Psychiatric disorders associated with immune checkpoint inhibitors: a pharmacovigilance analysis of the FDA Adverse Event Reporting System (FAERS) database

Chaozheng Zhou,[a,g] Shengkun Peng,[b,g] Anqi Lin,[a,g] Aimin Jiang,[c,g] Yuanxi Peng,[a,g] Tianqi Gu,[a] Zaoqu Liu,[d] Quan Cheng,[e,f,***] Jian Zhang,[a,**] and Peng Luo[a,*]

[a]Department of Oncology, Zhujiang Hospital, Southern Medical University, Guangzhou, China
[b]Department of Radiology, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, 610072, Sichuan Province, China
[c]Department of Urology, Changhai Hospital, Naval Medical University (Second Military Medical University), Shanghai, China
[d]Department of Interventional Radiology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China
[e]Department of Neurosurgery, Xiangya Hospital, Central South University, Changsha, Hunan, China
[f]National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha, China

eClinicalMedicine
2023;59: 101967
Published Online xxx
https://doi.org/10.1016/j.eclinm.2023.101967

Summary

Background With the increasing use of immune checkpoint inhibitors (ICIs) for tumour immunotherapy, the immune-related adverse events (irAEs) caused by their collateral effect on the immune system pose a key challenge for the clinical application of ICIs. Psychiatric adverse events are a class of adverse events associated with ICIs that are realistically observed in the real world. We aim to provide a comprehensive study and summary of psychiatric adverse events associated with ICIs.

Methods We obtained ICI adverse reaction reports during January 2012–December 2021 from the FDA Adverse Event Reporting System (FAERS) database. ICI reports underwent screening to minimize the influence of other adverse reactions, concomitant medications, and indications for medication use that may also contribute to psychiatric disorders. Disproportionality analysis was performed to find psychiatric adverse events associated with ICIs by comparing ICIs with the full FAERS database using the reporting odds ratio (ROR). Influencing factors were explored based on univariate logistic regression analysis. Finally, the Cancer Genome Atlas (TCGA) pan-cancer transcriptome data were combined to explore the potential biological mechanisms associated with ICI-related pAEs.

Findings Reports of psychiatric adverse events accounted for 2.71% of the overall ICI adverse event reports in the FAERS database. Five categories of psychiatric adverse events were defined as ICI-related psychiatric adverse events (pAEs). The median age of reports with ICI-related pAEs was 70 (interquartile range [IQR] 24–95), with 21.54% of reports having a fatal outcome. Cases with indications for lung cancer, skin cancer and kidney site cancer accounted for the majority. The odds of ICI-related pAEs increased in older patients (65–74: OR = 1.44 [1.22–1.70], $P < 0.0001$: ≥75: OR = 1.84 [1.54–2.20], $P < 0.0001$). The occurrence of ICI-related pAEs may be related to NOTCH signalling and dysregulation of synapse-associated pathways.

Interpretation This study investigated psychiatric adverse events highly associated with ICI treatment, their influencing factors and potential biological mechanisms, which provides a reliable basis for further in-depth study of ICI-related pAEs. However, as an exploratory study, our findings need to be further confirmed in a large-scale prospective study.

Funding This work was supported by the Natural Science Foundation of Guangdong Province (2018A030313846 and 2021A1515012593), the Science and Technology Planning Project of Guangdong Province (2019A030317020) and the National Natural Science Foundation of China (81802257, 81871859, 81772457, 82172750 and 82172811). Guangdong Basic and Applied Basic Research Foundation (Guangdong - Guangzhou Joint Fouds) (2022A1515111212). This work was supported by Key Research and Development Projects of Sichuan Science and Technology (2022YFS0221,

*Corresponding author. Department of Oncology, Zhujiang Hospital, Southern Medical University, 253 Industrial Avenue, Guangzhou, 510282, Guangdong, China.
**Corresponding author. Department of Oncology, Zhujiang Hospital, Southern Medical University, 253 Industrial Avenue, Guangzhou, 510282, Guangdong, China.
***Corresponding author. Department of Neurosurgery, Xiangya Hospital, Central South University, Changsha, Hunan, China.
E-mail addresses: luopeng@smu.edu.cn (P. Luo), zhangjian@i.smu.edu.cn (J. Zhang), chengquan@csu.edu.cn (Q. Cheng).
[g]These authors equally contributed.

2022YFS0074, 2022YFS0156 and 2022YFS0378). Sichuan Provincial People's Hospital Hospital Young Talent Fund (2021QN08).

Keywords: Immune checkpoint inhibitors; Psychiatric; Immunotherapy; Immune-related adverse events; FAERS

Research in context

Evidence before this study

Neuropsychiatric adverse reactions are one of the categories of adverse events associated with ICIs that have a small incidence and varying symptom severity. While possible neurological adverse events associated with ICIs have been well summarized, study and summary of psychiatric adverse events associated with ICIs is still lacking. Psychiatric adverse events associated with ICIs are a real-world occurrence and reported sporadically.

Added value of this study

Our pharmacovigilance analysis based on ICIs data in the FAERS database comprehensively investigated and identified five categories of psychiatric adverse events highly associated with ICIs.

Implications of all the available evidence

Our study is the first to investigate ICI-related psychiatric adverse events. Results of this study will provide a better basis for understanding possible psychiatric adverse events and help clinicians pay attention to them and intervene early. Large population-based prospective studies are needed for further study of ICI-related psychiatric adverse events.

Introduction

Immune checkpoint inhibitors (ICIs) have become an extremely important part of cancer treatment. It was reported in 2018 that for 44% of oncology patients, ICIs were a suitable treatment.[1] To date, ICIs targeting cytotoxic T lymphocyte-associated protein 4 (CTLA-4) (ipilimumab and tremelimumab), programmed cell death 1 (PD-1) (nivolumab, pembrolizumab, and cemiplimab), and programmed cell death ligand 1 (PD-L1) (atezolizumab, avelumab, and durvalumab) have been approved by the U.S. Food and Drug Administration (FDA) for use in humans.[2] ICIs have been widely used in the treatment of various malignancies, such as ipilimumab for late-stage melanoma, pembrolizumab approved by the FDA as a first-line agent for non-small cell lung cancer (NSCLC), and atezolizumab approved for bladder cancer.[3] While ICIs are widely used in cancer treatment, their collateral effect on the immune system, namely, various immune-related adverse events (irAEs), pose a great challenge to the clinical application of ICIs.[4,5] The occurrence of irAEs may be related to overactivation of the immune system and disturbance of immune homeostasis in patients after ICI treatments.[5] The most common complications caused by ICIs include skin, gastrointestinal, and endocrine toxicities. However, the rarer complications include neurologic, renal, ocular, and cardiovascular toxicities.[6]

The number of pharmacovigilance studies reporting on ICI-related irAEs are increasing in the face of their complexity, varying severity, and various influencing factors. These studies on the adverse effects of ICIs can help to identify potential clinical adverse effects associated with ICIs, draw clinical attention to them, and bring additional benefits to patients treated with ICIs. In patients with cancer and pre-existing autoimmune disease, studies have suggested that their irAEs occur with high frequency but can be managed without discontinuing ICIs.[7,8] In-depth study of the impact of ICI treatment strategies, various clinical characteristics of patients, and interactions between different drugs on ICI-related irAEs will facilitate appropriate, targeted, and safe treatment strategies for different patients while expanding the applications of tumour immunotherapy. Baldini et al. found that elderly oncology patients were more likely to develop serious and multiple irAEs after anti-PD-1 (L1) treatment than younger patients, suggesting a more comprehensive evaluation before and after ICI administration for elderly patients.[9,10]

Neuropsychiatric adverse reactions are one of the categories of adverse reactions associated with ICIs that have a small incidence and varying symptom severity. Serious neuropsychiatric adverse reactions have also been reported in some clinical trials and post marketing studies. The common neurotoxicities from ICIs can be divided into those found in the central nervous system and in the peripheral nervous system, and studies have been performed to systematically summarize the possible neurological adverse events associated with ICIs.[11–14] For example, a study by L. Spain et al. found that the neurotoxicity of ICIs (such as motor peripheral neuropathy and aseptic meningitis) is common and may occur in patients receiving a combination of ipilimumab and nivolumab, requiring more clinical attention for such patients.[15] However, a comprehensive study and

summary of psychiatric adverse events associated with ICIs is still lacking. The occurrence of psychiatric adverse events in cancer patients treated with ICIs remains unknown and has rarely been investigated in preapproved pivotal trials. However, psychiatric adverse events associated with ICIs are a real-world occurrence. For example, Larkin et al. reported six cases of patients with melanoma treated with nivolumab or nivolumab/ipilimumab combination therapy who presented with psychiatric abnormalities such as altered mental state, confusion, aphasia, and agitation.[16] After pembrolizumab treatment, nearly 1% of 173 patients with advanced melanoma resistant to ipilimumab developed a confusional state and peripheral sensory neuropathy.[17] The actual clinical and epidemiological impact of these relatively rare adverse events (e.g., psychiatric disorders) can be better assessed in real world data (e.g., the FAERS database) than in registration trials.[18]

In summary, given the potential clinical benefit, a comprehensive analysis is needed to explore the relationship between ICIs and psychiatric adverse events and the factors influencing them. Based on the ICI reports in the FAERS database from 2012 to 2021, psychiatric adverse events were counted, and disproportionality analysis was conducted to identify psychiatric adverse reactions and explore possible influencing factors and potential biological mechanisms that are highly related to ICIs. This study aims to provide an in-depth and comprehensive understanding of psychiatric adverse events associated with ICIs and to provide a useful reference for clinical practice.

