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Safety profile of traditional Chinese herbal injection: An analysis of a spontaneous reporting system in China

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Abstract

Purpose: Although a series of serious adverse events have continually raised concerns about the potential toxicity of traditional Chinese medicine injections (TCM injections), studies on this subject are still sparse. We conducted a descriptive analysis of a spontaneous reporting system in China to describe the safety profile of TCM injections.

Methods: The safety profile of TCM injections is described by descriptive analysis of 559 066 adverse reports collected from Guangdong Provincial Center for adverse drug reaction (ADR) Monitoring in China during 2003 to 2017.

Results: The percentage of new or serious ADRs of TCM injections is much higher than average percentage of China's spontaneous reporting system (SRS) as a whole (48.70% vs <25%). Compared with conventional injections, TCM injections have a slightly lower percentage of serious ADRs (6.02% vs 6.72%) and much higher percentage of unknown (new) ADRs (46.74% vs 24.13%). The gender and age distribution for TCM injections are similar to conventional injections. The reporting rates of ADRs increased with age. Anaphylactic shock and anaphylactoid reaction are high-risk ADRs for TCM injections and, anaphylactic shock is ranked number 1 in causing deaths (50.00%).

Conclusions: There are some differences and similarities on the safety profile between TCM injections and conventional injections. TCM injections have higher risk of adverse effects than any other dosage forms of TCM medications and higher percentage of new or serious adverse effects than conventional injections. A lot of work need to be done to clarify the huge amount of potential unknown adverse effects related to TCM injections.

KEYWORDS

adverse drug reaction, pharmacoepidemiology, spontaneous reporting system, traditional Chinese medicine, traditional Chinese herbal injection

1 | INTRODUCTION

Traditional Chinese medicine (TCM) is a medical practice based on experience accumulated for thousands of years and with its own epistemology and methodology.^{1,2} It has long been an important part of

the health care system of China.³⁻⁵ There are more than 9000 TCM preparations presently approved for use in China.^{6,7} Traditional Chinese herbal injection, which have combined traditional knowledge of TCM with many modern pharmaceutical concepts and technologies, is a relatively new dosage form of TCM product. Traditional Chinese

herbal injection, frequently referred to as “TCM injection,” all contain extract of traditional Chinese herbal materials. But it will be recognized as a conventional injection when it contains one or a few well-characterized active ingredients extracted from traditional Chinese herbal materials and mainly uses the concept of modern medicine to describe the specifications and clinical usage. TCM injections, however, usually contain numerous poorly characterized or unknown ingredients and mainly use the concept of traditional TCM to describe the characteristics and clinical usage.⁸

As of 31 December 2017, 134 TCM injections from 224 manufacturers were approved to be sold in China.⁸ Facilitated by various health insurance programs, TCM injections are well recognized and widely used in all levels of hospitals and clinics in China.^{9,10} It has been estimated that the annual sales of TCM injections have reached more than 30 billion RMB and accounted for one third of all TCM sale in hospitals.¹¹

Adverse drug reactions (ADRs) are one of the main causes of death and a critical public health problem worldwide.^{12,13} In the past decades, a number of serious adverse events have continually raised concerns about the safety and potential toxicity of TCM injections.^{14–16} Most TCM products based the safety and efficacy on the long-time clinical use in the history. For many TCM injections, especially for those approved many years before, the registration requirements for evidence on safety and efficacy were much lower than conventional injections. This has made some presently approved TCM injections lack strong evidence on safety and efficacy. Strictly speaking, there was not much practical evidence on the safety and efficacy for TCM injections in ancient China, and therefore, it is essential to reexamine the safety and efficacy of TCM injections and encourage postmarketing safety studies. Nevertheless, safety studies on TCM injections are still sparse.

Spontaneous reporting system (SRS) has the advantage of covering a large number of patients and wide range of drugs and being relatively cost-effective for the monitoring of drug safety. They have been proven vital to postmarketing surveillance and are effective at detecting many types of ADRs, especially rare ones. They are also useful for characterizing features of the adverse effects of medicinal products. This article aims to describe the safety profile of TCM injections by analysis of a provincial SRS database in China.

2 | METHODS

2.1 | The data source

Data used in the study were collected during 2003 to 2017 from Guangdong Provincial Center for ADR Monitoring in China. It contains reports of adverse drug events spontaneously submitted by health care professionals, manufacturers, and other members of the public in Guangdong province. The web-based Guangdong Provincial Center for ADR Monitoring, one of the largest provincial ADR centers with a population of over 100 million for drug monitoring, has

KEY POINTS

- The risk of adverse drug reactions (ADRs) for traditional Chinese medicine (TCM) injections is much higher than any other dosage forms of TCM medications.
- TCM injections have a much higher percentage of unknown (new) ADRs than conventional injections.
- A lot of work needs to be done to clarify the huge amount of unknown (new) ADRs related to TCM injections.
- Anaphylactic shock and anaphylactoid reaction are high-risk ADRs for TCM injections. Anaphylactic shock is ranked number 1 in causing deaths.

been operative since November 2001. The ADR Monitoring Center and the database are described in detail elsewhere.¹⁷

2.2 | Data preprocessing

We carefully performed data cleaning and preprocessing to ensure that all the data are clean and well described. All the information of concomitantly used solvents was deleted from relevant reports with the assumption that all the reported ADRs were caused by the injectable drugs and had nothing to do with the concomitantly used solvents, such as water for injection or solutions of glucose and/or sodium chloride. As the reporting rate of nonserious ADRs in the below 20-years-of-age group may be influenced by adverse reports of vaccines, this study excluded all the adverse reports related to vaccines for all age groups. Considering the potential effects of concomitant drugs, this study excluded reports with concomitant drug use. Only reports with one drug suspected were used in the safety analysis of TCM injections.

