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A Real-world Study of the Adverse Effects of Tizanidine Based on Mining the FAERS Database

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Abstract: *Objective*: Tizanidine is a medication commonly used to relieve muscle spasms and has a wide range of clinical applications. However, as its use has increased, reports of related adverse reactions have also risen. In-depth analysis of tizanidine's adverse reaction patterns and potential safety risks through data mining is of great significance for guiding clinical decision-making and patient management. *Methods*: This study is based on the FAERS database, retrieving data from 2004 Q1 to 2025 Q1. The primary suspect drug was grouped, and the proportional imbalance method (ROR method) was used for signal detection of adverse drug events. *Results*: The adverse reactions of tizanidine are diverse and involve multiple systems, with nervous system diseases being the most common type of adverse event, accounting for 16.18% of the total reports. The proportion of adverse events reported by female and elderly patients is relatively high, and in terms of the outcome of adverse events, the proportion of hospitalizations is high, accounting for 30.31%, indicating a significant likelihood that tizanidine's adverse events require hospitalization. Additionally, hypotension, drowsiness, drug ineffectiveness, and completed suicide are common adverse events, suggesting that the medication can cause significant central nervous system, cardiovascular, and mental health-related issues during its use. Signal mining using the ROR method shows high ROR values for adverse events such as potassium-losing nephropathy and decerebrate rigidity, indicating a potential causal relationship with tizanidine usage. Furthermore, the median time to the occurrence of adverse events after administration is 3 days, revealing that tizanidine-related adverse events often manifest shortly after administration, particularly within the first few days. *Conclusion*: The potential adverse reactions of tizanidine in clinical use, particularly those related to the nervous system, mental health, and cardiovascular aspects, warrant significant attention. Enhanced drug safety monitoring, especially individualized treatment and close monitoring in high-risk patient groups, can maximize the safety of medication use.

Keywords: Tizanidine; FAERS; Adverse reactions; Signal mining; ROR

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1. Background

Tizanidine is an α_2 adrenergic receptor agonist widely used clinically to alleviate skeletal muscle spasms and other symptoms [1]. With the expansion of its clinical application and the increasing number of users, reports of its adverse events have gradually attracted attention [2]. Although traditional clinical trials can reveal adverse reactions to the drug to a certain extent, they may not fully cover the adverse reactions of the drug in the real world due to the strict control of the trial environment, relatively limited sample sizes, and shorter study periods. The FAERS database, as an important source of real-world data, collects a large number of spontaneous reports on adverse drug events, with advantages such as large sample sizes and diverse populations. In the context of real-world research, a systematic analysis of tizanidine adverse event data in the FAERS database is expected to supplement and improve the existing understanding of the drug's safety. This can provide valuable data support for subsequent drug development improvements and updates to clinical medication guidelines, thereby promoting the in-depth development of pharmacoepidemiology and drug safety research, and ensuring the safety of medication for patients.

2. Data processing and statistical methods

2.1. Data source

The raw data were downloaded from the FAERS database on the official FDA website (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html). The data retrieval range for this study spans from 2004 Q1 to 2025 Q1.

2.2. Target drug

The drug of interest is identified by searching for BaseName_EN="TIZANIDINE".

2.3. Target population

Patients in the database whose primary suspected drug is the target drug are included in the target drug population, while other patients are included in the other drug population.

2.4. Data

Processing and analysis duplicates were removed according to the FDA's recommended de-duplication method. Statistical analysis was conducted using SAS 9.4.

2.5. Signal detection methods and calculation

The proportional reporting ratio (PRR) method was used for signal detection of adverse drug events. The reporting odds ratio (ROR) method was employed to detect adverse event signals.

3. Results

3.1. Basic characteristics of adverse event reports

Table 1 shows that reports from female patients accounted for 62.60% (1389 cases) of the total, males accounted for 27.36% (595 cases), and reports with unspecified gender accounted for 10.04% (218 cases), indicating room for improvement in data collection and reporting. In terms of age distribution, reports for patients under 18 years old

