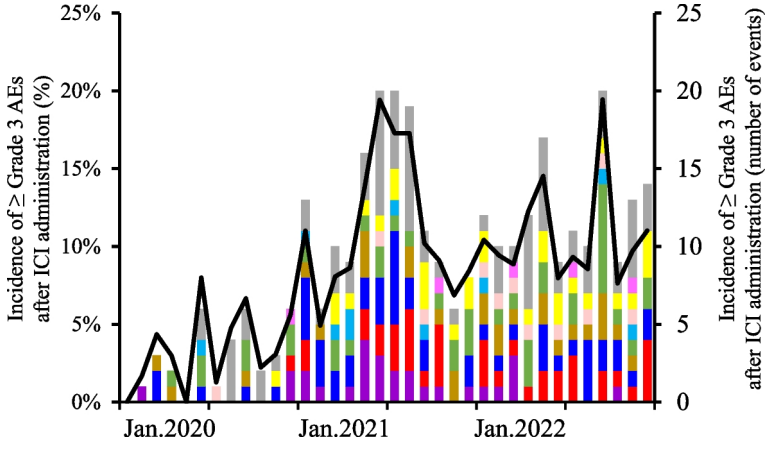

Fig. 2 Occurrence of AEs ≥ Grade 3 after administration of ICI and changes in incidence of AEs ≥ Grade 3 over time after administration. In Japan, the number of COVID- 19 cases peaked in 2022, and COVID- 19 vaccination was initiated in April 2021. The history of ICI approvals in Japan is shown in Supplementary Table 2. Monthly percentage of patients with AEs ≥ Grade 3 after treatment with ICI, and the number of AEs in each category: 1. Blue: respiratory disorders. 2. Green: hepatobiliary disorders. 3. Red: cardiac and vascular disorders. 4. Brown: gastrointestinal disorders. 5. Yellow: endocrine disorders. 6. Purple: neuromuscular disorders. 7. Beige: skin disorders. 8. Pink: blood and lymphatic system disorders. 9. Light blue: renal disorders. 10. Gray: other disorders