The causalities between the reported ADRs and the suspected drugs were evaluated according to the criteria established by World Health Organization (WHO).¹⁸ We excluded reports with unlikely or unassessable results in causality assessment. We also excluded reports with no causality assessment information available. Only reports with a causality assessment of certainly, probably, or possibly drug related were included in the analysis.

To address the problem of variable drug nomenclature, the generic names of drugs were standardized according to Catalogue of Generic Names for Common Prescription Drugs¹⁹ and Chinese Pharmacopoeia.²⁰ The ADR names were coded according to World Health Organization-Adverse Reaction Terminology (WHO-ART) preferred terms.

To reports in which death was reported as the outcome, all the reports and related follow-up documentation were analyzed in detail by a panel of experts, including physicians, pharmacists, and pharmacologists. The expert panel assessed the reporter's judgments, death diagnosis, and all other available information about potential

contributing factors, such as age, concomitant diseases, and patient health conditions. The panel also excluded duplicates and reports in which death was not ADR-related and cases of overdose (intentional or accidental) in line with the WHO definition of an ADR.²¹

Between January 2003 and December 2017, 559 066 reports were collected from the database. There were 553 466 reports left after removing duplicate reports and reports on vaccine and medical devices. After deleting information of solvents concomitantly used for injectable drugs, such as water for injection or injections of glucose and/or sodium chloride, there were 470 757 reports with one drug suspected, which account for 85.06% of the total reports. In the remaining cases, there were 57 292 reports (10.35%) with two drugs suspected and 25 417 reports (4.59%) with three or more drugs suspected. In order to prevent bias caused by concomitantly used other drugs, only 470 757 reports with one drug suspected were actually used in the analysis of TCM injections.

We also excluded 4467 reports with unlikely or unassessable results in causality assessment and 368 reports with no causality assessment information available. Only 465 922 reports with a causality assessment of certainly, probably, or possibly drug related were included in the analysis.

2.3 | Data analysis

A descriptive analysis of the ADR reports was conducted, and reporting odds ratios (RORs) of serious ADRs with 95% confidence intervals (95% CIs) were calculated. RORs, one of the measures of disproportionality that entail comparisons of observed with expected proportions of an adverse event associated with a drug,²² were used as an estimate of the relative risk of serious ADRs. It is identical to the calculation of an odds ratio from a case-control study that compares each drug in turn to all other drugs, and its calculation is described in detail elsewhere.^{3,23,24}

3 | RESULTS

3.1 | General descriptions of ADR reports related to TCM injections

There were 465 922 reports on 1810 separate individual TCM products, 50 243 reports on 110 individual TCM injections in the database. Among the 110 individual TCM injections involved, 103 are presently approved by China Food and Drug Administration (CFDA), and four were formerly approved by CFDA and have now been suspended, and three are presently approved hospital preparations by Guangdong provincial drug regulatory agency and can only be used in the applicant hospital. Therapeutic classes and generic names of the 110 TCM injections were illustrated in Table S1.

By the end of 2017, there were 134 TCM injections presently approved to be sold on the market.⁸ Among the 134 approved TCM injections, 31 TCM injections do not have any ADR reports in the dataset. None of 31 TCM injections have ever been warned of

dangerous ADRs in the Adverse Drug Reaction Information Bulletins, which are issued by CFDA as an important index to reflect the state of risk communication and risk reduction for medicinal products. Basic information of the 31 TCM injections is listed in Table S2.

For better understanding of the adverse effects of TCM injections compared with conventional injections, a statistics on annual numbers of ADR reports of TCM injections and conventional injections is illustrated in Figure 1. In the dataset, there were 50 243 reports on TCM injections, accounting for 82.56% of the total number of reports of TCM products; there were 330 930 reports on conventional injections, accounting for 81.70% of total number of reports of conventional medicines. Detailed information on annual number of reports and corresponding percentages for conventional injections and TCM injections is illustrated in Table S3.

3.2 | The status of seriousness and awareness of the reported ADRs

ADRs are classified as serious or nonserious in terms of seriousness, known, or unknown (new) in terms of awareness. As serious and unknown (new) ADRs have greater risk to patients' life and health; the understanding of serious and unknown (new) ADRs have always been the focus of scientific research.

According to Administrative Measures on Reporting and Monitoring of ADRs issued by CFDA in 2011,²⁵ unknown (new) ADRs are adverse effects not described in the labels or inserts of the medicine, or the nature, seriousness, outcome, or frequency is not the same as or worse than described in the labels or inserts of the medicine. Serious ADRs are adverse events caused by drugs that result in any of the following outcomes: death, life-threatening, cancer, or a congenital anomaly/birth defect, an inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, and ADRs, which may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.²⁵

The status of seriousness and awareness of the ADRs for TCM injections and conventional injections is illustrated in Table 1.

Among the 50 243 reports related to TCM injections, there were 3026 serious reports and 47 217 nonserious reports. Serious reports accounted for 6.02% of the total reported incidents. There were 26 761 known reports and 23 482 unknown (new) reports. Unknown (new) reports accounted for 46.74% of the total number of reports. Compared with conventional injections, TCM injections have a slightly lower percentage of serious ADRs (6.02% vs 6.72%, .000) and much higher percentage of unknown (new) ADRs (46.74% vs 24.13%, .000).