were few, comprising only 2.86% (67 cases). Reports from patients aged 18–64 were more numerous, with those aged 18–44 accounting for 19.25% (427 cases) and those aged 45–64 accounting for 29.34% (651 cases). Reports from patients aged 65 and above accounted for 14.40% (330 cases), but a significant proportion of reports (33.78%) had unspecified age (690 cases). From the perspective of the report year, the number of adverse event reports for Tizanidine has fluctuated annually since 2004, peaking in 2019 with 7.80% (167 cases) and followed closely by 2018 with 7.74% (166 cases). There has been a noticeable increase in reports since 2010, indicating the ongoing importance and continuity of monitoring this drug. Regarding the identity of reporters, consumers (Consumer) submitted the most reports, accounting for 31.55% (699 cases). This was followed by other health professionals (Other health professional) at 14.70% (326 cases), pharmacists (Pharmacist) at 21.70% (481 cases), and physicians (Physician) at 22.53% (483 cases). In terms of adverse event outcomes, hospitalization (Hospitalization: Initial or Prolonged) had a high proportion at 30.31% (658 cases), indicating a significant likelihood of requiring hospital treatment for adverse events related to Tizanidine. Life-threatening events (Life-threatening) were reported in 6.13% (133 cases), death in 1.40% (30 cases), and disability (Disability) in 2.32% (78 cases), reflecting the severity of certain adverse events.

Table 1. Characteristics of AEs reports

Characteristics	Case (%)
Sex	
Female (%)	1359 (62.60)
Male (%)	594 (27.36)
Not specified (%)	218 (10.04)
Age	
<18 (%)	62 (2.86)
18-44 (%)	426 (19.62)
45-64 (%)	637 (29.34)
≥65 (%)	356 (16.40)
Not specified (%)	690 (31.78)
Report year	
2004 (%)	105 (4.84)
2005 (%)	75 (3.45)
2006 (%)	53 (2.44)
2007 (%)	46 (2.12)
2008 (%)	54 (2.49)
2009 (%)	83 (3.82)
2010 (%)	80 (3.68)
2011 (%)	74 (3.41)
2012 (%)	57 (2.63)
2013 (%)	56 (2.58)
2014 (%)	103 (4.74)

Table 1 (Continued)

Characteristics	Case (%)
2015 (%)	131 (6.03)
2016 (%)	165 (7.60)
2017 (%)	103 (4.74)
2018 (%)	166 (7.65)
2019 (%)	125 (5.76)
2020 (%)	113 (5.20)
2021 (%)	150 (6.91)
2022 (%)	126 (5.80)
2023 (%)	113 (5.20)
2024 (%)	134 (6.17)
2025 (%)	59 (2.72)
Reporter	
Consumer (%)	685 (31.55)
Lawyer (%)	2 (0.09)
Not specified (%)	222 (10.23)
Other health professional (%)	308 (14.19)
Pharmacist (%)	471 (21.70)
Physician (%)	483 (22.25)
outcome	
Life-Threatening (%)	133 (6.13)
Hospitalization: Initial or prolonged (%)	658 (30.31)
Disability (%)	72 (3.32)
Death (%)	304 (14.00)
Congenital anomaly (%)	3 (0.14)
Required intervention to prevent permanent impairment/damage (%)	31 (1.43)
Other (%)	879 (40.49)

3.2. Proportion of adverse events by system organ class

As shown in **Figure 1**, nervous system disorders are the most common tizanidine-related adverse events, accounting for 16.18% (1417 cases) of the total reports. Special attention should be paid to related symptoms such as dizziness and drowsiness. General disorders and administration site conditions are the second most common category, accounting for 14.46% (1267 cases). Reports related to psychiatric disorders account for 12.28% (1076 cases), including hallucinations and depression. Adverse events related to investigations account for 8.32% (729 cases), suggesting that frequent health monitoring and laboratory tests may be necessary during the use of this medication. Injury, poisoning, and procedural complications account for 7.79% (682 cases), indicating that tizanidine may increase the risk of injury or poisoning complications, necessitating enhanced prevention and

monitoring. Gastrointestinal adverse events account for 6.31% (553 cases), showing that the use of tizanidine may cause gastrointestinal discomfort such as nausea and vomiting. Cardiac disorders-related adverse events account for 5.51% (483 cases), indicating that attention should be given to the drug's impact on the cardiovascular system, such as arrhythmias. Other relatively common adverse reactions include vascular disorders (4.59%, 402 cases), musculoskeletal and connective tissue disorders (4.34%, 380 cases), and respiratory disorders (3.04%, 266 cases). Less common adverse event categories include skin and subcutaneous tissue disorders (2.98%, 261 cases), renal and urinary disorders (1.87%, 164 cases), and eye disorders (1.82%, 159 cases). Although these events are less frequently reported, they still require attention. Even rarer adverse reactions, such as blood and lymphatic system disorders, ear and labyrinth disorders, and endocrine disorders, have fewer reports but should not be overlooked.

