Drug-Induced QT Prolongation and Torsade de Pointes in Spontaneous Adverse Event Reporting: A Retrospective Analysis Using the Japanese Adverse Drug Event Report Database (2004–2021)

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Accepted: 9 August 2022 / Published online: 22 August 2022
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Abstract

Background Drugs with new mechanisms of action are continually being developed, but it is difficult to capture whether a drug induces QT prolongation/torsade de pointes (TdP) in preclinical and preapproval clinical trials.

Objective To evaluate drugs associated with drug-induced QT prolongation/TdP using a real-world database in Japan.

Patients and methods A search was performed in the Japanese Adverse Drug Event Report (JADER) database for QT prolongation and TdP. The reporting odds ratio (ROR) was calculated to identify potential drug-induced QT prolongation/TdP association.

Results Among the reported 4,326,484 data entries, 3410 patients exhibited QT prolongation/TdP (2707 with QT prolongation, 703 with TdP) with the suspected drugs. Of these patients, 53.9% were females. The highest occurrence was in the 70- to 79-year-old age group (24.7%). The most common types of drugs involved were cardiovascular drugs, central nervous system (CNS) drugs, anticancer drugs, and anti-infective drugs; the rate of overdose was reportedly very low at 1.6%. The highest adjusted RORs were observed for nifekalant (351.41, 95% confidence interval (CI) 235.85–523.59), followed by vandetanib (182.55, 95% CI 108.11–308.24), evocalcet (181.59, 95% CI 132.96–248.01), bepridil (160.37, 95% CI 138.17–186.13), diarsenic trioxide (79.43, 95% CI 63.98–98.62), and guanfacine (78.29, 95% CI 58.51–104.74). Among the drugs launched in Japan during the last decade, vandetanib had the highest adjusted RORs.

Conclusions This study using the JADER database showed that antiarrhythmic drugs, calcium-sensing receptor agonists, small-molecule targeted anticancer drugs, and CNS drugs are associated with QT prolongation/TdP. Further pharmacoepidemiological studies, such as cohort studies using large databases, are needed to prove these causal relationships.

1 Introduction

An adverse drug reaction (ADR) is defined as an unwanted or unintended adverse event (AE) that occurs in a patient who receives a certain drug and for which a causal relationship with the drug is evident. Torsade de pointes (TdP) is a polymorphic ventricular tachycardia associated with QT prolongation, resulting in a cardiac ADR; this causes syncope due to the disruption of hemodynamics and can lead to the development of ventricular fibrillation, causing sudden cardiac death [1]. Because the main pharmacological effect of antiarrhythmic drugs is the suppression of cardiac repolarization, the risk of QT prolongation is high. Thus, this must be carefully managed in clinical practice. In addition, it is important to note that this serious proarrhythmic reaction occurs during treatment with non-antiarrhythmic drugs. Therefore, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) issued two guidance documents on the nonclinical (S7B)
and clinical (E14) evaluation of cardiac risk in 2005 [2, 3]; notably, the number of TdP cases caused by marketed drugs with proarrhythmic effects or new drugs remains high, as reported in the literature.

Regarding pharmacovigilance in postmarketing situations, the presence or absence of a causal relationship and its strength can be evaluated by collecting a large number of AE cases and analyzing them using pharmacoepidemiological methods. Therefore, it is necessary to collect a large number of AE cases to clarify causal relationships. As a result of this need, many countries have established spontaneous AE reporting systems to detect unknown AEs, and case reports of suspected ADRs on a national level have been collected through the use of these systems. In Japan, as in other countries, the Pharmaceuticals and Medical Devices Agency (PMDA) has established the Japanese Adverse Drug Event Reporting (JADER) database, and domestic AE reports that are currently available to the public are those provided to the PMDA by manufacturers and medical institutions since April 2004.

Although many drugs with new mechanisms of action are being developed, it is difficult to capture whether a drug induces TdP in preclinical and preapproval clinical trials. Therefore, such infrequent AEs are often detected after a drug is marketed and used in a large number of patients. The use of spontaneous report databases can be useful in identifying such cases. In Japan, as in other countries, a spontaneous report database, the JADER database, is used for drug safety monitoring. This study aimed to investigate drugs associated with QT prolongation/TdP using the JADER database in Japan.