Methods

Data source

We conducted a pharmacovigilance study on psychiatric adverse events associated with ICIs based on the FAERS database, a publicly available database of safety reports submitted by patients, healthcare professionals, and pharmaceutical companies.[19] The protocol of this study was developed in February 11, 2022 and was approved in February 20, 2022 (Supplementary File). ICIs, including anti-PD-1 agents (nivolumab, pembrolizumab, and cemiplimab), anti-PD-L1 agents (atezolizumab, avelumab, and durvalumab), and anti-CTLA-4 agents (ipilimumab and tremelimumab), were used as keywords to obtain report data of ICIs from the FAERS Publish Dashboard for the decade 2012–2021 (January 1, 2012–December 31, 2021). Only cases with suspected use of ICIs were included. In addition, reported adverse reactions in the FAERS database are coded based on preferred term (PT) codes from the Medical Dictionary for Regulatory Activities (MedDRA), which is logically structured to contain five levels. PTs are unique descriptors of a single medical concept, such as signs and symptoms and disease diagnosis. There are also "high-level terms" (HLTs) and "high-level group terms" (HLGTs) in its hierarchy. Finally, HLGTs are grouped into "systemic organ classes" (SOCs), which are grouped by aetiology, site of presentation, or purpose. Different PTs are grouped into different SOCs, but there is a primary SOC, a feature called multiaxiality. According to system organ class (SOC) = "psychiatric disorders" and primary SOC = "Yes", PTs of all psychiatric adverse reactions (N = 564) in MedDRA (version 24.1) were obtained and used for the subsequent analysis, thus ensuring that the analysed PTs were actual psychiatric adverse reactions from a clinical point of view.

Data processing procedure

We deduplicated the reports of ICIs obtained from the FAERS database, and the detailed screening process is shown in Fig. 1. Reports with the same value in fields including sex, age, country, event date, adverse reaction, drug and indication were identified as duplicate reports. The remaining reports were further screened to exclude reports of psychiatric adverse events that might be caused by other factors based on the following criteria: (1) PTs with the potential to induce psychiatric adverse reactions such as "metastases to meninges", "tumour associated fever", "infection", "metastases to central nervous system", "encephalopathy", and "encephalitis" among the reported adverse reactions; (2) treatment indications with "brain cancer metastatic", "metastases to central nervous system", and other cases with central nervous system (CNS) disease progression or brain metastases among the reported adverse reactions; and (3) concomitant drug prescriptions that may treat existing psychiatric disorders, such as benzodiazepines and antidepressants, as well as the concurrent use of corticosteroids or psychostimulants. While we can mitigate the impact of these non-ICI factors to some extent, complete elimination of their effects is not possible. In addition, we retained only adverse reaction reports for those aged 18 years or older. We further screened ICI treatment strategies based on adverse reaction reports, retaining reports of ICI monotherapy as well as reports of ICI combination therapy (only anti-CTLA4 plus anti-PD1/PD-L1 were considered). After the above steps of deduplication as well as screening of ICI data, the overall adverse reaction reports of patients treated with ICIs in the FAERS database used for further analysis were finally obtained (N = 91,683).

Signal mining

In the context of pharmacovigilance studies, disproportionality analysis primarily served as a tool to evaluate possible association between a specific adverse event and a particular drug which can then be investigated through clinical assessment of individual case reports.[20] The reporting odds ratio (ROR) compares the odds of reporting an event of interest for a particular drug to all other events, relative to the reporting odds for other drugs in the FAERS database,[21] and we used the

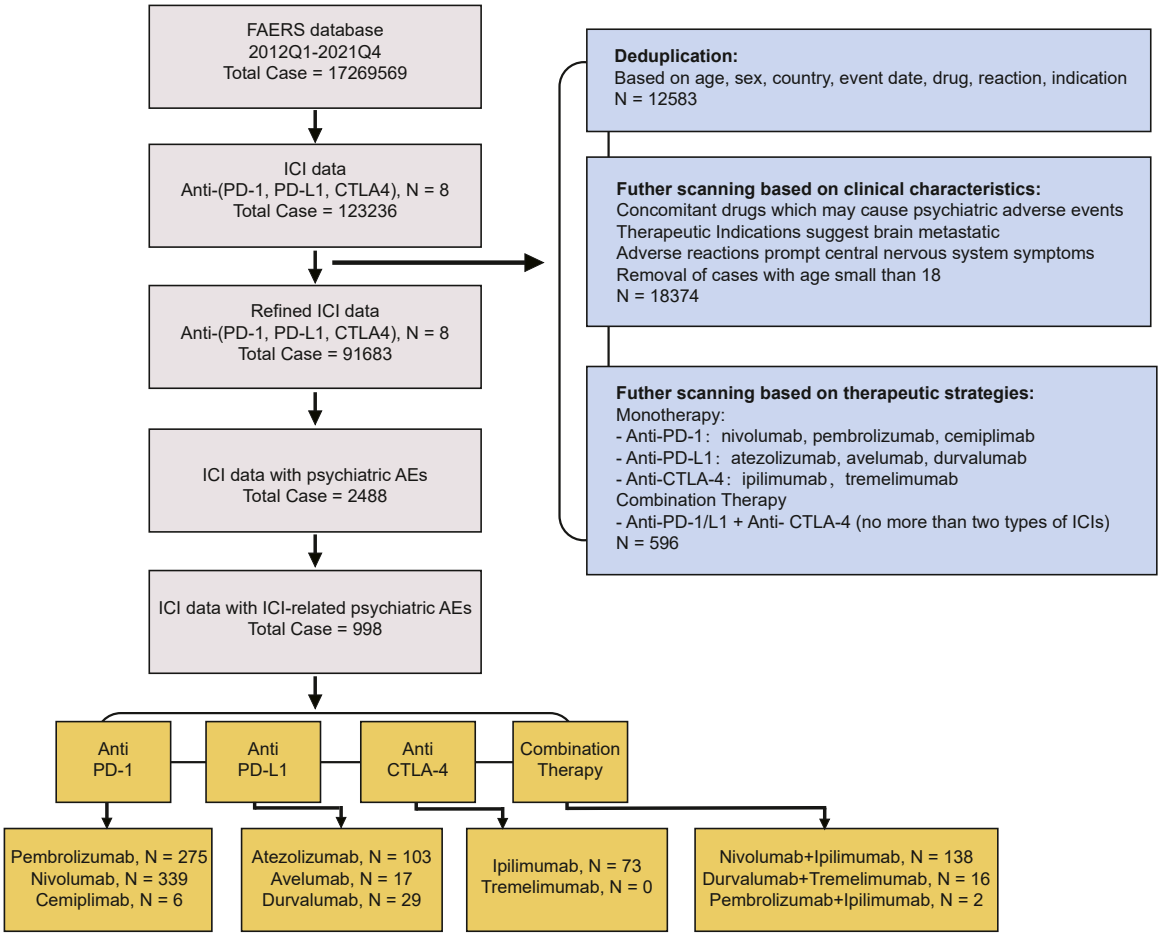

Fig. 1: Flow chart showing the analysis process of the study. A detailed description of the selection process of psychiatric adverse events for immune checkpoint inhibitors (ICIs) in the Food and Drug Administration Adverse Event Reporting System (FAERS).

ROR to detect signals of psychiatric adverse events in ICI reports in this study.[22] Using adverse reaction reports from the full FAERS database as comparators, we performed disproportionality analysis to assess potential association between psychiatric adverse reactions and ICIs by calculating the ROR.[23] Before conducting the disproportionality analysis of psychiatric adverse reactions and ICI-related psychiatric adverse events (ICI-related pAEs) correlated with ICIs, we first created a drug adverse reaction contingency table (Supplementary Table S1) and used this table as the basis for the subsequent calculation of ROR.

The following formula was used to calculate the ROR and 95% confidence interval (CI):

$$ROR = \frac{a/c}{b/d}$$

$$95\%\ CI = e^{\ln(ROR) \pm 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}.$$

Psychiatric adverse reaction signal was considered valid and highly associated with ICI treatment if the number of reports of psychiatric adverse events was not less than three and the lower limit of the 95% CI of the ROR exceeds one.[24] Overall, PTs of psychiatric disorders that meet the aforementioned conditions were defined as ICI-related pAEs. ICI reports with the occurrence of ICI-related pAEs were screened out for further analysis (N = 998).

Descriptive analysis

We performed a descriptive analysis of the clinical characteristics of reports with ICI-related pAEs after screening, including sex, age, age group, country, outcome, latest year of FDA acceptance, ICI treatment strategy, treatment indication, case priority, report type, and other clinical characteristics. Serious outcomes reported included life-threatening events or hospitalization, disability, and death. The onset time of ICI-related pAEs was obtained by subtracting the event start time

from the therapy start time.[25] Cumulative distribution curves were used to present event-to-onset information for ICI-related pAEs in different groups.

Calculating the enrichment scores of biological pathways in TCGA pan-cancer

We downloaded the transcriptome data in FPKM format from the University of California, Santa Cruz (UCSC) Xena database[26] for 26 cancer species in the TCGA project and converted the FPKM expression matrix into a transcripts per million (TPM) matrix.[27] We performed single-sample gene set enrichment analysis (ssGSEA) at the pan-cancer level with the GSVA package.[28] Based on the gene sets of Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways and Reactome pathways obtained from the MSigDB database,[29] which stores tens of thousands of annotated gene sets of biological process, we calculated the enrichment scores of these biological pathways in the samples of each cancer type. The enrichment score of a specific gene set represents the activity level of the biological process in which the members of the gene set are coherently up- or down-regulated.[30] The average enrichment score in a given pathway represents the activation level of that pathway in that type of cancer.[31] By analyzing the correlation between ICI-related pAEs ROR and the activation level of biological pathways from the pan-cancer level, we hope to identify the biological mechanisms that may be related to ICI-related pAEs.