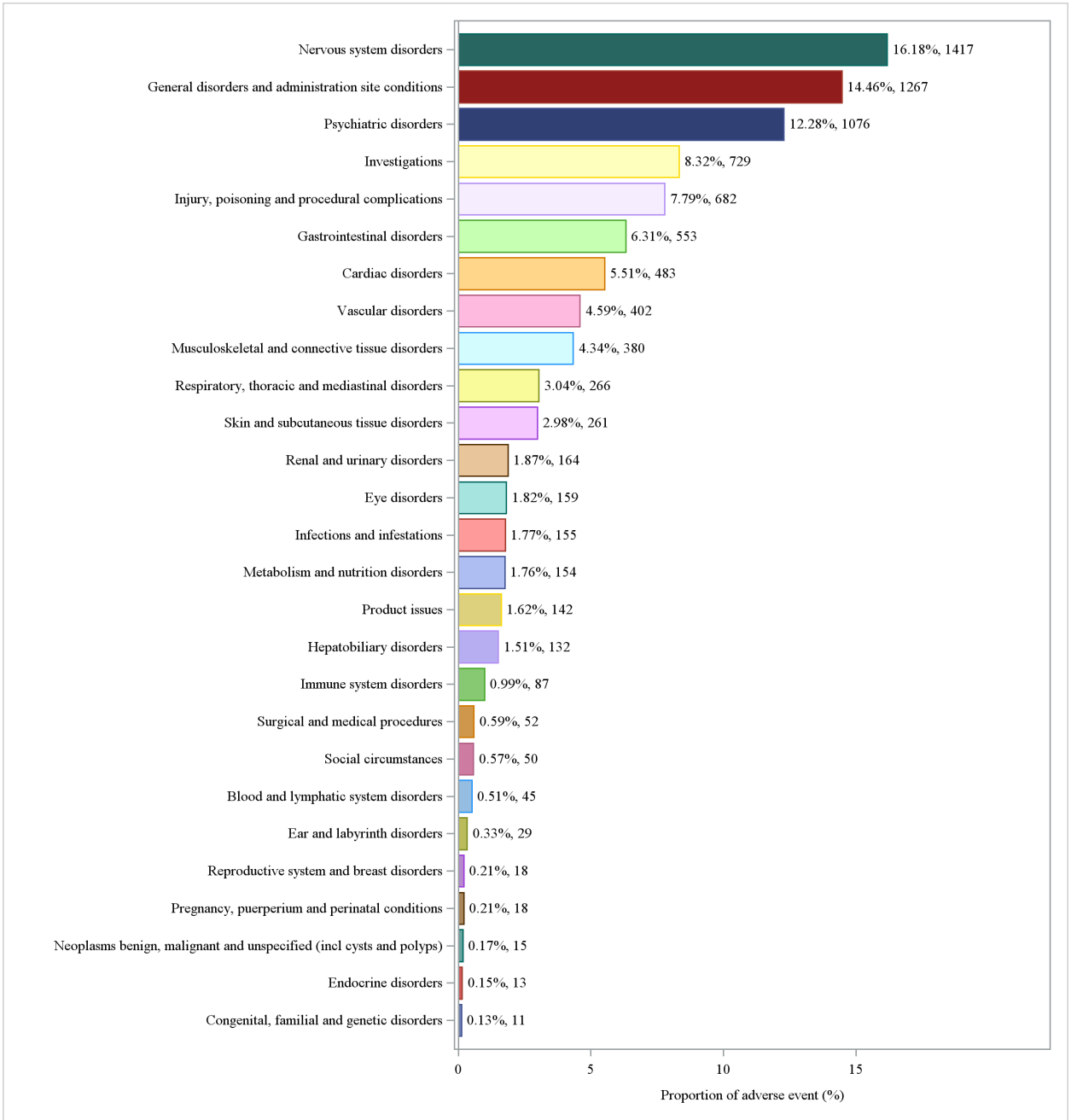

Figure 1. Proportion of adverse events by SOCs

3.3. Proportion of adverse events categorized by preferred terms

Figure 2 shows that hypotension is the most common adverse event, accounting for 2.31% (202 cases); somnolence accounts for 2.15% (188 cases); reports of drug ineffectiveness account for 2.09% (183 cases), indicating that some patients failed to achieve the expected therapeutic effect with tizanidine; reports of completed suicide account for 1.83% (160 cases), suggesting a potential association between the drug and suicide risk; dizziness accounts for 1.72% (151 cases); drug interaction accounts for 1.58% (138 cases), indicating that the concomitant use of tizanidine with other drugs may increase the risk of adverse events. Nausea accounts for 1.23% (108 cases), bradycardia for 1.13% (99 cases), reports of overdose for 1.02% (89 cases), and vomiting for 1.02% (89 cases). Other relatively common adverse events include hallucination (0.88%, 77 cases), toxicity to various agents (0.88%, 77 cases), confusional state (0.84%, 74 cases), and fatigue (0.84%, 74 cases). These symptoms further illustrate the effects of tizanidine on the central nervous system and its comprehensive reactions. Relatively less common but noteworthy adverse events include muscle spasms (0.80%, 70 cases), intentional overdose (0.80%, 70 cases), and pain (0.80%, 70 cases).