2 Methods

2.1 Data Sources

Information from the JADER database between April 2004 and October 2021 was used in this study. The JADER database compiles domestic AE reports provided to the PMDA by manufacturers and medical institutions and consists of the following four data tables [4]: the patient demographic information (DEMO) table, drug information (DRUG) table, adverse events (REAC) table, and primary disease (HIST) table. The DEMO table specifies the sex and age of patients. The DRUG table provides the drug name, dose, reason for use, and administration duration. The REAC table provides AEs, the results, and date of AE occurrence. The HIST table provides information on a patient’s underlying disease.

2.2 Data Extraction and Analysis

The DRUG table describes the involvement of the drug: all drugs classified as ‘suspected drugs,’ ‘interacting drugs,’ and ‘concomitant drugs’ were analyzed in this study. We counted the number of occurrences of QT prolongation and TdP from all the drugs reported with the same ID. In the JADER database, an AE is coded according to the terminology of preferred terms in the Japanese version 25.0 of the ICH Medical Dictionary for Regulatory Activities Japanese Maintenance Organization (MedDRA/J V25.0).

A standardized MedDRA Query (SMQ) was used to identify cases of QT prolongation and TdP: ‘Torsade de pointes/QT prolongation (SMQ code: 20000001).’ A search was performed in the JADER database for all AEs mapped to ‘Electrocardiogram QT Prolonged,’ ‘QT prolongation,’ and ‘Torsade de Pointes’ from April 2004 to October 2021. After removing duplicate data, only suspected cases of QT prolongation and TdP were extracted.

Disproportionality analysis was performed by case-non-case methodology based on the reporting odds ratio (ROR) and its 95% confidence interval (CI) [5]. The ROR was calculated by involving the whole database. ‘Cases’ were defined as the reported suspected cases of QT prolongation and TdP, while ‘Non-cases’ were defined as the other reported AEs. The RORs were calculated by univariate logistic regression analysis with each occurrence of QT prolongation and TdP as the objective variable and the use of the drug as the explanatory variable. Adjusted RORs were calculated by multivariate logistic regression analysis with sex, age, and underlying diseases as patient background variables that may be confounders in investigating the relationship between QT prolongation/TdP and medications. The presence of underlying disease as a risk factor for the development of QT prolongation/TdP was defined as ‘arrhythmia,’ ‘ventricular arrhythmia,’ ‘tachyarrhythmia,’ ‘supraventricular arrhythmia,’ ‘paroxysmal arrhythmia,’ ‘sinus arrhythmia,’ ‘nodal arrhythmia,’ ‘bradyarrhythmia,’ ‘ventricular tachyarrhythmia,’ ‘supraventricular tachyarrhythmia,’ ‘fetal arrhythmia,’ ‘fetal tachyarrhythmia,’ ‘arrhythmic storm,’ ‘proarrhythmic prevention,’ and ‘arrhythmogenic right ventricular dysplasia.’ A signal was considered when the lower limit of the 95% CI of the ROR exceeded 1.

Since it is difficult to compare drugs with very few reports, only drugs with a total of ten or more reports with the combination of QT prolongation and TdP were included in the analysis, and drugs that have been on the market for less than the last 10 years in Japan were included to make comparisons between more recent drugs.
drug-induced QT prolongation and 


dose exceeded the recommendation listed on the dosage and administration package insert of each drug. All missing values and blank data were treated as ‘Not specified.’ The distribution of the general characteristics of patients for each item was evaluated by Pearson’s Chi-square test. ‘Not specified’ data were excluded and tested. Analyses were conducted using JMP® 16.2.0 (SAS Institute Inc., Cary, NC, USA).

3 Results

Of the 4,326,484 total data entries reported in the JADER database from April 2004 to October 2021 in the JADER, 4115 QT prolongation and TdP cases were extracted as ‘suspect drug,’ ‘concomitant drug,’ or ‘interacting drug,’ including 2754 QT prolongation cases, 459 TdP cases, 409 QT prolongation and TdP cases, and 493 active substances.