Statistical analysis

We used the Kaplan–Meier method to estimate the event free probabilities for the time to onset of ICI-related pAE. Log-rank test and nonparametric Mann–Whitney U test were used to compare the median time to onset between different groups within cases of ICI-related pAEs. Since all cases had experienced the event of interest and their fatal outcome happened after ICI-related pAEs, we did not account for censoring or competing risk in our analysis. For the analysis of between-group differences in categorical variables and statistical tests in disproportional analysis, we used the Chi-square test or Fisher's exact test. Factors such as ICI treatment strategy, age, sex, whether the individual had combined chemotherapy or targeted therapy, and severity of the outcome were defined as exposure factors for ICI-related pAEs. Univariate logistic regression analysis was used to calculate the odds ratio (OR) for the occurrence of ICI-related pAEs under different exposures. Correlation analysis between pan-cancer level ICI-related pAEs RORs, and enrichment scores of biological pathways were performed using Spearman's rank correlation coefficient. The human anatomy heatmap was achieved by MOAHIT web tool.[32] Samples containing missing values were excluded during statistical analysis for each clinical characteristic (e.g., sex, age, time to onset, etc.). We controlled for multiple testing by calculating false discovery rate (FDR) value utilizing the Benjamini–Hochberg method via the '*P*.adjust' function from the 'stats' R package. In this study, $P < 0.05$ or FDR < 0.05 was considered statistically significant, and all statistical tests were two-tailed tests. All statistical analyses and visualizations were conducted using R software (https://www.r-project.org/; version 4.0.0). This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.[33]

Ethical statement

Since the FAERS database is accessible to the public and patient records are anonymized and de-identified, ethical clearance and informed consent are not required for this study.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Psychiatric adverse events among ICI users in the FDA adverse events reporting system, 2012–2021

We first investigated the occurrence of psychiatric adverse events among patients treated with ICIs in the FAERS database from 2012 to 2021. The detailed data processing procedure is shown in Fig. 1. After excluding cases in which psychiatric adverse events may have occurred due to concomitant medications and/or adverse reactions, and related treatment indications, statistics on psychiatric adverse reactions in cases treated with ICIs over the 10 year period were obtained. Psychiatric adverse events accounted for only a small fraction of the total adverse reactions in all of the ICI reports, with a case number of 2488 which accounted for 2.71% (2488/91,683) of the overall cases. In addition, the number of cases per year was only a small but relatively constant proportion (2.25%–3.41%) of the overall cases for that year (Fig. 2A). The occurrence of psychiatric adverse events also varied among different ICI treatment strategies. With the combination of anti-CTLA-4 and anti-PD-1 (L1), the number of cases with psychiatric adverse events was 2.99%; for monotherapy, the number of cases treated with anti-PD-1 with psychiatric adverse events was 1.91% (Fig. 2B). Overall, the proportion of psychiatric adverse events under various ICI treatment strategies suggests that it is a non-negligible part of the adverse events that may be associated with ICIs.

Scanning for ICI-related psychiatric adverse events

We counted the categories of psychiatric adverse events and the number of cases in the reports of ICIs (Supplementary Table S2). Confusional state (N = 557,

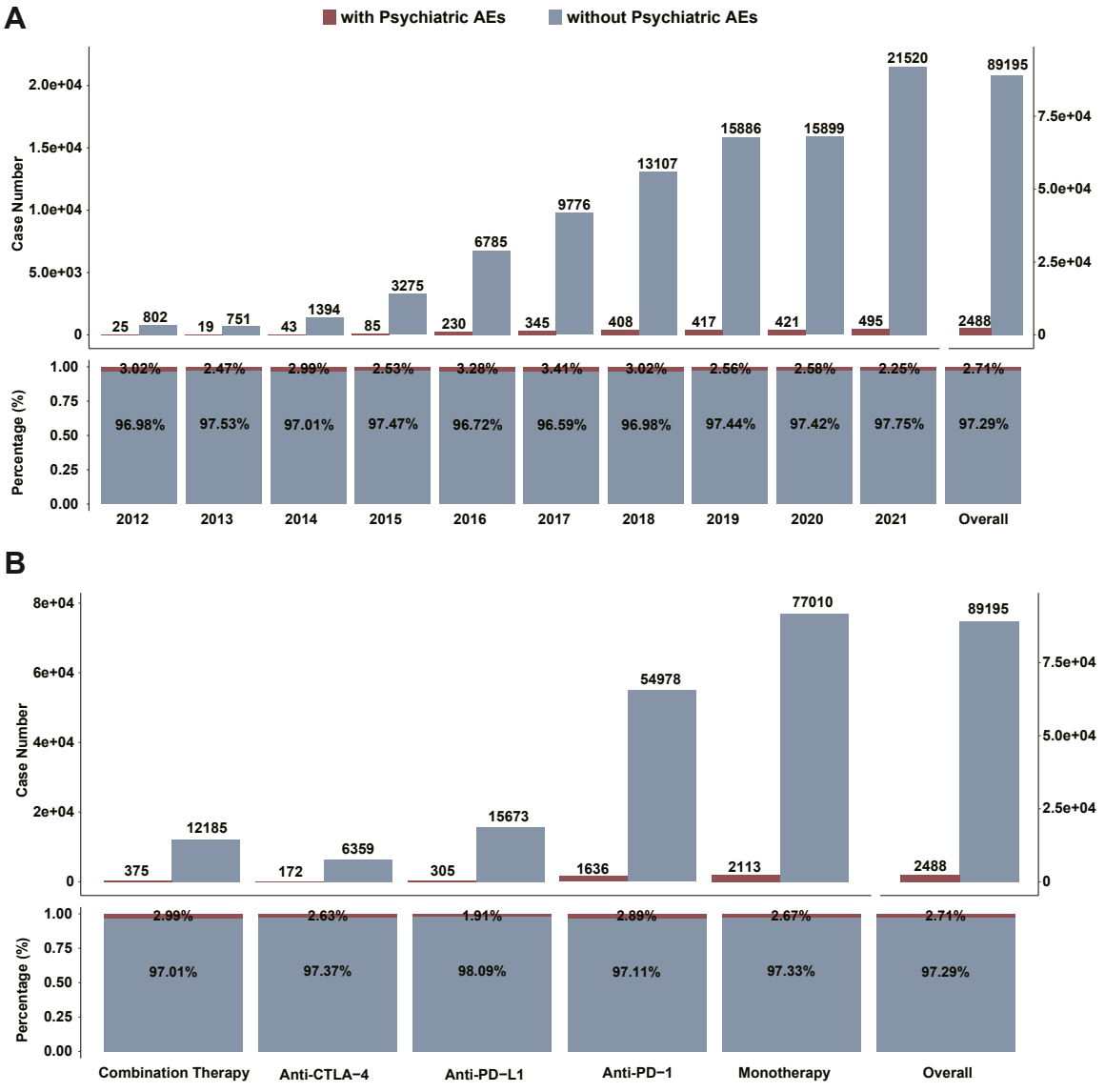

Fig. 2: Statistics on the occurrence of psychiatric adverse events in ICIs reports from the FAERS database during 2012–2021. A) The upper bar plot shows the number of ICI reports with psychiatric adverse reactions versus ICI reports without psychiatric adverse events in the FAERS database during 2012 and 2021, as well as the overall situation. The proportional bar plot below shows the amount of ICI reports with psychiatric adverse events versus ICI reports without psychiatric adverse events in the FAERS database during 2012 and 2021, as well as the overall situation. B) The upper bar plot shows the number of ICI reports with psychiatric adverse events versus ICI reports without psychiatric adverse events for different ICI treatment strategies in the FAERS database from 2012 to 2021 and the overall situation. The proportional bar plot below shows the amount of ICI reports with psychiatric adverse events versus ICI reports without psychiatric adverse events for different ICI treatment strategies in the FAERS database from 2012 to 2021 and overall situation. The ICI treatment strategies included ICI combination therapy, ICI monotherapy, and anti-CTLA-4, anti-PD-1, and anti-PD-L1. Red indicates reports with psychiatric adverse events, and blue indicates reports without psychiatric adverse events.

17.09%), insomnia (N = 389, 11.94%), anxiety (N = 298, 9.14%), depression (N = 260, 7.98%), and delirium (N = 231, 7.09%) were the five categories of psychiatric adverse events with the highest numbers of cases. We performed a disproportionality analysis by calculating the ROR of PTs with no less than 3 cases (N = 76) in the above psychiatric adverse events, using the full FAERS database as a comparator. After filtering by our criteria of a valid signal, we found different psychiatric adverse events associated with different ICI treatment strategies (Fig. 3A). Finally, five PTs for psychiatric disorders (confusional state, delirium, mental status changes,

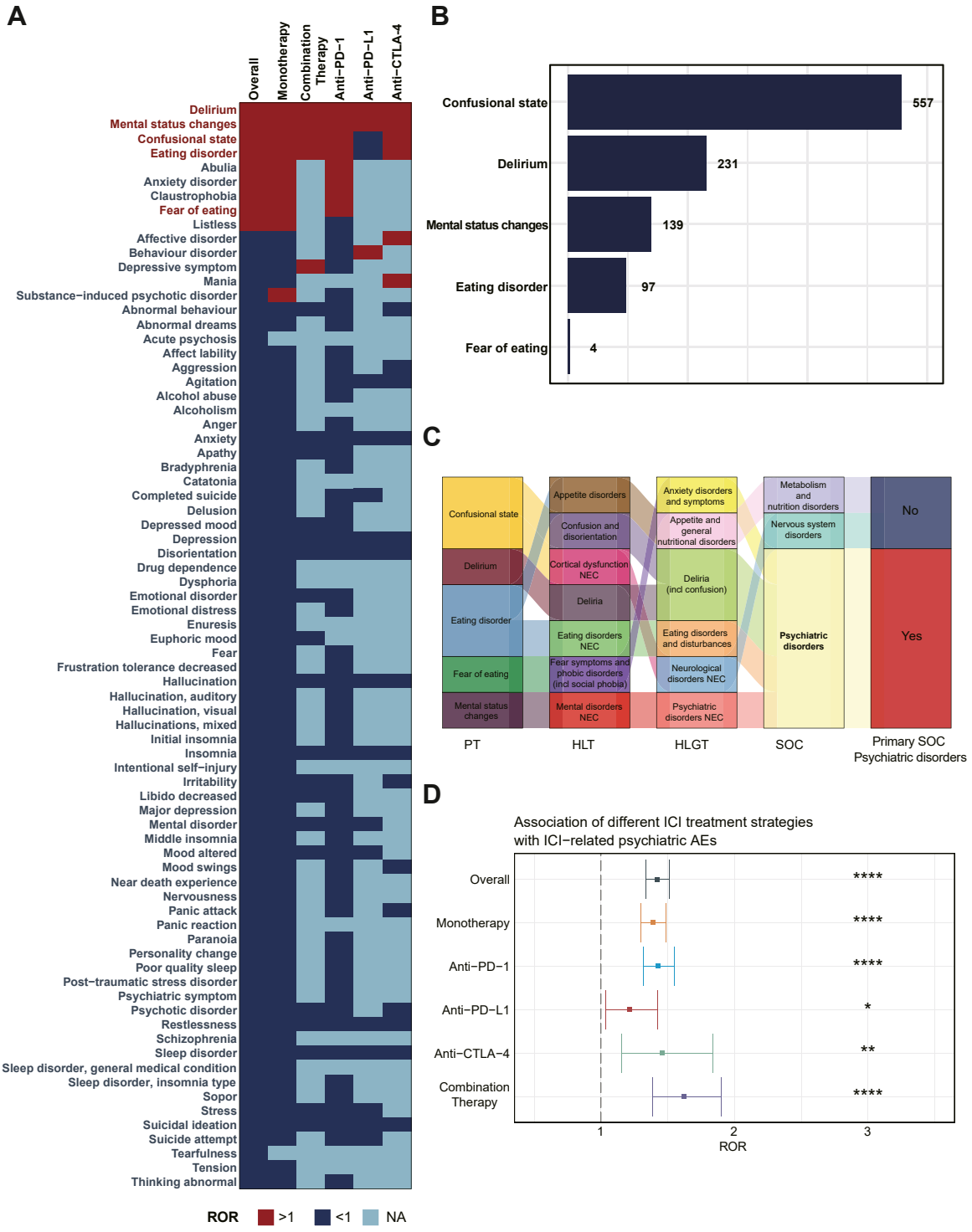

Fig. 3: Scanning for ICI-related psychiatric adverse events based on the FAERS database. A) The heatmap shows the ROR for 76 psychiatric adverse events (with cases no less than 3) in the FAERS database under different ICI treatment strategies (including overall situation, ICI combination therapy, ICI monotherapy, anti-CTLA-4, anti-PD-1, and anti-PD-L1). Red indicates ROR values greater than 1, dark blue indicates ROR values less than 1, and light blue indicates ROR values that could not be calculated. Psychiatric adverse events labelled with dark red colour meet the criteria that in the overall situation, the lower limit of the 95% confidence interval for the ROR greater than 1 and the number of cases occurring no less than 3. B) The bar plot shows the number of reported cases for five categories of ICI-related pAEs under different ICI treatment