3.3 | Age and gender distribution of the ADRs related to TCM injections

Among the 50 243 reports related to TCM injections, the number of reports of women (25 561) was slightly higher than that of men (24

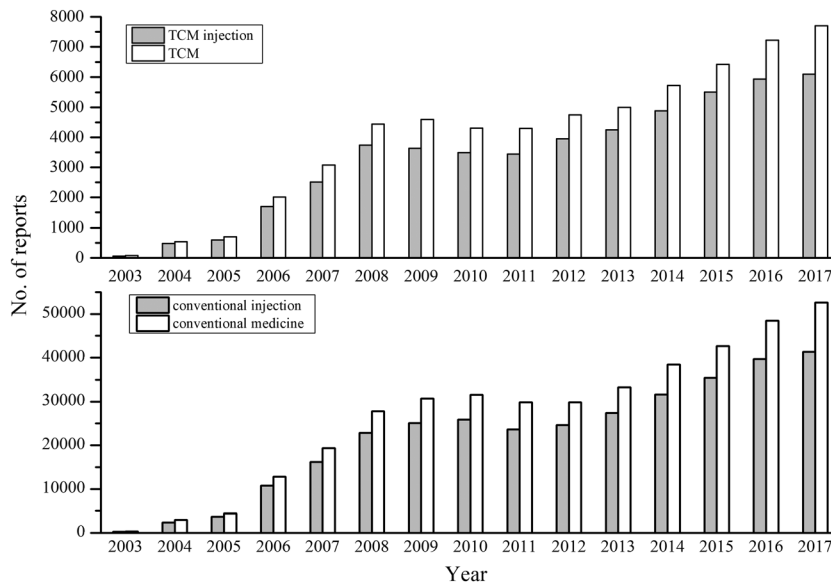


FIGURE 1 Annual number of adverse drug reaction reports for traditional Chinese medicine injections and conventional injections

TABLE 1 Statistics on seriousness and awareness of the ADRs for TCM injections and conventional injections

	TCM injection			Conventional injection		
	Nonserious, n (%)	Serious, n (%)	Total row, n (%)	Nonserious, n (%)	Serious, n (%)	Total row, n (%)
Known	25 774 (51.30)	987 (1.96)	26 761 (53.26)	238 431(72.05)	12 653 (3.82)	251 084 (75.87)
Unknown	21 443 (42.68)	2,039 (4.06)	23 482 (46.74)	70 241 (21.23)	9605 (2.90)	79 845 (24.13)
Total column	47 217 (93.98)	3,026 (6.02)	50 243 (100.00)	308 672 (93.28)	22 258 (6.72)	330,930 (100.00)

Abbreviations: ADRs, adverse drug reactions; TCM, traditional Chinese medicine.

673). But the differences in specific age groups became more significant than general. The age-specific reporting rates of TCM injections for male and female in Guangdong province is illustrated in Figure 2.

It is impressive that the reporting rates increased continuously with age. The influence of age for both serious and nonserious ADRs is similar except that the influence on serious ADRs was more

significant than nonserious ADRs. The elderly had the highest reporting rates of ADRs among all age groups. For comparison, age-specific reporting rates for conventional injections are shown in Figure S1. Some differences and similarities can be found between TCM injections and conventional injections. Gender factor also has great influence on the reporting rates of ADRs. Males have higher

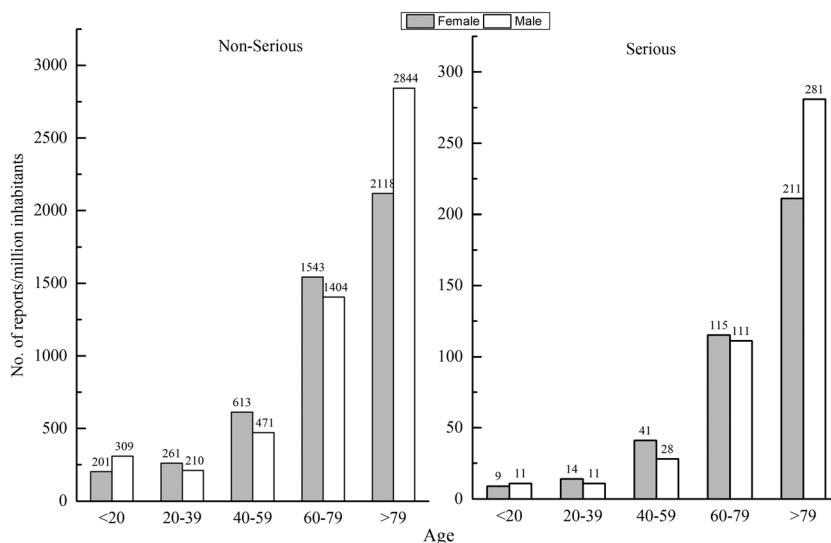


FIGURE 2 Age-specific adverse drug reaction reporting rates for traditional Chinese medicine injections (per million inhabitants)

reporting rates than females under the age of 20 or older than 80. Females have higher reporting rates than males in age groups between 20 and 80.

3.4 | ADRs frequently reported

Statistics on frequently reported ADRs (preferred terms) for TCM injections is illustrated in Table 2. It can be seen that easily recognized external symptoms of related physical conditions make a large proportion of the reported ADRs for TCM injections. For comparison, statistics on frequently reported ADRs (preferred terms) for conventional injections is shown in Table S4. Some differences and similarities can be seen in frequently reported ADRs between TCM injections and conventional injections. Statistics of frequently

reported ADRs for different therapeutic classes of TCM injections are illustrated in Tables S5 to S9, which provide a general view of the differences and similarities between different therapeutic classes of TCM injections.

3.5 | Statistics on outcome of the ADRs related to TCM injections

As to the outcome of ADRs related to TCM injections, 99.76% cured or relieved, 0.03% left with sequelae, and 0.04% died. Statistics on the outcomes of the ADRs of different therapeutic classes of TCM injections is illustrated in Table 3.