Table 1 shows the general characteristics of the patients included in the dataset for the suspected drugs. The 3410 ADR data entries of the suspected drugs consisted of 2707 QT prolongation cases, 703 TdP cases, and 230 QT prolongation and TdP cases. Of the 3410 total reports, 230 included both QT prolongation and TdP reports. These data also included one report of two QT prolongation cases and one TdP case and one report of two QT prolongation cases. A total of 53.9% of the patients were females and 41.4% were males. The sex of 4.7% of the patients was unknown. The age of the patients ranged from birth to over 100 years. The highest occurrence was in the 70- to 79-year-old age group (24.7%), followed by the 60- to 69-year-old age group (17.9%) and the 80- to 89-year-old age group (16.3%). In the JADER database, there were patients whose ages were listed under ‘infants, youth, and elderly’ in addition to the age group. Since these patients could not be incorporated into the appropriate age group because the exact age group was not known, they were tabulated as ‘infants, youth, and elderly’ as described.

Regarding the dose, 1.6% of cases were deemed to be overdoses, which was considered to be relatively low. These ADRs were more common in cases with standard doses (59.9%), not overdoses (1.6%). When ADRs occurred, dose discontinuation (53.1%) was common, while dose reduction was infrequent (5.9%); some ADRs had no dose changes (8.6%) or dose escalation (2.3%). Approximately 67.7% of these cases were nonserious, showing recovery or mild resolution, while life-threatening serious events included 0.8% of cases with sequelae, 4.7% with no recovery, and 1.8% with death.

Table 2 shows the types of reports and reporters of the cases included in the dataset for the suspected drugs. Approximately 80% of the types of AE reports were

| General characteristics of patients included in the dataset for the suspected drugs | n   | %    | p value 1 |
|---------------------------------|-----|------|-----------|
| No. of patients                 | 3178|      |           |
| No. of reported AEs             | 3410|      |           |
| QT prolongation                 | 2707| 79.4 |           |
| TdP                             | 703 | 20.6 | <0.0001   |
| Gender                          |     |      |           |
| Male                            | 1316| 41.4 |           |
| Female                          | 1713| 53.9 | <0.0001   |
| Not specified                   | 149 | 4.7  |           |
| Age, years 2                    |     |      |           |
| < 10                            | 71  | 2.2  |           |
| ≥ 10 to < 20                    | 107 | 3.4  |           |
| ≥ 20 to < 30                    | 92  | 2.9  |           |
| ≥ 30 to < 40                    | 150 | 4.7  |           |
| ≥ 40 to < 50                    | 235 | 7.4  |           |
| ≥ 50 to < 60                    | 372 | 11.7 |           |
| ≥ 60 to < 70                    | 569 | 17.9 |           |
| ≥ 70 to < 80                    | 785 | 24.7 |           |
| ≥ 80 to < 90                    | 518 | 16.3 |           |
| ≥ 90                            | 56  | 1.8  | <0.0001   |
| Infant                          | 10  | 0.3  |           |
| Youth                           | 5   | 0.2  |           |
| Adult                           | 32  | 1.0  |           |
| Elderly                         | 31  | 1.0  |           |
| Not specified                   | 145 | 4.6  |           |
| Dosage information              |     |      |           |
| Usual dosage                    | 2045| 59.9 |           |
| Overdose                        | 56  | 1.6  | <0.0001   |
| Not specified                   | 1313| 38.5 |           |
| Treatment for AEs               |     |      |           |
| Discontinuation                 | 1812| 53.1 |           |
| Dose reduction                  | 200 | 5.9  |           |
| Dose escalation                 | 78  | 2.3  |           |
| No change in dosage             | 294 | 8.6  | <0.0001   |
| Not specified                   | 1030| 30.2 |           |
| Outcome                         |     |      |           |
| Death                           | 63  | 1.8  |           |
| Serious (sequelae, unrecovered) | 188 | 5.5  |           |
| Non-serious                     | 2310| 67.7 | <0.0001   |
| Not specified                   | 853 | 25.0 |           |

1 p value indicates Pearson’s Chi-square test. ‘Not specified’ was excluded and tested

AE adverse drug event, TdP torsade de pointes

2Of the 3410 total reports (2707 QT prolongation cases, 703 TdP cases), there were 230 reports of both QT prolongation and TdP, one report of two QT prolongation cases and one TdP case, and one report of two QT prolongation cases

3Infant, Youth, Adult, and Elderly were also excluded from the age group analysis
spontaneous reports by healthcare professionals, and fewer than 20% were reported in clinical trials. The reporters were mainly physicians, pharmacists, and healthcare professionals (88.5%). In the number of reported cases, the most common types of drugs involved were cardiovascular drugs (890 cases), central nervous system (CNS) drugs (764 cases), and anticancer drugs (762 cases), followed by anti-infective drugs (416 cases), metabolic and endocrine drugs (135 cases), anesthetics (114 cases), nephrological and urological drugs (29 cases), Chinese herbal medicines (so-called Kampo, 22 cases), and respiratory drugs (21 cases).