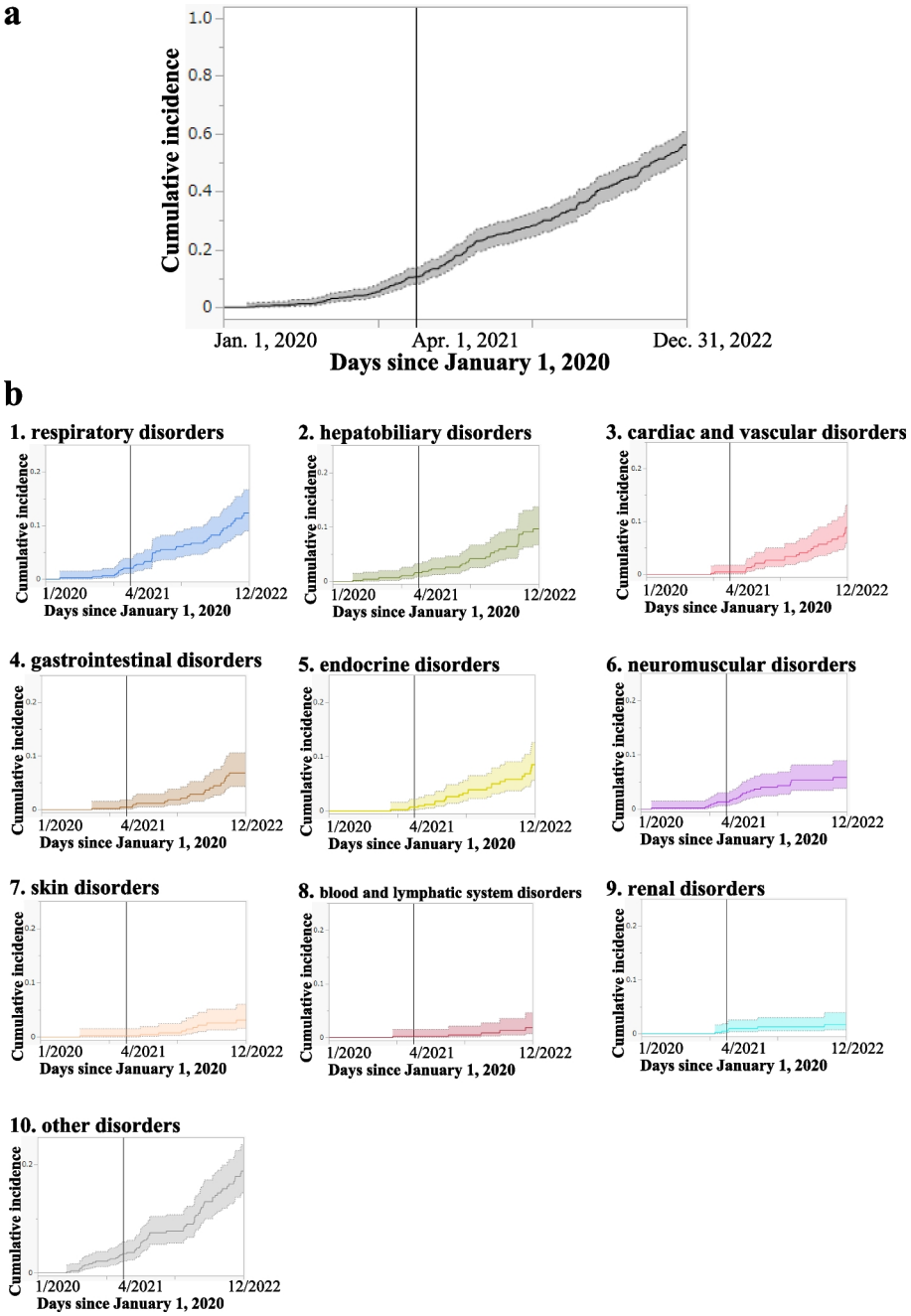

Fig. 3 Cumulative incidence of first-time AEs ≥ Grade 3 after January 2020. **a** All AEs ≥ Grade 3, **b** Category of AEs ≥ Grade 3. The figure shows the cumulative incidence of the first-time AEs ≥ Grade 3 occurring after ICI administration during a 3-year period from January 1, 2020 to December 31, 2022. Overall, first-time AEs ≥ Grade 3 occurred in 265 patients from a population of 472 (excluding 55 patients who received an ICI prior to January 1, 2020, and for whom the onset date of their first AE was unknown [527–55 = 472). The vertical line at 456 days corresponds to April 1, 2021. The shaded area shows the 95% confidence interval

limited to the 191 patients who were followed up both before and after April 2021 showed that the incidence rate of AEs ≥ Grade 3 after ICI administration increased significantly during the later period (15.2% (29/191) in the earlier period *vs.* 42.4% (81/191) in the later period; McNemar test, $p < 0.0001$). In the same 191 patients, combined use of anti-CTLA- 4 antibody during the later period also increased significantly. Similarly, in the different patient groups, the incidence of AEs ≥ Grade 3 after ICI administration increased significantly during the later period, regardless of concomitant use of an anti-CTLA- 4 antibody (Supplementary Table 1).

For longitudinal comparison, the background of the eligible patients, including their ICI regimens in 2019 (the

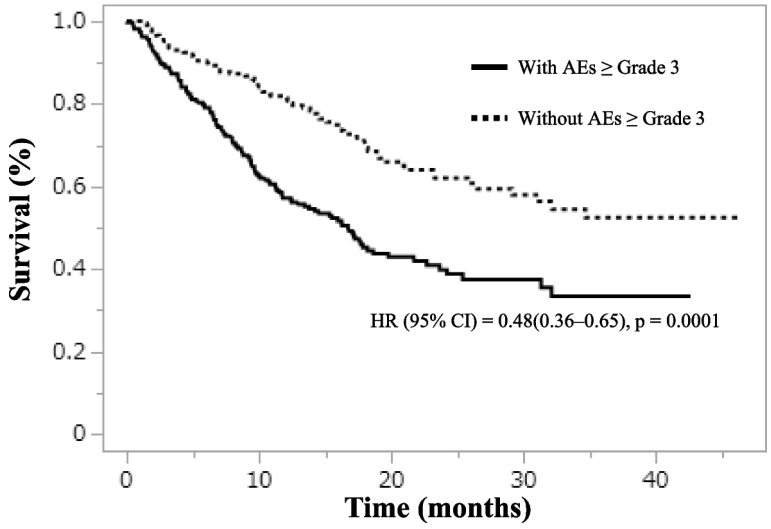

Fig. 4 Influence of AE onset on patient prognosis. Kaplan–Meier curve analysis depicting overall survival (OS) of patients with or without AEs ≥ Grade 3 after ICI administration. All patients with AEs ≥ Grade 3 ——— and without AEs ≥ Grade 3 .....