eating disorder, fear of eating) that were highly associated with the treatment of ICIs in the overall context were defined as ICI-related psychiatric adverse events (ICI-related pAEs) (Supplementary Table S3). Fear of eating was the ICI-related pAEs with the lowest numbers of cases but high ROR signals in the overall contexts (Fig. 3B). Fig. 3C provides the affiliation of the PTs for ICI-related pAEs with other hierarchies in MedDRA, and their primary SOC was psychiatric disorder. Based on the full FAERS database, we again calculated the ROR for ICI-related pAEs. Overall, ICI treatments were significantly associated with the occurrence of ICI-related pAEs (ROR = 1.423 [1.336–1.515], FDR < 0.0001), but there were differences between treatment strategies for ICIs (Fig. 3D). In addition, anti-PD-L1 treatment was significantly associated with the occurrence of ICI-related pAEs with the lowest ROR (ROR = 1.214 [1.033–1.427], FDR = 0.027) (Fig. 3D and Supplementary Table S4).

Descriptive analysis of cases with ICI-related psychiatric adverse events

After screening the reports of ICIs in the FAERS database, we obtained cases with ICI-related pAEs (N = 998) and statistically described the clinical characteristics of these cases (Table 1). The median age of the patients was 70 years (interquartile range [IQR] 24–95, with data available in 783 case reports). Using 65 and 75 years as the cut-off, we divided the patients into 3 different age groups, with the majority of patients older than 65 years (N = 525, 52.6%). The majority of reported cases were male (N = 615, 61.6%), and most cases were reported from the United States (N = 505, 50.6%). Cases with a fatal outcome accounted for 21.54% (215/998). Anti-PD-1 as well as ICI combination therapy accounted for most of the ICI treatment strategies (Anti-PD-1: 62.1%, 620/998; combination therapy: 15.6%, 156/998) (Fig. 4A). Concomitant chemotherapy and targeted therapy treatments accounted for 9.4% (94/998) and 11.6% (116/998) of cases with ICI-related pAEs, respectively. Among the cases with ICI-related pAEs, cases with indications for lung cancer (28.4%, 283/998), skin cancer (17.6%, 176/998) and kidney site cancer (10.9%, 109/998) accounted for the majority (Fig. 4B).

Time to onset analysis

More than 70% of cases of ICI-related pAEs occurred during the first two months of initiating ICI treatments, with a median onset time of 30 days (IQR 15–77) (Supplementary Figure S1A). The median onset time was significantly shorter in the fatal group than in the non-fatal group (Days: 26 vs. 32, $P = 0.017$) (Fig. 4C). The median onset time was 14 days longer in cases receiving concomitant targeted therapy than in cases not receiving concomitant targeted therapy (Days: 30 vs. 44, $P = 0.026$) (Fig. 4D). Different ICI treatment strategies may not influence the median onset time of ICI-related pAEs ($P = 0.83$) (Fig. 4E). Notably, the median onset time was highest under combination therapy at 33 days (IQR 14–70.25); the shortest median onset time was achieved with anti-CTLA-4 treatment at 27 days (IQR 20–37). However, we did not observe that age, gender, and concomitant chemotherapy had a significant impact on the onset time of ICI-related pAEs (Supplementary Figure S1B). Additional Kaplan–Meier plot with Log-rank test also validated above results (Supplementary Figure S2).

Comparison between the fatal and non-fatal groups

In cases where ICI-related pAEs occurred, more than 20% of cases had a fatal outcome. Although the occurrence of ICI-related pAEs may not be the direct cause of death, analysis of the differences between the fatal and non-fatal groups may suggest clues to improve patient outcomes. Males ($P = 0.069$) as well as patients in the higher age group ($P = 0.26$) tended to be more represented in the fatal group (Supplementary Figure S1C and D). The proportion of cases with combination chemotherapy ($P = 0.90$) or targeted therapy ($P = 0.72$) did not differ significantly between the fatal and non-fatal groups (Supplementary Figure S1E and F). There was no significant difference in the distribution of the number of cases with different cancer original site between the fatal and non-fatal groups ($P = 0.055$). Among the top three most common therapeutic indications, cases with lung cancers had a higher mortality rate (24.73%, 70/283) than skin site cancers (21.59%, 38/176) and kidney site cancers (15.60%, 17/109).

Influencing factors for ICI-related pAEs

We have additionally examined co-reported adverse events that may act as influencing factors for ICI-related pAEs. Among the 998 cases with ICI-related pAEs that we screened, 88% of cases were accompanied by the occurrence of other adverse events, while 12% of cases had only ICI-related pAEs (Fig. 5A). Among cases with other concomitant adverse events, general disorders and administration site conditions, nervous system disorders,

strategies. C) Sankey diagram depicting the hierarchical relationship of PTs for five categories of ICI-related pAEs in MedDRA. NES indicates not classified elsewhere. PT indicates the preferred term, HLT indicates the high level term, HLGT indicates the high level group term, and SOC indicates the system organ class. D) Forest plot shows the ROR of ICI-related pAEs (considering the five categories of ICI-related pAEs as one category of adverse events) under different ICI treatment strategies (including overall situation, ICI combination therapy, ICI monotherapy, and anti-CTLA-4, anti-PD-1, and anti-PD-L1). NS indicates Not Significant, $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; $^{****}P < 0.0001$.

Clinical characteristics	Fatal (N = 215)	Non-fatal (N = 783)	Total (N = 998)	*P*-value
Gender				
Male	145 (67.4%)	470 (60.0%)	615 (61.6%)	0.069
Female	61 (28.4%)	272 (34.7%)	333 (33.4%)	
Missing	9 (4.2%)	41 (5.2%)	50 (5.0%)	
Age				0.026
Mean (SD)	69.5 (10.2)	67.6 (11.8)	68.1 (11.5)	
Median [Min, Max]	71.0 [24.0, 91.0]	69.0 [26.0, 95.0]	70.0 [24.0, 95.0]	
Missing	20 (9.3%)	195 (24.9%)	215 (21.5%)	
Age group				0.26
18–65	55 (25.6%)	203 (25.9%)	258 (25.9%)	
65–74	79 (36.7%)	216 (27.6%)	295 (29.6%)	
≥75	61 (28.4%)	169 (21.6%)	230 (23.0%)	
Missing	20 (9.3%)	195 (24.9%)	215 (21.5%)	
Time to onset				
Mean (SD)	73.6 (114)	121 (204)	107 (184)	0.017
Median [Min, Max]	26.0 [1.00, 451]	32.0 [1.00, 1470]	30.0 [1.00, 1470]	
Missing	106 (49.3%)	512 (65.4%)	618 (61.9%)	
Country				0.002
US	106 (49.3%)	399 (51.0%)	505 (50.6%)	
JP	42 (19.5%)	72 (9.2%)	114 (11.4%)	
IT	5 (2.3%)	19 (2.4%)	24 (2.4%)	
GB	4 (1.9%)	28 (3.6%)	32 (3.2%)	
FR	11 (5.1%)	51 (6.5%)	62 (6.2%)	
DE	10 (4.7%)	18 (2.3%)	28 (2.8%)	
CA	7 (3.3%)	53 (6.8%)	60 (6.0%)	
AU	4 (1.9%)	18 (2.3%)	22 (2.2%)	
Other country	24 (11.2%)	101 (12.9%)	125 (12.5%)	
Missing	2 (0.9%)	24 (3.1%)	26 (2.6%)	
Received year				0.019
2012	2 (0.9%)	5 (0.6%)	7 (0.7%)	
2013	0 (0%)	8 (1.0%)	8 (0.8%)	
2014	4 (1.9%)	19 (2.4%)	23 (2.3%)	
2015	11 (5.1%)	26 (3.3%)	37 (3.7%)	
2016	23 (10.7%)	64 (8.2%)	87 (8.7%)	
2017	32 (14.9%)	105 (13.4%)	137 (13.7%)	
2018	48 (22.3%)	117 (14.9%)	165 (16.5%)	
2019	30 (14.0%)	139 (17.8%)	169 (16.9%)	
2020	23 (10.7%)	149 (19.0%)	172 (17.2%)	
2021	42 (19.5%)	151 (19.3%)	193 (19.3%)	
Treatment strategy				0.58
Anti-PD-1	139 (64.7%)	481 (61.4%)	620 (62.1%)	
Anti-PD-L1	33 (15.3%)	116 (14.8%)	149 (14.9%)	
Anti-CTLA4	16 (7.4%)	57 (7.3%)	73 (7.3%)	
Combination therapy	27 (12.6%)	129 (16.5%)	156 (15.6%)	
Plus chemotherapy				0.9
No	194 (90.2%)	710 (90.7%)	904 (90.6%)	
Yes	21 (9.8%)	73 (9.3%)	94 (9.4%)	
Plus targeted therapy				0.72
No	192 (89.3%)	690 (88.1%)	882 (88.4%)	
Yes	23 (10.7%)	93 (11.9%)	116 (11.6%)	
Indication organ				0.055
Lung	70 (32.6%)	213 (27.2%)	283 (28.4%)	
Skin	38 (17.7%)	138 (17.6%)	176 (17.6%)	
Kidney	17 (7.9%)	92 (11.7%)	109 (10.9%)	