Although mild adverse events or external symptoms of related physical conditions made a large proportion of the reported ADRs

TABLE 2 Most frequently reported ADRs for TCM injections (top 12)

Rank	Total Reports		Serious Reports	
	ADRs (WHO-ART Preferred Term)	No. (%) of reports (n = 93,666) ^a	ADRs (WHO-ART Preferred Term)	No. (%) of reports (n = 7683) ^b
1	Rash	13,737 (14.67)	Rigors	1101 (14.33)
2	Pruritus	12,836 (13.70)	Dyspnoea	1032 (13.43)
3	Rigors	11,396 (12.17)	Hyperthermia	569 (7.41)
4	Chest pain	6,814 (7.27)	Chest pain	479 (6.23)
5	Fever	5,149 (5.50)	Anaphylactic shock	391 (5.09)
6	Dyspnoea	5,146 (5.50)	Fever	373 (4.85)
7	Palpitations	4,143 (4.42)	Palpitations	276 (3.59)
8	Dizziness	4,111 (4.39)	Dizziness reaction	270 (3.51)
9	Flushing	4,018 (4.29)	Anaphylactoid	237 (3.08)
10	Nausea	2,846 (3.04)	Pruritus	208 (2.71)
11	Anaphylactoid reaction	2,811 (3.00)	Rash	201 (2.62)
12	Vomiting	2,088 (2.23)	Cyanosis	181 (2.36)

Abbreviations: ADRs, adverse drug reactions; TCM, traditional Chinese medicine.

^a93 666 drug-ADR combinations obtained from the split of the adverse reactions of the total 50 243 original reports.

^b7683 drug-ADR combinations obtained from the split of the adverse reactions of the total 3026 original reports.

TABLE 3 Statistics on the outcome of the ADRs of different therapeutic classes of TCM injections

Outcome of ADRs	Blood Circulation Promoting N (%)	Antipyretic N (%)	Anticancer N (%)	Pain-alleviating N (%)	Other TCM Injections N (%)	Total Row N (%)
Cured	17 149 (34.13)	10 851 (21.60)	5113 (10.18)	177 (0.35)	1029 (2.05)	34 319 (68.31)
Relieved	8321 (16.56)	4657 (9.27)	2291 (4.56)	62 (0.12)	469 (0.93)	15 800 (31.45)
Not relieved	24 (0.05)	8 (0.02)	4 (0.01)	0 (0.00)	1 (0.00)	37 (0.07)
Death	7 (0.01)	10 (0.02)	0 (0.00)	0 (0.00)	1 (0.00)	18 (0.04)
Left with sequelae	6 (0.01)	5 (0.01)	2 (0.00)	0 (0.00)	0 (0.00)	13 (0.03)
Missing	29 (0.06)	22 (0.04)	5 (0.01)	0 (0.00)	0 (0.00)	56 (0.11)
Total column	25 536 (50.82)	15 553 (30.96)	7415 (14.76)	239 (0.48)	1500 (2.99)	50 243 (100.00)

Abbreviations: ADRs, adverse drug reactions; TCM, traditional Chinese medicine.

for TCM injections, there were still 18 death reports related to TCM injections, six males and 12 females, and covered every age group. Detailed information of the 18 death reports is illustrated in Table 4.

There were 12 TCM injections involved in the 18 death reports. Qingkailing injection and Yuxingcao injection (*Houttuynia cordata injection*) ranked top 2 high-risk injections in causing deaths.

3.6 | Statistics on frequently reported TCM injections and the routes of administration

Most frequently reported TCM injections for different therapeutic classes and the corresponding number of serious reports and relevant RORs are illustrated in Table 5. ROR is used to represent the scale of risks of serious adverse events for an individual TCM injection or a therapeutic class of TCM injections.

Statistics on routes of administration is to measure the reporting rates of ADRs affected by the route of administration. Detailed information on main routes of administration and the corresponding

numbers of reports for TCM injections is shown in Table 6. For comparison, statistics on main routes of administration and the corresponding number of reports for conventional injections is shown in Table S10.

The ranking order of reporting frequency for different routes of administration for TCM injections is similar to conventional injections, ie, intravenous drip ranked number 1, followed by Intravenous push and Intramuscular injection. There are some differences between them. For example, TCM injections have a higher percentage of intravenous drip than conventional injections (93.50% vs 87.31%).

3.7 | Statistics on sources of the ADR reports

Statistics on sources of the ADR reports for TCM injections, including professions of the reporters and types of the reporting bodies, is shown in Table 7. As can be seen from Table 7, medical institutions reported 49 977 reports, accounting for 99.47% of the total number. Only 266 reports (0.53%) came from other reporting bodies, such as