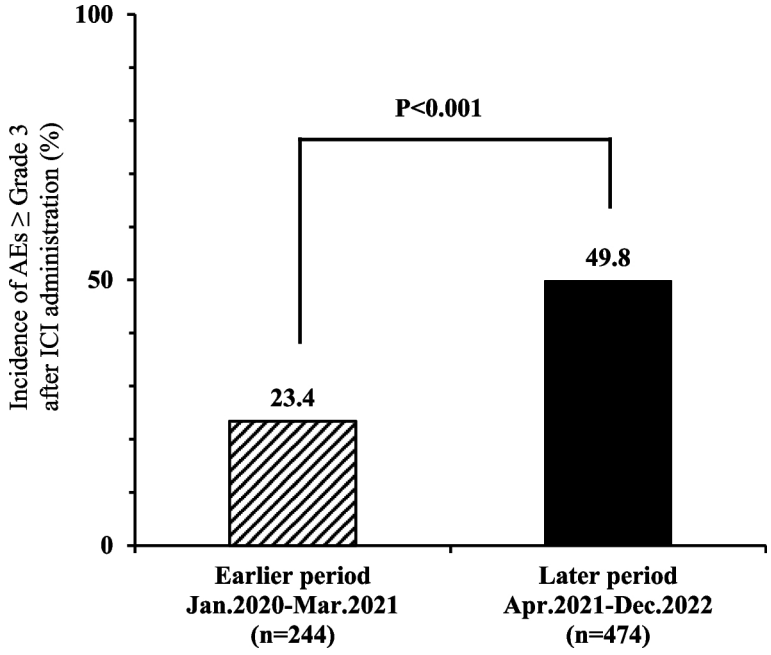

Fig. 5 Incidence of AEs ≥ Grade 3 after ICI administration during the earlier and later periods. (Mixed-effects model). In all patients during the earlier period ▨ and later period ■. In Japan, the number of COVID- 19 cases peaked in 2022, and COVID- 19 vaccination was initiated in April 2021. The history of ICI approvals in Japan is shown in Supplementary Table 2

period prior to COVID- 19), is presented in Supplementary Table 3. In 2019, the incidence of AEs ≥ Grade 3 after ICI administration was 31.0% (44/142) across all regimens, and 50.0% (2/4) for anti-CTLA- 4 antibody combination therapy (Supplementary Fig. 2). The number of AE reports following ICI administration, as well as the proportion of ICI-related reports relative to all reported drugs in the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS), from January 2019 to March 2022 are shown in Supplementary Fig. 3. The number of AE reports in which ICIs were identified as the primary suspected (PS) or secondary suspected (SS) agents demonstrated an increasing trend, starting from the third quarter of 2021. Additionally, the proportion of ICI-related reports relative to all reported drugs showed a slight increase during the fourth quarter of 2021.

Discussion

In the present study, the incidence of AEs ≥ Grade 3 during the entire period of ICI administration during the COVID- 19 pandemic period was 52.8%. Although the

methods used to evaluate AEs vary between studies, the data suggest that the incidence of serious AEs after ICI administration range from 10–75%, with the incidence of serious irAEs ranging from 10–30% [12–16]. Although there are various guidelines for managing irAEs [9, 11, 17], these AEs may be latent in conditions that are difficult to define and classify, such as fatigue and neuropathy [18]; therefore, careful long-term observation and evaluation of all AEs after ICI administration may help to prevent and/or treat serious irAEs. In the present study, we found that patients with Grade 3 or higher irAEs had a significantly worse prognosis than those without irAEs. Meanwhile, a meta-analysis of randomized controlled trials evaluating the association between irAE incidence and OS reported no clear correlation overall; however, in the melanoma trial subset, there was a negative association between treatment effects and gastrointestinal Grade 3–4 irAEs, and treatment effects and OS [19]. Conversely, other studies suggest that irAEs may contribute to improved OS, even in cases with severe irAEs, without compromising survival benefits [14]. The relationship between irAEs and OS likely varies depending on the evaluation method and patient-specific factors; therefore, careful long-term observations and further investigations are warranted to clarify this complex interplay.