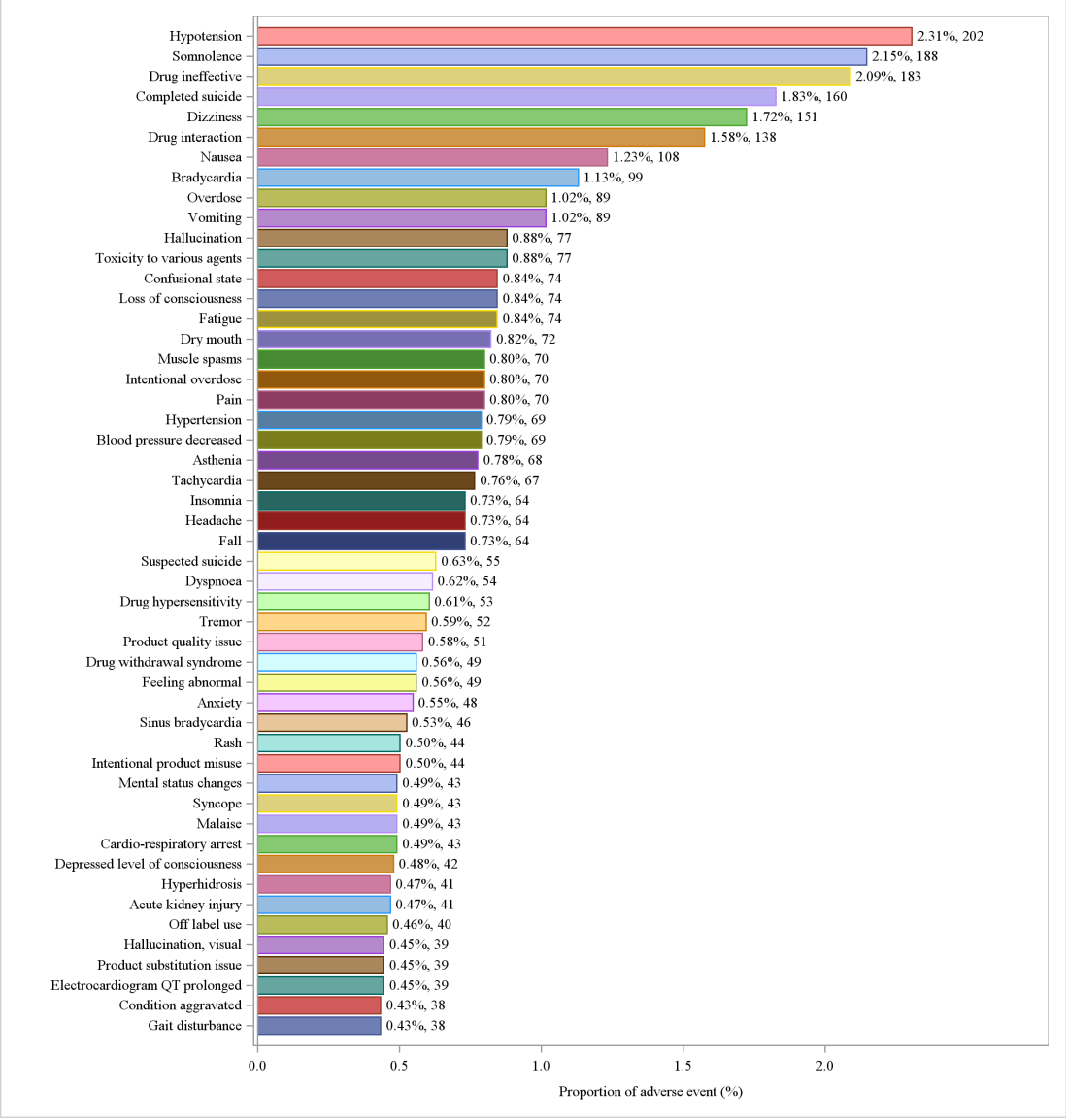

Figure 2. Proportion of adverse events by PTs

3.4. Forest plot of ROR signal strength

A higher ROR value indicates a stronger association between a specific drug and an adverse event. A higher ROR value suggests that this adverse event is more common in patients using the drug and implies a possible causal relationship. **Figure 3** shows that the ROR value for Potassium Wasting Nephropathy is 2396.32 (95% CI: 1349.30–4255.81), suggesting that tizanidine use may significantly increase the risk of kidney-related issues. The ROR value for Decorticate Posture is 454.89 (95% CI: 211.29–979.36); for Electrocardiogram U-wave Abnormality, the ROR value is 273.67 (95% CI: 100.59–744.55), indicating that tizanidine may significantly affect cardiac electrical activity. The ROR value for Withdrawal Hypertension is 229.77 (95% CI: 108.08–488.47), suggesting that hypertension may occur after discontinuation of tizanidine. The ROR value for Norepinephrine Increased is 156.84 (95% CI: 49.89–493.12), highlighting the need to closely monitor the effect of tizanidine on norepinephrine levels. The ROR value for Visual Snow Syndrome is 124.46 (95% CI: 39.70–390.22), indicating that tizanidine may have a severe impact on the visual system. The ROR value for Suspected Suicide is 99.77 (95% CI: 76.38–130.32), suggesting a potential association between tizanidine and suicide risk. The ROR value for Muscle Strength Abnormal is 75.22 (95% CI: 28.06–201.61), indicating that tizanidine may impair muscle strength. Other high ROR value adverse events include Lymphocyte Stimulation Test Positive (63.23), Hypertensive Crisis (55.21), Sinus Bradycardia (33.28), and Dissociative Disorder (30.87).