Table 3 shows the drugs associated with QT prolongation/TdP that were ranked according to their adjusted RORs. The highest adjusted RORs for QT prolongation/TdP were observed for nifekalant (antiarrhythmic drug), followed by vandetanib (small-molecule targeted anticancer drug), evocalcet (calcium-sensing receptor agonist), bepridil (antiarrhythmic drug), diarsenic trioxide (anticancer drug), and guanfacine (CNS drug). Other major drugs included disopyramide and amiodarone (antiarrhythmic drugs), clarithromycin and levofloxacin (anti-infective drugs), sevoflurane (anesthetic), nilotinib, gilteritinib, and osimertinib (small-molecule targeted anticancer drugs), methadone and donepezil (CNS drug), anagrelide (antimetabolic anticancer drug), cinacalcet (calcium-sensing receptor agonist), and famotidine (gastrointestinal drug).

Drugs associated with QT prolongation/TdP, particularly those launched in Japan during the last decade, are shown in Table 4. Vandetanib (small-molecule targeted anticancer drug) had the highest ROR, followed by evocalcet (calcium-sensing receptor agonist), guanfacine (CNS drug), and methadone (CNS drug). Other major drugs included nilotinib, gilteritinib, osimertinib, crizotinib, and carfilzomib (small-molecule targeted anticancer drugs), venlafaxine, olanzapine, and aripiprazole (CNS drugs), anagrelide (antimetabolic anticancer drug) and cinacalcet (calcium-sensing receptor agonist).

### Table 2

| Type of report | n  | %  | p value<sup>1</sup> |
|---------------|----|----|---------------------|
| Spontaneous report | 2707 | 79.3 | |
| Clinical trial | 621 | 18.2 | |
| Other | 85 | 2.5 | <0.0001 |
| Not specified<sup>2</sup> | 1 | 0.0 | |
| Type of reporter | | | |
| Physician | 2354 | 69.0 | |
| Pharmacist | 314 | 9.2 | |
| Physician/pharmacist | 147 | 4.3 | |
| Physician/healthcare professional | 9 | 0.3 | |
| Physician/healthcare professional/consumer, etc. | 3 | 0.1 | |
| Physician/unknown | 1 | 0.0 | <0.0001 |
| Pharmacists, etc. | 6 | 0.2 | |
| Physician/consumer, etc. | 82 | 2.4 | |
| Pharmacists, etc. | 28 | 0.8 | |
| Consumers, etc. | 18 | 0.5 | |
| Physician/unknown | 1 | 0.0 | |
| Not specified<sup>2</sup> | 233 | 6.8 | |

<sup>1</sup>p value indicates Pearson’s Chi-square test
<sup>2</sup>‘Not specified’ was excluded and tested
The RORs for small molecule-targeted anticancer drugs, calcium-sensing receptor agonists, and CNS drugs were particularly high among those of drugs launched in the past decade.

Drug-induced QT prolongation/TdP is caused by high doses and high blood levels of a drug, but they are not always defined by the dose or blood level alone. Sex,
advanced age, bradycardia, electrolyte imbalance (such as hypokalemia and hypomagnesemia), heart failure, etc., are exacerbating factors [6]. In this study, the majority of reported patients were elderly individuals (aged 60–89 years). A recent large Swedish cohort study showed that the incidence of drug-induced TdP was higher in the elderly age group than in the younger age group [7]. In the elderly age group, the 70- to 79-year-old age group was most frequently reported in the JADER database. The highest frequency of drug use in this age group in Japan may be related to this result [8]. Women are known to be more susceptible to drug-induced QT prolongation and TdP than men, which may be attributed to the sex hormone regulation of ion channels [9]. In this study, women were shown to be more prone to drug-induced QT prolongation and TdP than men (53.9% vs. 41.4%), which is consistent with other reports [10, 11].