The incidence of AEs ≥ Grade 3 after ICI administration increased throughout the study period, but especially after April 2021 (Figs. 2, 3, and 5). Furthermore, the comparison limited to the identical patients and different patients who could be followed before and after April 2021 revealed that the incidence of AEs ≥ Grade 3 after ICI administration was significantly higher during the later period (after April 2021) (Supplementary Table 4). Even within FAERS, the number of AE reports following ICI administration from January 2019 to March 2022 showed an upward trend, starting from the second quarter of 2021 (Supplementary Fig. 3). A report analyzing irAEs listed in the VigiBase, an international pharmacovigilance database containing information reported from 2008 to January 2023, noted a steep increase in myotoxicity (i.e., myocarditis, myositis, myasthenia gravis) and pancreatico-hepatic irAEs from 2021–2022, although there was a general decline after 2020 [20]. Furthermore, a recent study suggests an increase in the prevalence of ICI-mediated muscle damage, including myositis and myocarditis, in the COVID- 19 era [21]. With respect to hepatitis and dysautonomia, drug safety surveillance analyses have also been conducted using FAERS [22, 23], which reported an annual increase in ICI-induced thrombocytopenia from 2012–2022 [24]. These studies suggested that multiple risk factors and clinical peculiarities related to specific irAEs can be identified as "signals" that may guide clinical practice and future research [20].

In Japan, the combination of ICI and chemotherapy was approved in December 2018, and is now indicated for use in clinical practice in combination with cytotoxic drugs such as platinum-based drugs, and molecular targeted drugs such as bevacizumab (Supplementary Table 2). The background characteristics of patients receiving ICIs in 2019 suggest substantial differences in application of combination regimens involving anti-PD-(L)1 and anti-CTLA- 4 antibodies, as well as chemotherapy, as well as in differences in treatment lines (Supplementary Table 3). For example, a higher proportion of patients in the 2019 cohort received ICIs as the 3rd line or later drug when compared with the 2020–2022 cohort (32.4% in 2019 *vs.* 16.2% in 2020–2022), suggesting that a higher proportion of patients in the 2019 cohort had terminal cancer. By contrast, in the 2020–2022 cohort, the use of anti-CTLA- 4 antibodies, as well as the proportion of patients receiving combination therapy (ICI plus chemotherapy), increased. These factors may have influenced the incidence rate of AEs. Therefore, careful consideration of patient background is essential when interpreting the incidence of AEs following ICI administration. In addition, January 2020 marked the start of the COVID-19 pandemic, and a COVID- 19 vaccination campaign was launched in April 2021, with approximately 80% of the population receiving the vaccine. The retrospective nature of the study means that it was not possible to accurately investigate COVID- 19 infection (including subclinical infections) and COVID- 19 vaccination status in the patients enrolled in the present study.

Around April 2021, various ICI regimens began to be used in clinical practice in Japan. Anti-CTLA- 4 therapy enhances tumor immune responses by inhibiting the immune-checkpoint molecule CTLA- 4 on T cells, thereby promoting T-cell activation and proliferation. By contrast, anti-PD-(L)1 therapy restores T-cell anti-tumor activity by blocking the PD- 1/PD-L1 pathway, which is mediated by tumor cells and immunosuppressive cells. Combined use of anti-CTLA- 4 and anti-PD-(L)1 agents increases the risk of early onset and severe irAEs due to multilayered activation of the immune response. In particular, the incidence of skin disorders, gastrointestinal symptoms (e.g., colitis) and endocrine disorders (e.g., pituitary inflammation) increases significantly [13, 25]. Notably, Grade 3 or higher irAEs are more frequent in those receiving CTLA- 4 monoclonal antibodies (mAbs) than in those receiving PD- 1 inhibitors (31% *vs.* 10%, respectively), highlighting the need for careful monitoring and management when utilizing these therapies in combination [26]. One of the reasons for the increased incidence of AEs after ICI administration may be the concomitant use of anti-CTLA- 4 antibodies; however, the incidence of ≥ Grade 3 AEs after ICI administration

increased markedly around April 2021, regardless of the concomitant use of anti-CTLA- 4 (Supplementary Table 4). These results suggest that other factors, which were not identifiable in this study, might be contributing to the increase in AEs ≥ Grade 3 after ICI administration.