TABLE 4 Detailed information on death reports related to TCM injections

Case	Gender	Age	Death Year	Suspected Drugs	ADR(s) Reported	Primary Diseases (ICD-10) ^a
1	Female	41	2009	Qingkailing injection	Anaphylactic shock	Cough (R05)
2	Male	41	2009	Qingkailing injection	Anaphylactic shock, Heart failure, Respiratory failure	Bacterial pneumonia, not elsewhere classified (J15)
3	Male	45	2014	Qingkailing injection	Anaphylactic shock	Acute upper respiratory infections of multiple and unspecified sites (J06)
4	Female	83	2017	Qingkailing injection	Rigors, Syncope, Death	Chronic ischaemic heart disease, unspecified (I25.9) Bronchitis, not specified as acute or chronic (J40)
5	Male	57	2005	Yuxingcao injection	Anaphylactic shock	Unspecified jaundice (R17), Type 2 diabetes mellitus (E11)
6	Female	33	2006	Yuxingcao injection	Sudden death	Heart failure (I50), Cough (R05)
7	Female	1	2006	Yuxingcao injection	Anaphylactoid reaction	Bronchitis, not specified as acute or chronic (J40)
8	Female	6	2006	Yuxingcao injection	Tics, Cyanosis	Gastroenteritis and colitis of unspecified origin (A09.9), Acidosis (E87.2), Volume depletion (E86)
9	Female	61	2006	Ciwujia injection	Anaphylactic shock	Emphysema (J43)
10	Male	59	2017	Danshenduofensuanyan injection	Death, Arrhythmia	Atherosclerotic heart disease (I25.1), Type 2 diabetes mellitus (E11)
11	Male	74	2007	Dengzhanhuasu injection	Anaphylactic shock	Cerebral infarction (I63), Simple chronic bronchitis (J41.0)
12	Female	57	2017	Dilong injection	Anaphylactic shock	Asthma, unspecified (J45.9)
13	Female	49	2015	Reduning injection	Anaphylactic shock	Acute upper respiratory infections of multiple and unspecified sites (J06)
14	Female	60	2014	Shengmai injection	Heart failure, Respiratory failure	Marasmic kwashiorkor (E42)
15	Female	41	2015	Shuxuetong injection	Laryngeal oedema	Other spondylosis (M47.8)
16	Female	0	2006	Tanreqing injection	Asystolia	Bronchopneumonia, unspecified (J18.0)
17	Female	80	2017	Xiangdan injection	Death	Intervertebral disc disorder, unspecified (M51.9), Radiculopathy (M54.1)
18	Male	64	2017	Xeshuantong injection	Anaphylactic shock	Acute myocardial infarction (I21)

Abbreviations: ADRs, adverse drug reactions; TCM, traditional Chinese medicine.

^aICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision

TABLE 5 Most frequently reported TCM injections for different therapeutic classes (top 6)

Categories	Rank	Drugs	Total Reports N (%)	Serious Reports	
				N	ROR (95% CI)
Promote blood circulation			25 536 (50.82)	1,63	1.19 (1.11-1.28)
	1	Xueshuantong injection	3806 (7.58)	229	1.00 (0.87-1.15)
	2	Shengmai injection	3329 (6.63)	223	1.13 (0.98-1.30)
	3	Xuesaitong injection	2700 (5.37)	172	1.07 (0.91-1.25)
	4	Shuxuening injection	2177 (4.33)	110	0.82 (0.68-1.00)
	5	Danshen injection	2136 (4.25)	110	0.84 (0.69-1.02)
	6	Shuxuetong injection	2010 (4.00)	243	2.25 (1.95-2.58)
Antipyretic			15 553 (30.96)	809	0.80 (0.74-0.87)
	1	Qingkailing injection	6594 (13.12)	330	0.80 (0.71-0.90)
	2	Tanreqing injection	2149 (4.28)	95	0.71 (0.58-0.88)
	3	Shuanghuanglian injection	1748 (3.48)	49	0.44 (0.33-0.59)
	4	Xiyanping injection	1710 (3.40)	104	1.01 (0.83-1.24)
	5	Reduning injection	1481 (2.95)	100	1.13 (0.92-1.39)
	6	Xuebijing injection	637 (1.27)	59	1.60 (1.22-2.10)
Anticancer			7415 (14.76)	405	0.89 (0.80-0.99)
	1	Shenmai injection	4593 (9.14)	236	0.83 (0.73-0.95)
	2	Shenqifuzheng injection	859 (1.71)	37	0.70 (0.50-0.97)
	3	Kangai injection	496 (0.99)	34	1.15 (0.81-1.63)
	4	Aidi injection	478 (0.95)	24	0.82 (0.55-1.24)
	5	Xiangguduotang injection	374 (0.74)	38	1.77 (1.27-2.49)
	6	Fufang Kushen injection	205 (0.41)	10	0.80 (0.42-1.51)
Pain-alleviating			239 (0.48)	9	0.61 (0.31-1.19)
	1	Zhengqingfengtongning injection	178 (0.35)	4	0.36 (0.13-0.96)
	2	Fufang Fengshining injection	14 (0.03)	1	1.20 (0.16-9.18)
	3	Yemugua injection	13 (0.03)	0	-
	4	Zushima injection	9 (0.02)	0	-
	5	Dinggongteng injection	7 (0.01)	1	2.60 (0.31-21.60)
	6	Jiangu injection	6 (0.01)	0	-
Other TCM injections			1500 (2.99)	140	1.64 (1.37-1.95)
	1	Shenfu injection	862 (1.72)	82	1.66 (1.32-2.09)
	2	Yiqifumai powder for injection	255 (0.51)	36	2.58 (1.81-3.68)
	3	Shenkang injection	167 (0.33)	3	0.28 (0.09-0.89)
	4	Fufang Shexiang injection	113 (0.22)	8	1.19 (0.58-2.44)
	5	Dilong injection	23 (0.05)	3	2.34 (0.70-7.89)
	6	Gualoupi injection	23 (0.05)	3	2.34 (0.70-7.89)

drug distributors, manufacturers, or consumers. For comparison, a statistical description of sources of the ADR reports for conventional injections is shown in Table S11.

The number of total cases, serious cases, or death cases occurred in different levels of medical institutions is shown in Table 8. For the record, hospitals were classified according to the National Standards for Hospital Classification issued by the National Health and Family Planning Commission of PRC (<http://www.moh.gov.cn/mohzcfgs/pgz/200804/18713.shtml>).