(Table 1 continues on next page)

Clinical characteristics	Fatal (N = 215)	Non-fatal (N = 783)	Total (N = 998)	*P*-value
(Continued from previous page)				
Head and neck	10 (4.7%)	24 (3.1%)	34 (3.4%)	
Bladder	6 (2.8%)	27 (3.4%)	33 (3.3%)	
Brain	3 (1.4%)	21 (2.7%)	24 (2.4%)	
Liver	3 (1.4%)	20 (2.6%)	23 (2.3%)	
Lymphoid	5 (2.3%)	18 (2.3%)	23 (2.3%)	
Uterus	1 (0.5%)	22 (2.8%)	23 (2.3%)	
Pancreas	8 (3.7%)	12 (1.5%)	20 (2.0%)	
Prostate	4 (1.9%)	15 (1.9%)	19 (1.9%)	
Large intestine	4 (1.9%)	13 (1.7%)	17 (1.7%)	
Stomach	6 (2.8%)	10 (1.3%)	16 (1.6%)	
Breast	5 (2.3%)	9 (1.1%)	14 (1.4%)	
Cholecyst	4 (1.9%)	7 (0.9%)	11 (1.1%)	
Ovary	3 (1.4%)	8 (1.0%)	11 (1.1%)	
Pleura	0 (0%)	9 (1.1%)	9 (0.9%)	
Hematologic	1 (0.5%)	5 (0.6%)	6 (0.6%)	
Esophagus	3 (1.4%)	2 (0.3%)	5 (0.5%)	
Others	3 (1.4%)	16 (2.04)	19 (0.3%)	
Unspecified	21 (9.8%)	102 (13%)	123 (12.3%)	
Case priority				
Direct	13 (6.0%)	53 (6.8%)	66 (6.6%)	<0.001
Expedited	199 (92.6%)	651 (83.1%)	850 (85.2%)	
Non-expedited	3 (1.4%)	79 (10.1%)	82 (8.2%)	
Reporter type				
Consumer	26 (12.1%)	162 (20.7%)	188 (18.8%)	0.005
Healthcare professional	189 (87.9%)	610 (77.9%)	799 (80.1%)	
(Missing)	0 (0.0%)	11 (1.4%)	11 (1.1%)	

Table 1: **Characteristics of reports with ICI-related psychiatric adverse events sourced from the FAERS database (January 1 2012–December 31 2021).**

and gastrointestinal disorders were the top three most frequently reported concomitant adverse events which occurred in more than 50% of ICI-related pAE cases. Metabolism and nutrition disorders were present in 38.25% of cases, while co-reported immune system disorders were present in only 2.38% of cases (Fig. 5B). Additionally, hyponatremia (4.99%), diarrhea (10.22%), rash (5.11%), and pneumonia (5.45%), which were associated with ICI, were among the top 30% of co-reported adverse events (Fig. 5C).

We further explored factors that might influence the occurrence of ICI-related pAEs by univariate logistic regression analysis based on the total ICI reports. Sex was not an influencing factor for ICI-related pAEs. Compared to the odds of ICI-related pAEs for patients under 65, patients aged 65–70 have 1.44 times higher odds (OR = 1.44 [1.22–1.70], $P < 0.0001$) and those over 75 have 1.84 times higher odds (≥75: OR = 1.84 [1.54–2.20], $P < 0.0001$). Whether ICIs are combined with chemotherapy or targeted therapy were not an influencing factor of ICI-related pAEs (plus chemotherapy: OR = 0.9 [0.72–1.11], $P = 0.90$; plus targeted therapy: OR = 1.15 [0.94–1.39], $P = 0.16$). Compared with anti-PD-1, other ICI treatment strategies including ICI combination therapy did not significantly affect the occurrence of ICI-related pAEs and the OR was small ($P > 0.05$) (Fig. 5D and Supplementary Table S5).

Analysis of the intrinsic biological mechanism associated with ICI-related pAEs

We also explored the potential biological mechanisms underlying the occurrence of ICI-related pAEs. At the pan-cancer level, the ICI-related pAE ROR varied with the cancer type. The ROR of ICI-related pAEs was highest in brain lower grade glioma (LGG) (ROR = 11.38, 95% CI [3.50–37.06], FDR = 0.0074) and lowest in esophageal carcinoma (ESCA) (ROR = 0.78, 95% CI [0.33–1.90], FDR = 0.81) (Fig. 6A and Supplementary Table S6). Combining the transcriptome data analysis for TCGA pan-cancers, we observed that the pan-cancer level ICI-related pAE ROR was significantly positively associated with the NOTCH signalling pathway (R = 0.698, FDR = 0.038), neurexins and neuroligins signature (R = 0.734, FDR = 0.038), and synaptic adhesion-like molecules signature (R = 0.685, FDR = 0.038) (Fig. 6B).

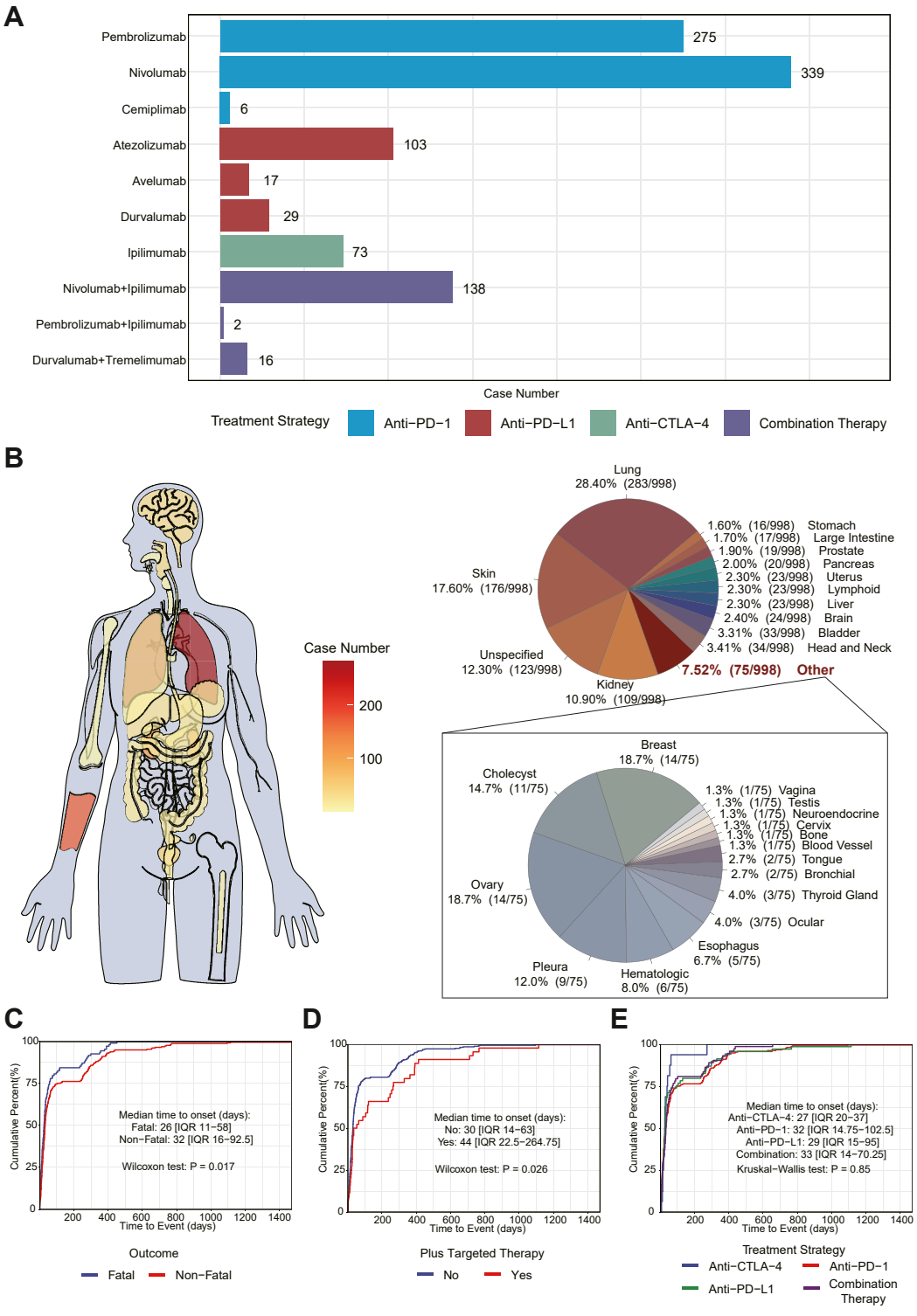

Fig. 4: Descriptive analysis of reports with ICI-related psychiatric adverse events. A) The bar plot shows the number of reports with ICI-related pAEs for different ICI treatment strategies. B) The site statistics for cancer occurrence in reports with ICI-related pAEs. On the left is the anatomical diagram of the patient's original cancer site and the number of cases. The darker the colour, the more cases with cancer originated form this site. The pie chart on the right shows the proportional composition of the patient's cancer original sites. The pie chart on the top shows the proportional distribution of the case numbers for organs which were greater than 15. Among them, cancer sites with a case number

Discussion

While irAEs associated with ICIs have been widely reported and studied,[6] there is a lack of comprehensive studies on the possible psychiatric adverse events associated with ICIs. This study is the first pharmacovigilance study of psychiatric adverse events associated with ICIs based on real-world data from the FAERS database. Using the full FAERS database as a comparator, we identified five psychiatric adverse events that were highly relevant to the treatment of ICIs by disproportionality analysis, explored the clinical characteristics of the reports in which such adverse reactions occurred, and explored the associated biological mechanisms in conjunction with the pan-cancer transcriptomic data.