It is likely that subclinical infection of cancer patients with COVID- 19 caused complications [27–29]. COVID-19 predisposes to acute respiratory distress syndrome, and the risk may be higher in cancer patients. Cancer patients are at increased risk for thrombosis, which can also be exacerbated by COVID- 19, as well as organ damage due to overproduction of cytokines in response to infection. As mentioned earlier, the COVID- 19 pandemic in Japan began in 2020, and COVID- 19 vaccinations became available in April 2021. Cancer patients are at increased risk of complications from SARS-CoV- 2 infection [4, 6, 30], and so vaccination is recommended; however, data regarding the safety of COVID- 19 vaccines in cancer patients receiving chemotherapy or immunotherapy are limited [31]. Studies that have examined the safety of cancer patients who received ICI after COVID- 19 vaccination suggest that the vaccine is safe "in the short term" [32–37]; however, case reports suggest that severe irAEs such as cytokine release syndrome, acute myocarditis, psoriasis, hepatitis, and diabetic ketoacidosis have occurred immediately after administration of the COVID- 19 vaccine to cancer patients who had received ICIs [7, 38–44]. Furthermore, anti-CTLA-4-deficient patients have suffered mild COVID- 19 infections and experienced AEs after receiving a COVID- 19 vaccine [45]. These findings suggest that careful long-term observation of the safety of COVID- 19 vaccines in cancer patients treated with ICI should continue.

The present study has several limitations. Although we tried to minimize recall bias and inconsistencies in medical record documentation, and AEs were evaluated using the CTCAE, and irAEs were determined in accordance with ASCO and ESMO guidelines, the retrospective nature of the study introduces inherent limitations that affect the reliability of AEs classification, and the completeness of the data. Additionally, distinguishing AEs caused by ICIs from those related to cancer progression, other treatments, or underlying disease remains a significant challenge. Importantly, in the context of this study, factors such as COVID- 19 vaccination and subclinical infections were not evaluated comprehensively. Therefore, while an increase in AEs was observed during the COVID- 19 era, it cannot be concluded definitively that this rise is attributable to COVID- 19 infection or vaccination. Additionally, we could not fully exclude the influence of other confounding factors such as healthcare delays, changes in treatment policy, or pandemic-related psychological stress. This study only demonstrates the fact that AEs increased at a single center in Japan during a specific period; the potential impact of regional healthcare system differences during the pandemic were not evaluated. A lack of prospective data collection undermines the study's conclusions about long-term trends in AE incidence and causative factors. Predictive biomarkers for irAEs, such as cytokine profiles and T-cell activation markers, have been explored to optimize ICI therapy [46, 47]. To reduce the risk of irAEs, regular measurement of biomarkers and monitoring of AEs through X-rays and ECG testing is required. In addition, to ensure prompt and efficient collaboration in the event of irAEs, it is crucial to develop treatment algorithms in collaboration with other specialists. To mitigate the risk of AEs during a pandemic, enhanced monitoring protocols, including more frequent follow-up visits, proactive screening for infections, and early detection of irAEs, could potentially improve patient outcomes. Additionally, considering patient-specific factors and pandemic-related constraints, adjusting ICI regimens (e.g., modifying dosing intervals or selecting ICI combinations with a lower risk profile for AEs) may be beneficial. Future research should evaluate the effectiveness of these strategies in reducing severe AEs while maintaining treatment efficacy. Future prospective multicenter clinical studies that collect accurate data on cancer progression, comorbidities (e.g., immune-related comorbidities), organ function, biomarkers, immune function, infection, concomitant medications, and vaccination status are desirable.

In conclusion, the real-world data reported herein show that long-term severe AEs occur at a high frequency after ICI administration. In addition, the number of severe AEs after ICI administration increased after April 2021. Various factors may be associated with the occurrence of AEs ≥ Grade 3 after ICI administration, and so long-term careful observation and prospective multicenter clinical studies are required in the future.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12865-025-00711-w.

Supplementary Material 1.

Supplementary Material 2.

Acknowledgements
Not applicable.

Authors' contributions
Sakiko K, HK, Shinya K and CS made substantial contributions to study conception, design, analysis, and data interpretation. CN, NA, KH, KS, RS, TF, MY, YS, HN, ME, MN, HT, KA, MY, KS and YY enrolled patients and collected data. AK performed statistical analysis. Sakiko K and HK wrote the paper. Shinya K and CS critically reviewed the drafts, and all authors approved the final version.

Funding
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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The present study was approved by the Clinical Research Ethics Review Committee of Saga University Hospital (Saga University Clinical Research Review Board; Approval No.: 2023-12-02), and conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki. The need for informed consent was waived owing to the retrospective nature of the study. The official website of our institution was used to allow patients to opt out from participation.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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