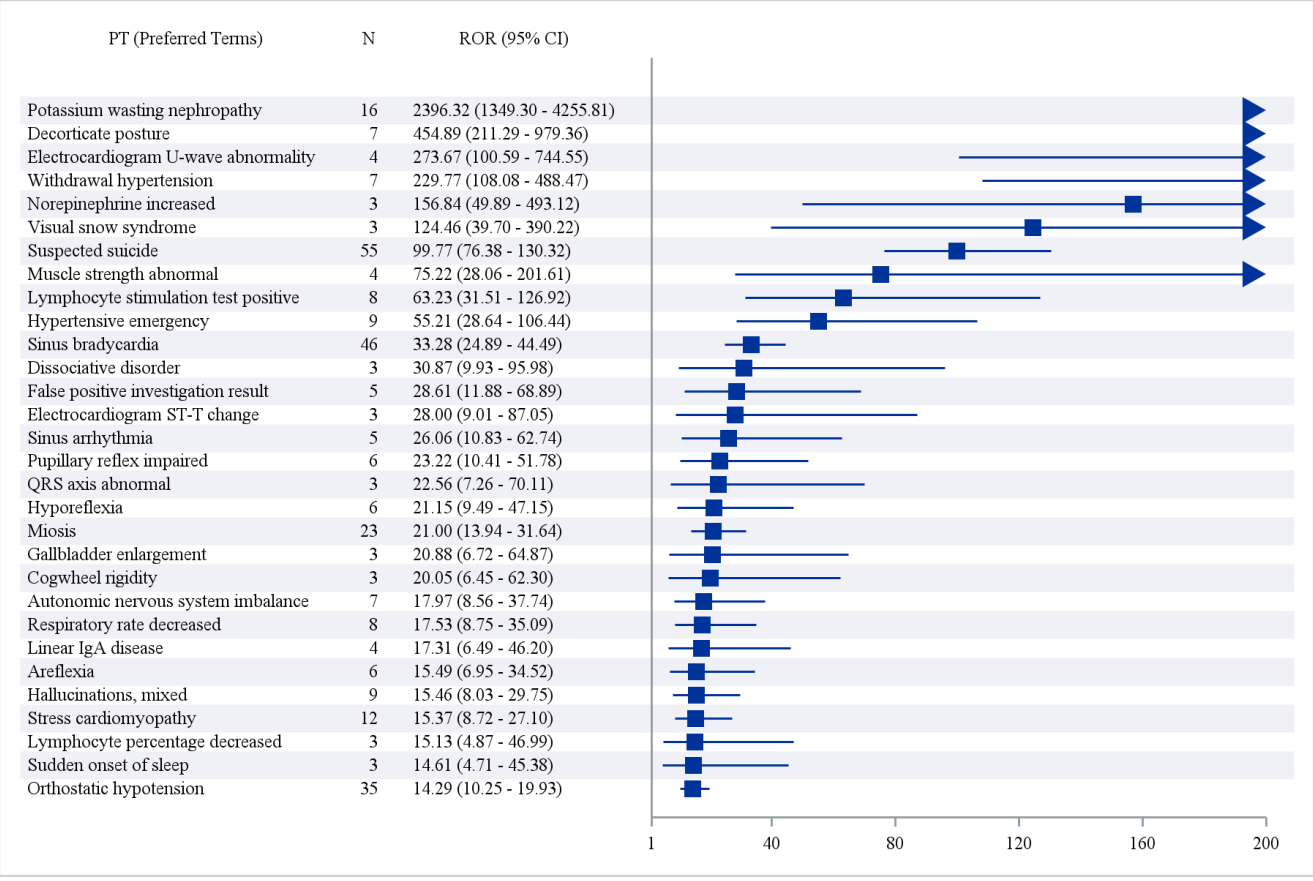

Figure 3. Forest plot of ROR signal strength

3.5. Survival curve of adverse events

As shown in **Figure 4**, the median time to adverse event occurrence post-medication is 3 days (IQR 0.00–53.00

days). This indicates that half of the adverse events occur within 3 days after medication, suggesting that the adverse reactions of tizanidine often manifest rapidly within a short period. From the perspective of cumulative percentage, the occurrence of adverse events accumulates rapidly over time, particularly growing fastest within the initial few days. Approximately 60% of adverse events occur within the first 10 days post-medication, indicating a significant early occurrence trend. As time progresses, the cumulative curve tends to flatten, indicating that most adverse events have been reported within 60 days post-medication. By 360 days post-medication, almost all possible adverse events have occurred and been reported. Despite the overall trend showing a concentration of early occurrences, some adverse events occur after a longer period, highlighting the importance of individual differences. Some patients may experience adverse events several months post-medication. This indicates that adverse events related to tizanidine are more likely to manifest in the short term post-medication, especially within the first few days, necessitating enhanced monitoring during the initial phase of medication. As the duration of medication extends, the rate of adverse event occurrence gradually decreases, but continuous monitoring remains necessary to ensure the long-term safety of patients.