Cardiovascular drugs, especially antiarrhythmic drugs, have long appeared to be representative of drugs that cause cardiotoxicity. As such, patients and medical personnel have been warned of their risks and proper use by academic societies and medical practice guidelines in Japan [12–14]. More recently, concerns about QT prolongation, arrhythmic death, and sudden cardiac death have increased, especially for antiarrhythmic drugs. Thus, preventive measures, such as the use of therapeutic drug monitoring and electrocardiogram monitoring, have been implemented to prevent AEs [12]. Furthermore, it should be noted that patients who are prone to AEs may be treated in an alternative manner that does not use high-risk drugs. Thus, although the number of AEs appears to be decreasing when compared to prior years, the number of AEs reported with cardiovascular drugs is still higher than that of other pharmacological drug classes. It should be noted that these underlying diseases are more common in elderly individuals than in young individuals. These results were largely consistent with the US Food and Drug Administration Adverse Event Reporting System study by Fung et al. [15].

Antiarrhythmic drugs that have class III activity and inhibit outward potassium currents, such as nifekalant, bepridil, amiodarone, and disopyramide, prolong the QT interval. Nifekalant, a pure class III antiarrhythmic drug, has been approved only in Japan for the treatment of life-threatening VF or VT with structural heart disease and selectively blocks potassium channels, especially the rapid component of the delayed rectifier potassium current (Ikr) [16]. On the other hand, this pharmacological effect of nifekalant is likely to induce marked QT prolongation and TdP [17]. In Japan, bepridil is used as an antiarrhythmic drug because of its unique electrophysiological properties, which display a fast kinetic block of the inward sodium current, block several outward potassium currents, and inhibit sodium-calcium exchange [18, 19]. In Europe and North America, bepridil has been used as an anti-anginal drug. In particular, bepridil is widely used for persistent atrial fibrillation in Japan because of its effectiveness in the conversion of persistent atrial fibrillation to sinus rhythm [14]. However, bepridil has serious adverse effects, such as sudden cardiac death, TdP with QT prolongation, and excessive bradyarrhythmia [20].

Vandetanib, a multitarget tyrosine kinase inhibitor for the treatment of medullary thyroid carcinoma in Japan, is known to have a high risk of QT prolongation [21, 22]. In this study, vandetanib showed the second highest ROR in the JADER database, and this ADR was consistent with previous reports in other countries [23].

Evocalcet, a calcium-sensing receptor agonist developed in Japan, also showed a high ROR in this study. The package inserts and interview form for evocalcet (Orkeda® tablets) mention QT prolongation (0.6%), and three cases have been reported in clinical trials in Japan [24]. This description was established to alert the public to the fact that hypocalcemia was observed in clinical studies in Japan and that QT prolongation is a possible symptom based on hypocalcemia. In this study, the high frequency of drug-induced QT prolongation/TdP due to anticancer drugs was considered to be a novel feature. One reason for this may be related to the fact that the study by Fung et al. [15] was based on an older AE spontaneous report survey from 1969–1998, whereas our results included more recently marketed anticancer drugs with newer mechanisms of action; thus, the types of drugs and their uses differed substantially from those reviewed by Fung et al. [15]. The risk of QT prolongation with arsenic trioxide, which is used to treat acute promyelocytic leukemia, is well known to be the most relevant [25, 26]. It is also known that QT prolongation/TdP can occur with small-molecule targeted anticancer drugs including tyrosine kinase inhibitors (e.g., nilotinib, gilteritinib, Osimertinib, and crizotinib) and proteasome inhibitors (e.g., carfilzomib) [21, 27]. As many anticancer drugs with new mechanisms have been developed in recent years, such as antineoplastic monoclonal antibodies and protein kinase inhibitors, there has been an increase in their use [28]; this may be an explanation for the number of patients who experienced QT prolongation/TdP who were also being treated with anticancer drugs.