4 | DISCUSSION

4.1 | Safety features of TCM injections

In order to prevent the confounding of other similar drugs, TCM injections in this study are restricted to injections containing extract of traditional Chinese herbal materials and denoted by the letter “Z” in front of the registered identifier of approval, which is symbol of traditional TCM in China's drug registry system. Injections containing

TABLE 6 Main routes of administration and the corresponding number of reports for TCM injections

Route of administration	No. of reports	Percentage (%)
Intravenous drip	46,976	93.50
Intravenous push	2,395	4.77
Intramuscular injection	762	1.52
Special route ^a	110	0.22
Total	50,243	100.00

Abbreviations: ADRs, adverse drug reactions; TCM, traditional Chinese medicine.

^aSpecial route: trathecal injection, acupoint injection, pain point injection, injection for block therapy of pain spot, and subcutaneous injection at the lesion site and so on.

TABLE 7 Sources of the ADR reports for TCM injections

Sources of reports	N	%
Profession of the reporter		
Physician	35 712	71.08
Nurse	9497	18.9
Pharmacist	4587	9.13
Consumer or unknown reporter	447	0.88
Type of reporting body		
Medical institution	49 977	99.47
Distributor	95	0.19
Manufacturer	72	0.14
Consumer or unknown institution	99	0.20

Abbreviations: ADRs, adverse drug reactions; TCM, traditional Chinese medicine.

TABLE 8 Number of cases occurred in different levels of medical institutions

Hospital Level	Total Cases (N = 50 243)	Serious Cases n (%)	Death Cases n (%)
Tertiary hospitals	11 442	762 (6.66)	3 (0.03)
Secondary hospitals	19 106	1112 (5.82)	7 (0.04)
Primary hospitals	18 050	1046 (5.80)	4 (0.02)
Grassroots healthcare institutions	1248	72 (5.77)	4 (0.32)
Missing	397	34 (1.12)	0 (0.00)

Note. Grassroots health care institutions include community health service centers, urban health centers, township health centers, private clinics. (http://www.gov.cn/zhengce/content/2015-03/30/content_9560.htm).

extract of traditional Chinese herbal materials without a letter “Z” in front of the registered identifier of approval were not included in the study. ADR is defined as a reaction that is noxious and unintended and that occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of diseases, or for the modification

of physiological function. This definition excludes accidental or deliberate excessive dosage or maladministration.²¹

Statistics shows that ADRs related to TCM injections account for about 80% of all ADRs related to TCM medications, much higher than any other dosage forms. Similarly, ADRs related to conventional injections also account for about 80% of all ADRs related to conventional medications. It can be concluded that the dosage form of injections is mainly responsible for the extremely high reporting rates of ADRs for TCM injections. Besides, serious overuse of injectable medicine in China^{26,27} and the fact that ADRs related to injections usually occur quickly after the drug use and is relatively easy to recognize also contributed to the high percentages of ADR reports for injections, including TCM injections and conventional injections.

It has been reported that the percentage of new or serious reports in China's SRS system was less than 25%.²⁸ It is impressive that the percentage of new or serious reports related to TCM injections, as revealed in this study, reach up to 48.70%. Compared with conventional injections, TCM injections have a slightly lower percentage of serious ADRs (6.02% vs 6.72%) and much higher percentage of unknown (new) ADRs (46.74% vs 24.13%). A lot of work needs to be done to clarify such a huge amount of potential unknown adverse effects related to TCM injections.

The reporting rates of ADRs for TCM injections increased continuously with age, and this is true for both serious and nonserious ADRs. The elderly had the highest reporting rates of ADRs among all age groups. This result is expected and consistent with studies on drug-related ADRs for conventional medications.^{29,30} Age-related changes, such as those arising from changes in pharmacokinetics and pharmacodynamics, interindividual variability, polypharmacy, and other drug consumption that leads to drug interactions are all risk factors for ADRs. It is known that the elderly have the highest percentages of ADR-related hospitalizations.³¹⁻³³

Statistics in this study show some similarities between TCM injections and conventional injections in age and gender distributions. For example, mild adverse events or symptoms of related physical conditions make a large proportion of the reported ADRs for both TCM injections and conventional injections. Anaphylactic shock and anaphylactoid reaction are dangerous ADRs of high risk for both TCM injections and conventional injections. The results are consistent with literature.^{16,34,35}

Statistics show that 99.76% of ADRs caused by TCM injections were cured or relieved at the time of reporting. Very few died (0.04%) or left with sequelae (0.03%). This result is also basically consistent with literature.³⁶

Among the 18 death reports, the number of women who died of TCM injections was two times greater than men. The number of cases is too small to determine if it is truly a natural tendency or just caused by noise, and there was not enough information to make a reasonable explanation. It is noteworthy that anaphylactic shock is ranked as number 1 TCM injections in causing deaths (50.00%). Similarly anaphylactic shock also ranked as the first high-frequency ADR for serious reports of conventional injections. Anaphylactic shock is the

most common and dangerous ADR for both TCM injections and conventional injections.

In 2005 and 2006, four cases of death reports related to Yuxingcao injection were reported in Guangdong province. Death reports also frequently reported in other provinces, and the use of Yuxingcao injection in hospitals was halted by CFDA in 2006.³⁷ After a strict re-registration procedure, a limited number of manufacturers was authorized to resume production.¹⁵ The production and clinical use of Yuxingcao injection declined sharply after 2006.

ROR in spontaneous report databases offers advantages over PRR for it allows for estimation of relative risk.³⁸ Relative risks of causing serious ADRs can be concluded from RORs and 95% CIs for deferent therapeutic classes or deferent individual TCM injections. For example, RORs and the lower limits of 95% CIs for Shuxuetong injection and Shenfu injection are greater than 1, indicating that the risk of causing serious ADRs for the two TCM injections is higher than average risk of all TCM injections in the dataset. It can also be concluded that the therapeutic class of antipyretic, anticancer, and pain-alleviating TCM injections have lower risk of causing serious ADRs than other therapeutic classes.