Psychiatric adverse events are a stable but a less frequently occurring category of adverse reactions associated with ICIs. The FAERS database showed that psychiatric adverse events occurred in 2.71% (2.25%–3.41%) of the reports treated with ICIs for the 2012–2021 decade. The proportion of psychiatric adverse events was slightly higher in ICI reports of patients receiving combination therapy than in reports of patients receiving monotherapy (2.99% vs. 2.67%). We screened the ICI reports by excluding potential factors that could induce psychiatric adverse reactions and by searching in MedDRA based on standardized MedDRA queries (SMQs) for PTs of psychiatric disorders to ensure that we screened for true psychiatric adverse reactions associated with ICI treatment. Among the five ICI-related pAEs we defined, confusional states and eating disorders had metabolic and nutritional disorders and neurological disorders as secondary SOCs, respectively, in addition to psychiatric disorders as the primary SOC. They are both common psychiatric disorders. Anorexia nervosa (AN) and bulimia nervosa (BN) are specific eating disorders[34] that are closely related to psychiatric disorders. Takayama et al. reported a case of malnutrition due to severe anorexia and nausea during treatment with nivolumab.[35] Delirium or acute confusional state is a clinical syndrome characterized by impairment of consciousness, cognitive function or perception, with serious adverse consequences such as death and dementia.[36] The occurrence of both is usually associated with systemic disease, brain disease or drug toxicity, often induced by hypokalaemia and hyponatremia,[37] while the latter is associated with ICIs.[38,39] A confusional state is frequently reported in studies of adverse events of ICIs.[17,40–42] These results suggest that the ICI-related pAEs we found are likely to occur realistically during patients' treatment with ICIs. In addition, the occurrence of psychiatric adverse events is associated with multiple factors, such as CNS disease, disease progression, medications, and prolonged hospitalization.[43] This study, which screened ICI reports, was conducted to demonstrate that ICI-related pAEs are highly relevant to the treatment of ICIs. These ICI-related pAEs require more attention, early detection and intervention in clinical practice.

In a further investigation of factors affecting ICI-related pAEs, we observed higher odds of ICI-related pAEs was associated with a higher age group. Previous studies have been controversial regarding the effect of age on adverse drug reactions to ICIs. For example, there are studies that have shown that age does not affect the outcome of patients treated with ICIs despite the different profiles of toxicities in older and younger adults (early detection and intervention), but other studies suggest that age has an impact on the adverse effects caused by ICIs.[9,44] Undeniably, psychiatric disorders and other co-morbidities themselves are frequent in the elderly population with poor outcomes,[45] which may contribute to the development of ICI-related pAEs. While it may be difficult to separate the effects of age and co-morbidities in the development of pAEs, earlier identification and intervention should be implemented to improve the outcome of elderly patients.

In terms of treatment strategies for ICIs, we did not find any significant difference in the odds of ICI-related pAEs for different ICI treatment strategy groups, including ICI combination therapy. This differs from the general situation where combination therapy as well as anti-CTLA-4 are associated with more negative events following anti-PD-1 and anti-PD-L1 treatment.[46,47] Whether ICIs are combined with chemotherapy or targeted therapy is not an influencing factor of ICI-related pAEs, suggesting that the occurrence of these ICI-related pAEs is likely to be related to ICIs. In addition, it has been controversial whether ICI combined with chemotherapy has an effect on irAEs.[48,49] However, the sample size was smaller under different ICI treatment strategies when analysed by univariate logistic regression. Conclusions related to factors influencing ICI-related pAEs need to be further validated by larger studies or clinical trials.

In fact, our findings indicate that in 88% of the cases, the occurrence of ICI-related pAEs may be directly or indirectly related to the occurrence of other concomitant adverse events. Specifically, hyponatremia, a metabolic and nutritional disorder, was observed in 4.99% of cases with concomitant AEs. Previous studies have reported an association between ICI and hyponatremia, and the

less than 15 are classified as other (marked in red). The pie chart at the bottom shows the proportional distribution of the case numbers for cancer originated from other. C, D and E) From the left to right, the cumulative distribution curves demonstrate the onset time of ICI-related pAEs after treatment with ICIs in different subgroups (fatal status, whether plus targeted therapy and different ICI treatment strategies). Statistical tests were conducted using the nonparametric Wilcoxon rank sum test.

Fig. 5: Factors influencing ICI-related psychiatric adverse events. A) Bar plot shows the proportion of cases with and without co-reported AEs in cases with ICI-related pAEs. B) Bar plot shows the statistics of SOC regarding PTs of co-reported adverse events. The percentage values labeled in the figure represent the proportion of cases with such adverse events out of the total ICI-related pAE cases with co-reported adverse reactions. C) Bar plot shows the statistics of the top 30% PTs of co-reported adverse events. The colour indicates the SOC of the corresponding PT. The

latter is also a common symptom of paraneoplastic syndrome.[50] Additionally, co-reported gastrointestinal adverse events such as diarrhea and vomiting, and co-reported metabolic and nutritional adverse events such as dehydration, also occur in a certain proportion of patients. They may cause hyponatremia in patients, thereby indirectly affecting the occurrence of ICI-related pAEs. We posit that the concurrent presence of hyponatremia or inducing factors of hyponatremia may elucidate the mechanism behind the ICI-related pAEs in this subgroup of cases.

Our study identified psychiatric adverse events that were highly associated with ICIs based on real-world data. However, unlike ICI-related irAEs, we could only perform a preliminary exploration of the possible mechanisms of ICI-related pAEs by combining pan-cancer transcriptome data. According to the results, the ICI-related pAE ROR was much higher in patients with brain tumours (LGG, GBM) than in tumours at other sites. Although patients with brain tumours can exhibit psychiatric symptoms such as mood symptoms, mood changes and anorexia,[51] the fact that adverse events are recorded after ICI administration suggests that clinical attention should be given to possible psychiatric adverse events that may occur in patients with brain tumours after treatment with ICIs, especially mental status changes.

The present study correlated the activation level of biological pathways in various cancer types with the ROR of ICI-related pAEs. Activation of the NOTCH signalling pathway has been suggested to play an important role in neurodevelopment and adult brain homeostasis and is also associated with the development of bipolar disorder and epilepsy, as well as the formation of fear memory.[52,53] Additionally, NOTCH signalling also causes activation of the immune system, leading to autoimmune diseases and inflammation.[54] Synaptic-related pathways, which are closely linked to the occurrence of psychiatric disorders,[55,56] are also highly positively associated with the ROR of ICI-related pAE. The above evidence implies possible intrinsic biological mechanisms that may give rise to ICI-related pAEs. We observed the highest ICI-related pAE ROR in two types of CNS (Central Nervous System) tumours, GBM, and LGG. Although ICIs have difficulty crossing the blood–brain barrier (BBB), they may also act on GBM through some intrinsic immune system mechanisms.[57] In addition, PD-1 and PD-L1 are expressed in the tissues of the central nervous system.[58] This also suggests that the occurrence of psychiatric adverse reactions associated with ICIs may be closely related to the immune system. However, possible psychiatric disorders induced by CNS tumours themselves cannot be excluded. In conclusion, whether ICIs are associated with these psychiatric adverse reactions and by what mechanism still needs to be further explored and verified by more clinical studies.

There are some limitations of this study. First, the FAERS database is a worldwide spontaneous reporting system. It has some inherent selection bias, such as the ethnicity and geography of the reported cases, the timing of approval and market penetration of different drugs, the level of public awareness of specific adverse reactions, and the fact that not all reports of serious adverse reactions occurring are collected. Therefore, we could not obtain a causal relationship between ICIs and ICI-related pAEs, nor could we calculate the incidence of psychiatric adverse events or ICI-related pAEs. Furthermore, we could not obtain more detailed information about the reports, such as COVID-19 infection, and it is not yet possible to judge the effect of COVID-19 on ICI-related pAEs. Moreover, the lack of specific time of death for each report hindered us from conducting further competing risk analysis on the onset time of ICI-related pAEs. Second, due to the wide variety of anticancer drugs, such as ICIs, targeted therapy agents, chemotherapeutic drugs, biologics, etc., it is difficult for us to extract all the anticancer drugs in the FAERS database separately and to set the comparator of the disproportionality analysis as anticancer drugs. This may cause some indication bias and establish false positive associations. It is also difficult to compare the occurrence of psychiatric adverse events in chemotherapeutic drugs with ICIs. It is noteworthy that a large proportion of cases are classified as expedited reports (i.e., serious unmarked reports from the manufacturer), which may be from certain clinical trials. Third, a weakness of this study is that we were unable to fully differentiate between the medication indications, and the impact of other adverse reactions on ICI-related pAEs. Similarly, we did not provide strong evidence regarding the underlying biological mechanisms of psychiatric adverse reactions associated with ICIs. Finally, the psychiatric adverse events associated with ICIs that we identified have not been clinically validated, and there is a lack of research in this area. As this study is a complete case analysis and exploratory, our findings regarding ICI-related pAEs needs to be confirmed in

percentage values labeled in the figure represent the proportion of cases with such adverse events out of the total ICI-related pAE cases with co-reported adverse reactions. D) The forest plot shows the results of univariate logistic regression analysis regarding the factors influencing ICI-related pAEs. The exposure factors considered included sex (red), age (light blue), outcome (green), whether combined with chemotherapy (blue), whether combined with targeted therapy (orange) and ICI treatment strategy (grey). OR indicates odds ratio. NS indicates Not Significant, AE indicates adverse event, PT indicates preferred term, SOC indicates systemic organ class, *P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001.