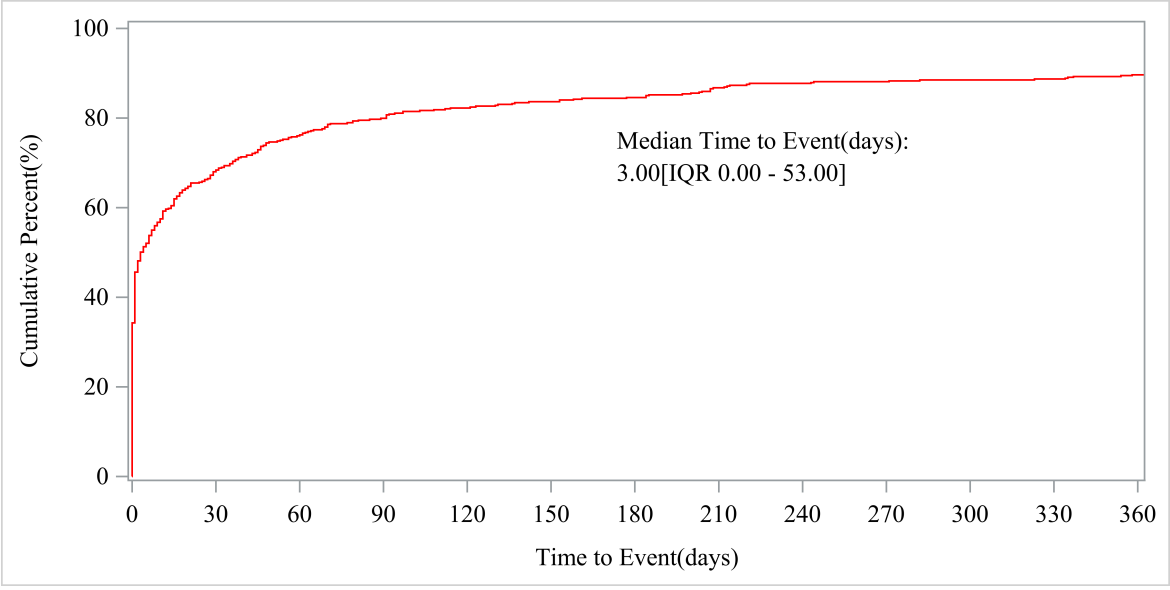

Figure 4. Survival curve of adverse events

4. Conclusion

This study reveals the patterns of adverse reactions and potential safety risks associated with the clinical use of Tizanidine through an analysis of the FAERS database. Tizanidine may induce adverse reactions affecting the nervous system, mental health, and cardiovascular system. By enhancing drug safety monitoring, particularly by implementing individualized treatment and close surveillance in high-risk patient groups, the safety of medication usage can be maximized. Future research should further explore the mechanisms of Tizanidine's adverse reactions to provide more precise theoretical support for optimizing clinical drug use.

5. Discussion

In this study, the authors conducted an in-depth analysis of adverse reactions related to Tizanidine using the

FAERS database, exploring the safety characteristics of this drug in actual clinical applications. As Tizanidine is commonly used to relieve muscle spasms, its clinical usage is quite extensive. However, with the increased application of the drug, reports of related adverse reactions have gradually increased, particularly in the fields of the nervous system, systemic reactions, and mental health. Understanding the occurrence of these adverse reactions and their potential risks can provide valuable references for medical personnel, guiding clinical decisions and patient management.

Through data mining of the FAERS database, the authors found that the adverse reactions of Tizanidine are diverse, involving multiple systems. Issues in the nervous system, systemic reactions, and mental health fields are particularly prominent [3]. Among these, drowsiness is the most common adverse reaction, accounting for 2.15% of the reports. This indicates that Tizanidine has a strong inhibitory effect on the central nervous system, which may lead to symptoms such as drowsiness and fatigue in patients [4]. Such symptoms may affect the daily life and work efficiency of some patients, potentially leading to treatment discontinuation. Therefore, medical personnel should be alert to the occurrence of such adverse reactions when using Tizanidine, especially in high-risk groups such as elderly patients and patients with other comorbidities [5].