Psychiatric drugs, antimicrobials, and neuroleptics have been implicated in predisposing patients to TdP associated with QT prolongation [29]. In this study, donepezil (acetylcholinesterase inhibitor for the treatment of Alzheimer’s disease), clarithromycin (macrolide anti-infective drug), levofloxacin (fluoroquinolone anti-infective drug), and aripiprazole (antipsychotic for the treatment of schizophrenia), which were developed and are widely used in Japan, had significant RORs for QT prolongation/TdP. Moreover, the ROR was also significant for Chinese herbal medicines. The exact mechanism of this cause is unknown.
but it is possible that an ingredient in Chinese herbal medicines induced hypokalemia, leading to QT prolongation [30].

Of particular note is the possibility that postmarketing safety measures, such as postmarketing surveillance and all-case surveillance (postmarketing surveillance of all patients who receive the anticancer drug), may have affected the number of reported cases of anticancer drugs. It should also be noted that the incidence rate cannot be calculated because these reported cases included patients who experienced QT prolongation/TdP, and the number of patients who received the drug but did not experience side effects cannot be ascertained. While there is less experience with their use, including years of administration, more interest in these newer drugs makes it easier to gather information on their AEs.

On the other hand, there is a limitation to this study in that the risk stratification method was not sufficient, and the prescribing physicians were often not cardiologists, which may have led to an underestimation of the actual situation; AEs may have been missed or AEs may have been detected later without prior knowledge. These AEs were more common in cases with standard doses, not overdoses, and when AEs did occur, the drug was discontinued in half of the cases. In addition, approximately 7% of these side effects were serious, causing death or sequelae. However, these are likely to be lethal cases and represent important findings. Approximately 80% of the types of AE reports were spontaneous reports by healthcare professionals including physicians and pharmacists, and less than 20% were reported in clinical trials.

Investigating AE reports using the JADER database is clinically important because it covers drugs approved in Japan, including drugs developed and widely used in the country, and would recognize the risk of QT prolongation/TdP for drugs used in accordance with the approved dosage and administration in Japan. This method would also inform physicians of the monitoring necessary for safe and appropriate treatment.

4.1 Study Limitations

A limitation of this study is that the database used is a spontaneous report database: (1) The number of all patients who received each drug cannot be ascertained in this database, and the frequency of occurrence of each AE type by patient cannot be calculated. (2) The number of reports is variable, depending on the level of interest of the reporter. (3) There are many missing values for each of the reported items. (4) The QT prolongation/TdP cases included in this study cannot accurately capture patients who died before being transported to the hospital. Therefore, this study is likely to underestimate the true number of QT prolongation/TdP patients, as many patients may not survive an episode before they reach the hospital. Finally, these data include several reporting biases, such as the Weber effect, notoriety bias, and the ripple effect, because of the AE reporting database. (5) The data used are not widely collected, including patient reports. A system allowing patients to directly report AEs has been in operation in Japan since March 2019, but the number of AE reports from patients is still low, probably due to the system’s short history and a lack of public acceptance. Most of the data used in this study were accumulated prior to the establishment of a system of reporting AEs directly by patients.

5 Conclusions

This study using the JADER database showed that the majority of reported patients were elderly individuals (aged 60–89 years) and female, and that antiarrhythmic drugs, calcium-sensing receptor agonists, small-molecule targeted anticancer drugs, and CNS drugs are associated with QT prolongation/TdP. However, these results should be evaluated with caution because information for all patients who took each drug in Japan is not available in the JADER database. Further investigations are needed regarding the association between anticancer agents and QT prolongation/TdP.

Declarations

Funding This research received no grants from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest T.S. has received lecture fees from AstraZeneca, Bayer, Bristol-Myers Squibb, Daichi-Sanken, and Ono Pharmaceutical and has received grant support from Daichi-Sanken and Ono Pharmaceutical. M.U. and M.H. have no conflicts of interest to declare.

Ethics approval Information on all cases retrieved from the JADER database of individual case safety reports is deidentified, and ethical approval is not needed.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and materials The dataset used in this study is publicly available at the following URL: https://www.pmda.go.jp/safety/info-services/drugs/adr-info/suspected-adr/0003.html.

Code availability Not applicable.

Author contributions MU and TS conceived of and designed the study. MU and MH investigated and analyzed the data. MU and MH drafted the manuscript. TS reviewed the manuscript and supervised the work. All authors read and approved the final manuscript.
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