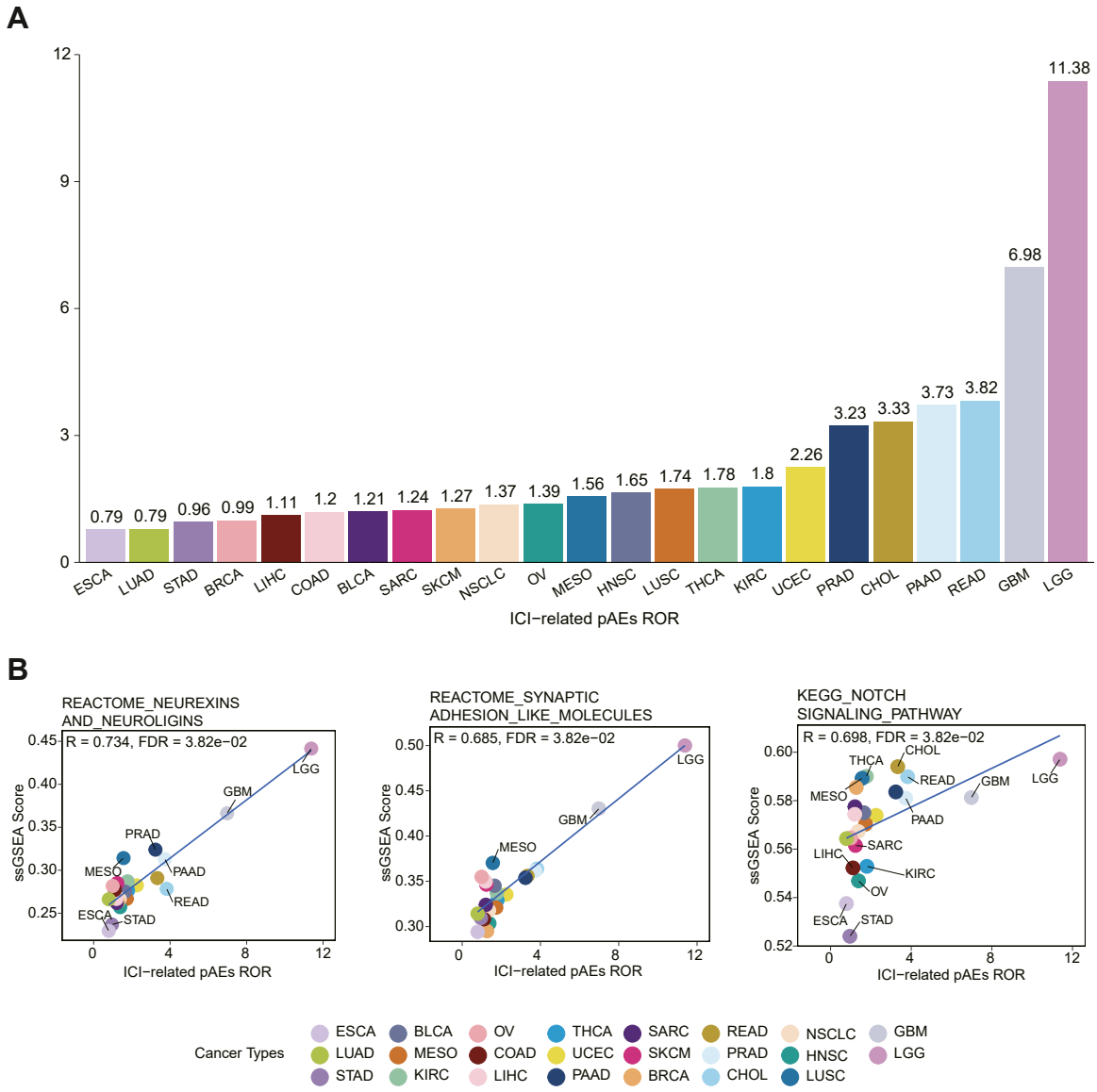

Fig. 6: Assessment of the association between ICI-related psychiatric adverse events and biological pathways. A) The bar plot shows the ROR of ICI-related pAEs in 23 different cancer types. Hematologic malignancies were not included in the analysis. Tumour types with less than 5 cases were not included in the analysis. B) The correlation analysis between the ROR of ICI-related pAEs and ssGSEA enrichment scores for the neurexins and neuroligins signature, synaptic adhesion-like molecules signature, and NOTCH signalling pathway. The Spearman's rank correlation coefficient was used for correlation analysis. LUAD: lung adenocarcinoma; SKCM: skin cutaneous melanoma; LUSC: lung squamous cell carcinoma; NSCLC: non-small cell lung carcinoma: KIRC: kidney renal clear cell carcinoma; PRAD: prostate adenocarcinoma; BLCA: bladder urothelial carcinoma; MESO: mesothelioma: BRCA: breast invasive carcinoma; UCEC: uterine corpus endometrial carcinoma; SARC: sarcoma: ESCA: esophageal carcinoma; PAAD: pancreatic adenocarcinoma; OV: ovarian serous cystadenocarcinoma; HNSC: head and neck squamous cell carcinoma: STAD: stomach adenocarcinoma; THCA: thyroid carcinoma; CHOL: cholangiocarcinoma; READ: rectum adenocarcinoma; COAD: colon adenocarcinoma; LIHC: liver hepatocellular carcinoma; LGG: brain lower-grade glioma; GBM: glioblastoma multiforme.

a large-scale prospective study. We will consider conducting future clinical studies to further validate our results.

In conclusion, based on real-world data from the FAERS database, this study comprehensively investigated and identified five categories of psychiatric adverse events highly associated with ICIs by conducting disproportionality analysis. Although the percentage of ICI-related pAEs among all ICI reports of adverse events is relatively low (1.09%, 998/91,683), our study supports the steady presence of ICI-related pAEs, with the occurrence ranging from 0.85% to 1.60% of the

total number of adverse event reports for ICIs for that year over the past decade (2012–2021). The results of this study provide a better basis for understanding possible psychiatric adverse events and help clinicians pay attention to them and intervene early. As our study is exploratory in nature, it is imperative to validate our findings through a prospective study. In the future, large population-based prospective studies are needed to help determine the actual incidence of ICI-related pAEs, and to fully elucidate the possible biological mechanisms and risk factors for better risk management.

Contributors

Conceptualization, P.L., J.Z. and Q.C.; Formal analysis, C.Z.Z., A.Q.L. and T.Q.G.; Resources, C.Z.Z., J.Z. and P.L.; Software, C.Z.Z., A.Q.L., S.K.P., Q.C., Y.X.P. and Z.Q.L.; Supervision, J.Z. and P.L.; Visualization, C.Z.Z., A.Q.L. and Y.X.P.; Writing–original draft, C.Z.Z.; Writing–review & editing, C.Z.Z. and A.Q.L.; Revision: C.Z.Z., S.K.P., A.M.J. and Y.X.P. All authors read and approved the final manuscript.

Data sharing statement

All the data generated or analyzed during this study are included in this published article and its supplementary files. ICI reports are available and can be retrieved form the FAERS Publish Dashboard (https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard). The TCGA pan-cancer transcriptomic data are available and can be obtained from the UCSC Xena database (https://xenabrowser.net/datapages/).

Declaration of interests

The authors declare that they have no competing interests.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.101967.

References

1 Haslam A, Prasad V. Estimation of the percentage of US patients with cancer who are eligible for and respond to checkpoint inhibitor immunotherapy drugs. *JAMA Netw Open*. 2019;2(5). https://doi.org/10.1001/JAMANETWORKOPEN.2019.2535.
2 Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. *Science*. 2018;359. https://doi.org/10.1126/science.aar4060.
3 Bagchi S, Yuan R, Engleman EG. Immune checkpoint inhibitors for the treatment of cancer: clinical impact and mechanisms of response and resistance. *Annu Rev Pathol*. 2021;16:223–249. https://doi.org/10.1146/annurev-pathol-042020-042741.
4 Ramos-Casals M, Brahmer JR, Callahan MK, et al. Immune-related adverse events of checkpoint inhibitors. *Nat Rev Dis Primers*. 2020;6(1). https://doi.org/10.1038/S41572-020-0160-6.
5 Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med*. Jan. 2018;378(2):158–168. https://doi.org/10.1056/NEJMra1703481.
6 Kennedy LB, Salama AKS. A review of cancer immunotherapy toxicity. *CA Cancer J Clin*. 2020;70(2):86–104. https://doi.org/10.3322/caac.21596.
7 Halle BR, Betof Warner A, Zaman FY, et al. Immune checkpoint inhibitors in patients with pre-existing psoriasis: safety and efficacy. *J Immunother Cancer*. 2021;9(10). https://doi.org/10.1136/JITC-2021-003066.
8 Tison A, Quéré G, Misery L, et al. Safety and efficacy of immune checkpoint inhibitors in patients with cancer and preexisting autoimmune disease: a Nationwide, Multicenter Cohort Study. *Arthritis Rheumatol*. 2019;71(12):2100–2111. https://doi.org/10.1002/art.41068.
9 Baldini C, Martin Romano P, Voisin AL, et al. Impact of aging on immune-related adverse events generated by anti-programmed death (ligand)PD-(L)1 therapies. *Eur J Cancer*. 2020;129:71–79. https://doi.org/10.1016/J.EJCA.2020.01.013.
10 Jing Y, Zhang Y, Wang J, et al. Association between sex and immune-related adverse events during immune checkpoint inhibitor therapy. *J Natl Cancer Inst*. 2021;113(10):1396–1404. https://doi.org/10.1093/jnci/djab035.
11 Roth P, Winklhofer S, Müller AMS, et al. Neurological complications of cancer immunotherapy. *Cancer Treat Rev*. 2021;97:102189. https://doi.org/10.1016/j.ctrv.2021.102189.
12 Perrinjaquet C, Desbaillets N, Hottinger AF. Neurotoxicity associated with cancer immunotherapy: immune checkpoint inhibitors and chimeric antigen receptor T-cell therapy. *Curr Opin Neurol*. 2019;32. https://doi.org/10.1097/WCO.0000000000000686.
13 Seki M, Kitano S, Suzuki S. Neurological disorders associated with immune checkpoint inhibitors: an association with autoantibodies. *Cancer Immunol Immunother*. 2022;71(4):769–775. https://doi.org/10.1007/s00262-021-03053-9.
14 Johnson DB, Manouchehri A, Haugh AM, et al. Neurologic toxicity associated with immune checkpoint inhibitors: a pharmacovigilance study. *J Immunother Cancer*. 2019;7(1). https://doi.org/10.1186/S40425-019-0617-X.
15 Spain L, Walls G, Julve M, et al. Neurotoxicity from immune-checkpoint inhibition in the treatment of melanoma: a single centre experience and review of the literature. *Ann Oncol*. 2017;28(2):377–385. https://doi.org/10.1093/ANNONC/MDW558.
16 Larkin J, Chmielowski B, Lao CD, et al. Neurologic serious adverse events associated with nivolumab plus ipilimumab or nivolumab alone in advanced melanoma, including a case series of encephalitis. *Oncologist*. 2017;22(6):709–718. https://doi.org/10.1634/THEONCOLOGIST.2016-0487.
17 Robert C, Ribas A, Wolchok JD, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. *Lancet*. 2014;384(9948):1109–1117. https://doi.org/10.1016/S0140-6736(14)60958-2.
18 Sisi M, Fusaroli M, De Giglio A, et al. Psychiatric adverse reactions to anaplastic lymphoma kinase inhibitors in non-small-cell lung cancer: analysis of spontaneous reports submitted to the FDA adverse event reporting system. *Targeted Oncol*. 2022;17(1):43–51. https://doi.org/10.1007/s11523-021-00865-8.
19 Li H, Sun X, Sun D, et al. Thromboembolic events associated with immune checkpoint inhibitors: a real-world study of data from the food and drug administration adverse event reporting system (FAERS) database. *Int Immunopharmacol*. 2021;98. https://doi.org/10.1016/j.intimp.2021.107818.
20 Caster O, Aoki Y, Gattepaille LM, Grundmark B. Disproportionality analysis for pharmacovigilance signal detection in small databases or subsets: recommendations for limiting false-positive associations. *Drug Saf*. 2020;43(5):479–487. https://doi.org/10.1007/s40264-020-00911-w.
21 Rothman KJ, Lanes S, Sacks ST. The reporting odds ratio and its advantages over the proportional reporting ratio. *Pharmacoepidemiol Drug Saf*. 2004;13(8):519–523. https://doi.org/10.1002/pds.1001.
22 Sakaeda T, Kadoyama K, Okuno Y. Statin-associated muscular and renal adverse events: data mining of the public version of the FDA adverse event reporting system. *PLoS One*. 2011;6(12):e28124. https://doi.org/10.1371/journal.pone.0028124.
23 Bate A, Evans SJW. Quantitative signal detection using spontaneous ADR reporting. *Pharmacoepidemiol Drug Saf*. 2009;18(6):427–436. https://doi.org/10.1002/pds.1742.
24 Yan YD, Zhao Y, Zhang C, et al. Toxicity spectrum of immunotherapy in advanced lung cancer: a safety analysis from clinical trials and a pharmacovigilance system. *eClinicalMedicine*. 2022;50:101535. https://doi.org/10.1016/j.eclinm.2022.101535.
25 Cirmi S, El Abd A, Letinier L, Navarra M, Salvo F. Cardiovascular toxicity of tyrosine kinase inhibitors used in chronic myeloid leukemia: an analysis of the FDA adverse event reporting system database (FAERS). *Cancers*. 2020;12(4). https://doi.org/10.3390/cancers12040826.
26 Goldman MJ, Craft B, Hastie M, et al. Visualizing and interpreting cancer genomics data via the Xena platform. *Nat Biotechnol*. 2020;38(6):675–678. https://doi.org/10.1038/s41587-020-0546-8.
27 Wagner GP, Kin K, Lynch VJ. Measurement of mRNA abundance using RNA-seq data: RPKM measure is inconsistent among samples. *Theory Biosci*. 2012;131(4):281–285. https://doi.org/10.1007/s12064-012-0162-3.