Furthermore, the study found that Tizanidine may be associated with the risk of suicide. Completed suicide reports accounted for 1.83%, although this proportion is small, it is sufficient to raise significant concern [6]. The correlation between Tizanidine and depressive symptoms is not fully understood, but the authors can speculate that it is closely related to the drug's effect on neurotransmitters and the nervous system [7]. Therefore, in the clinical use of Tizanidine, especially during long-term use, medical personnel should conduct thorough mental health assessments and monitoring of patients to detect and intervene in potential mental health issues early.

The study also shows that combining Tizanidine with other drugs may lead to adverse reactions due to drug interactions. Reports of drug interactions accounted for 1.58%, with some combined medications potentially leading to muscle strength impairment, increasing the risk when using Tizanidine [8]. Drug interactions are an important aspect of drug safety monitoring, especially in patient groups undergoing polypharmacy. Clinically, medical personnel need to understand the interactions between Tizanidine and other drugs and reasonably adjust the medication regimen to reduce the occurrence of adverse reactions [9].

This study used the disproportionality analysis method (ROR) for signal mining, identifying several high-risk adverse events. Besides drowsiness and suicide risk, other high ROR adverse events include hypertensive crisis, sinus bradycardia, and dissociative disorders. These signals suggest that Tizanidine may have serious effects on the cardiovascular system, nervous system, and endocrine system, particularly when used in elderly patients and those with comorbid hypertension and heart disease. Therefore, the use of Tizanidine needs to be comprehensively considered the patient's underlying health conditions, particularly cardiovascular and nervous system health [10–11].

Patient demographic differences are also an important factor affecting the adverse reactions of Tizanidine. According to the research results, female patients and elderly patients are more likely to experience adverse reactions when using Tizanidine [12]. The higher proportion of symptoms such as drowsiness and dizziness in female patients may be related to physiological differences like hormone levels and metabolic rates; while elderly patients, due to their gradually declining physiological functions, have poorer tolerance to drugs, making them more prone to side effects related to Tizanidine [13]. Therefore, medical personnel should reasonably adjust the dosage based on individual differences when prescribing Tizanidine to different populations and monitor the medication process more meticulously.