4.2 | Features of China's SRS system

A series of features of China's SRS system can be drawn from statistics of the adverse reports of TCM injections, as China obliges pharmaceutical manufacturers, distributors, and medical institutions to report all ADRs to the drugs they handle, including known and nonserious ADRs. Therefore, known and nonserious ADRs form the majority of the adverse reports in China's SRS databases. This could partly explain the reason why mild adverse events or external symptoms of related physical conditions have made a large proportion of the reported ADRs in both conventional injections and TCM injections. This feature has made China's SRS system somewhat like a less strict random sample of drug users and could be used for rough compare of frequency and severity of adverse effects between similar medications.²³

China's SRS system has unique feature on the reporting institutions of the adverse reports. About 94% of adverse events were reported by pharmaceutical companies in the United States.³⁹ Very differently, medical institutions have always been the main force for ADR monitoring in China, and drug manufacturers have not fully played their roles. Statistics show that 99.47% of the ADR reports for TCM injections were reported by medical institutions. Only 0.53% of reports came from other reporting sources, such as drug distributors, manufacturers, or consumers. Only 0.14% of the ADR reports for TCM injections were reported by manufacturers. It seems that China's SRS system has become a monodrama of the medical institutions, lack the active participation of drug distributors, manufacturers, or consumers. This result is consistent to relevant literature.²⁸

Since the pilot monitoring program for ADRs started in 1980s, medical institutions have always been the major participants for ADR monitoring, and the awareness and ability for ADR monitoring and reporting have been significantly improved. On the contrary, the

awareness and reporting capacity of the manufacturers and distributors still need to be improved. Although there were a lot of safety warnings about unsafe TCM injections, the withdrawals of unsafe TCM injections have relatively been rare.⁴⁰ The lack of active participation of manufacturers has been a major problem for further improvement of the safety of TCM injections.

The occupation distribution of the reporters reflects the roles of different professionals in China's SRS system. This study revealed that physicians ranked number 1 in reporting of adverse reports (71.08%), nurses ranked second (18.90%), and pharmacists ranked third (9.13%). The role and knowledge structure of pharmacists are advantageous for reporting ADRs. The present situation calls for more training to further improve the ability and enthusiasm to report adverse drug events for pharmacists.

This study revealed that the highest number of total reports, serious reports, and death reports came from secondary hospitals, followed by primary hospitals and tertiary hospitals. Grassroots health care institutions reported the least number of total reports and serious reports. However, the number of death reports from grassroots health care institutions was not that low. Actually, grassroots health care institutions have the highest percentage of death reports over the total number of reports (0.32%).

There are two reasons for this phenomenon. In health care system of China, the number and service capacity of grassroots health care institutions are seriously inadequate. This led to too many patients with minor illness flock to large hospitals. This could partly explain the reason why so little total reports or serious reports came from grassroots health care institutions. Meanwhile, grassroots health care institutions lack the ability and experience to deal with fatal adverse events and may cause a lot of preventable deaths to occur.

4.3 | Special safety issues of TCM injections

As TCM injections usually contain some poorly characterized or unknown active or inactive ingredients, the stability of the quality always have a challenging issue.⁸ Other factors may also contribute to the adverse effects of TCM injections, such as inappropriate manufacturing procedures, unknown impurities and allergens, and quality variation of raw herbal materials, and so on.

As every traditional Chinese herb contains numerous active or inactive ingredients,⁴¹ the mix of a TCM injection can be very complex even if the formulation relies on a single traditional Chinese herb. It will be even more complex when a TCM injection is made from several traditional Chinese herbs, which is typically the case for most TCM injections. All these have made the mechanisms of action, and causes of many ADRs remain unclear.^{42,43}

Despite the extensive safety testing during the drug development process, some adverse effects may still exist at the time of market introduction.⁴⁴ As most TCM injections were approved many years before, the evidence on safety and efficacy is not adequate by today's standards, it is necessary to reexamine the safety and efficacy of presently approved TCM injections, especially the safety aspects.

Data in this study suggest that irrational use may be an important factor for causing adverse events of TCM injections. There are mainly four routes of administration for TCM injections. The number of ADRs related to intravenous drip accounted for 93.50% of total adverse events. Only 6.29% of the reports involved intravenous push or intramuscular injection. Literature also revealed severe overuse of intravenous drip in China.^{26,27}

4.4 | Limitations

This study must be interpreted in context of certain limitations. As compound prescription is one of the key characteristics of TCM,⁴⁵ the combined use of TCM injections with other medicine may change the therapeutic effects as well as adverse effects.⁴⁶ As reports with multidrug therapies were excluded from the study, the results might not reflect the safety features of TCM injections under the circumstances of multidrug therapies.

In this study, we assumed that all the reported ADRs were caused by the injectable drugs and had nothing to do with the concomitantly used solvents and simply deleted these solvents from relevant reports. This may bring bias to the results of the study as there might be some cases with ADRs caused by concomitantly used solvents.

The shortcomings of the data source being used may also bring bias to the result of the study. As this study depicted the safety profile of TCM injections based on statistics of adverse events collected from SRS system. As underreporting is a significant problem for all adverse drug event (ADE) collection systems of this type and may provide a relatively small and perhaps biased view of the cases that actually exist in practice.⁴⁷ Besides, all the data were extracted from just one provincial ADR center in southern China, some degree of underrepresentation of some TCM injections may also bring bias to the result of the study.