28 Hänzelmann S, Castelo R, Guinney J. GSVA: gene set variation analysis for microarray and RNA-Seq data. *BMC Bioinformatics*. 2013;14(1):7. https://doi.org/10.1186/1471-2105-14-7.

29 Subramanian A, Tamayo P, Mootha VK, et al. Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proc Natl Acad Sci U S A*. 2005;102(43):15545–15550. https://doi.org/10.1073/pnas.0506580102.

30 Barbie DA, Tamayo P, Boehm JS, et al. Systematic RNA interference reveals that oncogenic KRAS-driven cancers require TBK1. *Nature*. 2009;462(7269):108–112. https://doi.org/10.1038/nature08460.

31 Jing Y, Liu J, Ye Y, et al. Multi-omics prediction of immune-related adverse events during checkpoint immunotherapy. *Nat Commun*. 2020;11(1):1–7. https://doi.org/10.1038/s41467-020-18742-9.

32 Zhou C, Lin A, Zhang J, Luo P. MOAHIT: a web tool for visualizing tumor multi-omics data with human anatomy heatmaps. *bioRxiv*. 2022. https://doi.org/10.1101/2022.09.07.506938.

33 von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370(9596):1453–1457. https://doi.org/10.1016/S0140-6736(07)61602-X.

34 Kessler RC, Berglund PA, Chiu WT, et al. The prevalence and correlates of binge eating disorder in the World Health Organization World Mental Health Surveys. *Biol Psychiatry*. 2013;73(9):904–914. https://doi.org/10.1016/j.biopsych.2012.11.020.

35 Takayama S, Arita R, Ishii T. Case report: prolonged anorexia with nausea caused by immune checkpoint inhibitors for malignant melanoma treated using Kampo medicines bukuryoingohangekobokuto and Ninjin'yoeito. *Front Pharmacol*. 2022;13:870823. https://doi.org/10.3389/fphar.2022.870823. Switzerland.

36 Eriksson C, Eriksson G, Johansson U, Guidetti S. Occupational therapists' perceptions of implementing a client-centered intervention in close collaboration with researchers: a mixed methods study. *Scand J Occup Ther*. 2020;27(2):142–153. https://doi.org/10.1080/11038128.2019.1573917.

37 Rai D, Garg RK, Malhotra HS, et al. Acute confusional state/delirium: an etiological and prognostic evaluation. *Ann Indian Acad Neurol*. 2014;17(1):30–34. https://doi.org/10.4103/0972-2327.128541.

38 Wanchoo R, Karam S, Uppal NN, et al. Adverse renal effects of immune checkpoint inhibitors: a narrative review. *Am J Nephrol*. 2017;45(2):160–169. https://doi.org/10.1159/000455014.

39 Wanchoo R, Sakhiya V, Jhaveri KD. Immune checkpoint inhibitor-associated electrolyte disorders: query of the food and drug administration adverse event reporting system. *Kidney Int*. 2021;100(4):945–947. https://doi.org/10.1016/j.kint.2021.06.001. United States.

40 Kähler KC, Hassel JC, Heinzerling L, et al. Management of side effects of immune checkpoint blockade by anti-CTLA-4 and anti-PD-1 antibodies in metastatic melanoma. *J Dtsch Dermatol Ges*. 2016;14(7):662–681. https://doi.org/10.1111/DDG.13047.

41 Conry RM, Sullivan JC, Nabors LB. Ipilimumab-induced encephalopathy with a reversible splenial lesion. *Cancer Immunol Res*. 2015;3:598. https://doi.org/10.1158/2326-6066.CIR-15-0035.

42 Maur M, Tomasello C, Frassoldati A, Dieci MV, Barbieri E, Conte PF. Posterior reversible encephalopathy syndrome during ipilimumab therapy for malignant melanoma. *J Clin Oncol*. 2012;30(6). https://doi.org/10.1200/JCO.2011.38.7886.

43 Pitman A, Suleman S, Hyde N, Hodgkiss A. Depression and anxiety in patients with cancer. *BMJ*. 2018;361:k1415. https://doi.org/10.1136/bmj.k1415.

44 Huang X, Tian T, Zhang Y, Zhou S, Hu P, Zhang J. Age-associated changes in adverse events arising from anti-PD-(L)1 therapy. *Front Oncol*. 2021;11:619385. https://doi.org/10.3389/fonc.2021.619385.

45 Skoog I. Psychiatric disorders in the elderly. *Can J Psychiatry*. 2011;56(7):387–397. https://doi.org/10.1177/070674371105600702.

46 Martins F, Sofiya L, Sykiotis GP, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. *Nat Rev Clin Oncol*. 2019;16(9):563–580. https://doi.org/10.1038/S41571-019-0218-0.

47 Naidoo J, Page DB, Li BT, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Ann Oncol*. 2015;26(12):2375–2391. https://doi.org/10.1093/ANNONC/MDV383.

48 Kurokawa K, Mitsuishi Y, Shimada N, et al. Association between the efficacy and immune-related adverse events of pembrolizumab and chemotherapy in non-small cell lung cancer patients: a retrospective study. *BMC Cancer*. 2022;22(1):1047. https://doi.org/10.1186/s12885-022-10133-1.

49 Wang M, Liang H, Wang W, et al. Immune-related adverse events of a PD-L1 inhibitor plus chemotherapy versus a PD-L1 inhibitor alone in first-line treatment for advanced non-small cell lung cancer: a meta-analysis of randomized control trials. *Cancer*. 2021;127(5):777–786. https://doi.org/10.1002/cncr.33270.

50 Petereit C, Zaba O, Teber I, Lüders H, Grohé C. A rapid and efficient way to manage hyponatremia in patients with SIADH and small cell lung cancer: treatment with tolvaptan. *BMC Pulm Med*. 2013;13(55). https://doi.org/10.1186/1471-2466-13-55.

51 Madhusoodanan S, Ting MB, Farah T, Ugur U. Psychiatric aspects of brain tumors: a review. *World J psychiatry*. 2015;5(3):273. https://doi.org/10.5498/WJP.V5.I3.273.

52 Hoseth EZ, Krull F, Dieset I, et al. Attenuated Notch signaling in schizophrenia and bipolar disorder. *Sci Rep*. 2018;8(1). https://doi.org/10.1038/S41598-018-23703-W.

53 Dias BG, Goodman JV, Ahluwalia R, Easton AE, Andero R, Ressler KJ. Amygdala-dependent fear memory consolidation via miR-34a and Notch signaling. *Neuron*. 2014;83(4):906–918. https://doi.org/10.1016/j.neuron.2014.07.019.

54 Radtke F, MacDonald HR, Tacchini-Cottier F. Regulation of innate and adaptive immunity by Notch. *Nat Rev Immunol*. 2013;13(6):427–437. https://doi.org/10.1038/nri3445.

55 Lankoff A, Brzoska K, Czarnocka J, et al. A comparative analysis of in vitro toxicity of diesel exhaust particles from combustion of 1st- and 2nd-generation biodiesel fuels in relation to their physicochemical properties-the FuelHealth project. *Environ Sci Pollut Res Int*. 2017;24(23):19357–19374. https://doi.org/10.1007/s11356-017-9561-9.

56 Südhof TC. Neuroligins and neurexins link synaptic function to cognitive disease. *Nature*. 2008;455(7215):903–911. https://doi.org/10.1038/nature07456.

57 Galstyan A, Markman JL, Shatalova ES, et al. Blood-brain barrier permeable nano immunoconjugates induce local immune responses for glioma therapy. *Nat Commun*. 2019;10(1):3850. https://doi.org/10.1038/s41467-019-11719-3.

58 Tian T, Liang R, Erel-Akbaba G, et al. Immune checkpoint inhibition in GBM primed with radiation by engineered extracellular Vesicles. *ACS Nano*. 2022;16(2):1940–1953. https://doi.org/10.1021/acsnano.1c05505.