The findings of this study provide important guidance for clinical practice. Firstly, medical personnel should

enhance individualized assessments when prescribing Tizanidine, particularly conducting timely drug safety evaluations for patients with cardiovascular diseases, nervous system diseases, and mental health issues [14]. Secondly, during the use of Tizanidine, special attention should be given to the occurrence of adverse reactions such as drowsiness, dizziness, and muscle weakness, and the treatment regimen should be adjusted promptly to avoid treatment discontinuation due to adverse reactions. Additionally, in patients using Tizanidine long-term, medical personnel should enhance monitoring of mental health to prevent the occurrence of depression and suicide risks. Regarding drug interactions, doctors should thoroughly evaluate the combined use of Tizanidine with other drugs to avoid adverse reactions caused by drug interactions. Through reasonable drug management and patient education, the incidence of drug adverse reactions can be effectively reduced, thereby improving patient medication safety.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Rudolph A, Dahmke H, Kupferschmidt H, et al., 2021, Coadministration of Tizanidine and Ciprofloxacin: A Retrospective Analysis of the WHO Pharmacovigilance Database. European Journal of Clinical Pharmacology, 77(6): 895–902. https://doi.org/10.1007/s00228-020-02981-2

[2] Giannouchos TV, Gomez-Lumbreras A, Malone DC, 2022, Risk of Tizanidine-induced Adverse Events after Concomitant Exposure To Ciprofloxacin: A Cohort Study in the U.S. The American Journal of Emergency Medicine, 2022(55): 147–151. https://doi.org/10.1016/j.ajem.2022.03.008

[3] Dai AI, Aksoy SN, Demiryurek AT, 2016, Comparison of Efficacy and Side Effects of Oral Baclofen Versus Tizanidine Therapy with Adjuvant Botulinum Toxin Type A in Children with Cerebral Palsy and Spastic Equinus Foot Deformity. Journal of Child Neurology, 31(2): 184–189. https://doi.org/10.1177/0883073815587030

[4] Morgom M, Sabir DM, Elbashir H, et al., 2023, A Case of Tizanidine Withdrawal Syndrome: Features and Management in the Emergency Department. Cureus, 15(11): e49248. https://doi.org/10.7759/cureus.49248

[5] Morgom M, Anjum S, Elgassim MA, et al., 2024, Emergency Response to Tizanidine Overdose: A Case Report on Critical Care Strategies. Cureus, 16(10): e70696. https://doi.org/10.7759/cureus.70696

[6] Amino M, Yoshioka K, Ikari Y, et al., 2015, Long-term Myocardial Toxicity in a Patient with Tizanidine and Etizolam Overdose. Journal of Cardiology Cases, 13(3): 78–81. https://doi.org/10.1016/j.jccase.2015.10.009

[7] Frascarolo S, Moutinot B, Sartori C, 2021, Focus on Tizanidine in Primary Care Medicine. Revue Médicale Suisse, 17(746): 1374–1376.

[8] Nair A, Rangaiah M, Borkar N, 2023, Efficacy and Safety of Oral Tizanidine Premedication as Pre-emptive Analgesia in Adult Patients Undergoing Elective Surgeries: A Systematic Review. Saudi Journal of Anaesthesia, 17(2): 214–222. https://doi.org/10.4103/sja.sja_780_22

[9] Setzer K, Baldwin N, Mersfelder T, et al., 2025, Profound Hypotension Following Concomitant Administration of Tizanidine and Lisinopril. BMJ Case Reports, 18(2): e262982. https://doi.org/10.1136/bcr-2024-262982

[10] Zhu LL, Wang YH, Zhou Q, 2024, Tizanidine: Advances in Pharmacology & Therapeutics and Drug Formulations. Journal of Pain Research, 2024(17): 1257–1271. https://doi.org/10.2147/JPR.S461032

[11] Bader D, Adam A, Shaban M, et al., 2021, Pediatric Tizanidine Toxicity Reversed with Naloxone: A Case Report.

International Journal of Emergency Medicine, 14(1): 73. https://doi.org/10.1186/s12245-021-00397-y

[12] Killam-Worrall L, Brand R, Castro JR, et al., 2024, Baclofen and Tizanidine Adverse Effects Observed Among Community-Dwelling Adults Above the Age of 50 Years: A Systematic Review. The Annals of Pharmacotherapy, 58(5): 523–532. https://doi.org/10.1177/10600280231193080

[13] Su Zhang VR, Niu F, Lee EA, et al., 2023, Safety of Baclofen Versus Tizanidine for Older Adults with Musculoskeletal Pain. Journal of the American Geriatrics Society, 71(8): 2579–2584. https://doi.org/10.1111/jgs.18349

[14] Goyal L, Mallick D, Zapata MR, et al., 2022, Tizanidine Toxicity from Ciprofloxacin: A Cautionary Tale. Cureus, 14(12): e32492. https://doi.org/10.7759/cureus.32492