5 | CONCLUSION

Statistics proved that the risk of adverse effects of TCM injections, like conventional injections, is much higher than any other dosage forms. The risk of new or serious ADRs for TCM injections is much higher than other TCM medications. Compared with conventional injections, TCM injections have a slightly lower percentage of serious ADRs and a much higher percentage of unknown (new) ADRs. A lot of work needs to be done to clarify such a huge amount of potential unknown adverse effects related to TCM injections. The risks of ADRs increased with age. Anaphylactic shock and anaphylactoid reaction are high-risk ADRs for TCM injections. A series of features of China's SRS system can also be drawn from statistics of the adverse reports of TCM injections. China's SRS system somewhat like a less strict random sample of drug users and could be used to depict the safety profile of a drug or a group of drugs.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

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

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Supplementary Table 1 Therapeutic classes and generic names of the 110 TCM injections

Categories	The drugs
Blood circulation promoting (N=37)	Xueshuantong injection, Shengmai injection, Xuesaitong injection, Shuxuening injection, Danshen injection, Shuxuetong injection, Xiangdan injection, Dengzhanhuasu injection, Xingnaojing injection, Danhong injection, Honghua injection, Huangqi injection, Danshen Duofensuan powder for injection, Ciwujia injection, Honghuahuangsesu powder for injection, Dengzhanxin injection, Kudiezi injection, Dazhuhongjingtian injection, Guanxinning injection, Fufang Danshen injection ^b , Mailuoning injection, Lulutong injection ^b , Honghuahuangsesu Luhua injection, Danxiangguanxin injection ⁿ , Fufang Danggui injection, Fufang Maodongqing injection ^a , Xiatianwu injection, Yinxingneizhi injection, Danxiang Putaotang solution for intravenous drip, Dengzhanhuasu Putaotang injection, Dengzhanhuasu powder for injection, Xuesaitong powder for injection, Xueshuantong powder for injection, Danshen powder for injection, Danshen solution for intravenous drip, Danhong solution for intravenous drip, Danshen Duofensuan powder for injection.
Antipyretic (N=32)	Qingkailing injection, Tanreqing injection, Shuanghuanglian injection, Xiyanping injection, Reduning injection, Xuebijing injection, Yuxingcao injection, Yinzhihuang injection, Chaihu injection, Shuganning injection, Lianbizhi injection, Kuhuano injection, Huangtengsu injection, Fufang Banbianlian injection, Kumu injection, Banlangen injection, Danmu injection, Yezhuo injection, Zhongjiefeng injection, Yujin injection, Chuanxinlian injection, Tuijiedu injection, Fufang Pugongying injection, Baihuasheshecao injection, Ganyanling injection, Lingyangjiao injection, Yinhuang injection, Sangjiangganmao injection, Shenggangbingdu injection, Yanhuanglian injection, Shuanghuanglian powder for injection, Qingkailing powder for injection.
Anticancer (N=14)	Shenmai injection, Shenqifuzheng injection, Kangai injection, Aidi injection, Xiangguduotang injection, Fufang Kushen injection, Yadanziyuru injection, Kanglaite injection, Renshenduo injection, Huachansu injection, Xiaoaiping injection, Chansu injection, Delisheng injection ^b , Zhulingduotang injection.
Pain-alleviating (N=12)	Zhengqingfengtongning injection, Fufang Fengshining injection, Yemugua injection, Zushima injection, Dinggongteng injection, Jiangu injection, Honghuixiang injection, Huangruixiang injection, Yitongshu injection, jishiteng injection, Xuelian injection, Xueshangyizhihaozongjian injection.
Other TCM injections ^c (N=15)	Shenfu injection, Yiqifumai powder for injection, Shengkang injection, Fufang Shexiang injection, Dilong injection, Gualoupi injection, Chuankezhi injection, Yimucao injection, Lurong injection, Xiaozhiling injection, Buguzhi injection, Ganlean injection ^b , Gaolishen injection ^a , Lishen injection ^a , Zhichuanling injection.

^a Presently approved as hospital preparations by Guangdong provincial drug regulatory agency and the use are strictly confined to the approved hospitals.

^b Formerly approved by CFDA and has now been suspended.

^c Other TCM injections include injections for diseases of the skin, haemorrhoids, parasites and so on.

Supplementary Table 2 TCM injections with no ADR reported in the dataset

No.	Generic names	Description of composition or raw herbal materials
1	Kangsaixianyan injection	LONICERAE JAPONICAE CAULIS.
2	Maodongqing injection	ILEX PUBESCENS HOOK. ET ARN.
3	Tianjihuang injection	HYPERICUM JAPONICUM THUNB. EX MURRAY.
4	Banlanjiedu injection	BAPHICACANTHIS CUSIAE RHIZOMA ET RADIX.
5	bozhijun injection	GANDERMA CAPENSE.
6	Breviscapine sodium chloride injection	BREVISCAPINE.
7	lemahui injection	VERONICA LINARIIFOLIA SUBSP. DILATATA.
8	Quchongbanjiu injection	VERNONIA ANTHELMINTICA.
9	Renshentangtai injection	GLYCOPEPTIDES OF GINSENG RADIX ET RHIZOMA.
10	Tubeimuzaogan injection	TOTAL SAPONINS EXTRACTED FROM THE BULBS OF BOLBOSTEMMA PANICULATUM [MAXIM] FRANQUET.
11	Xiaotongning injection	SINOMENINE HYDROCHLORIDE.
12	Xinmailong injection	POLYPEPTIDES, NUCLEOSIDES AND COMPOUND AMINO ACIDS ETC FROM PERIPLANETA AMERICANA.
13	Fengdu powder for injection	THE VENOM FROM THE STING GLANDS OF THE WORKER BEES OF APIS CERANA FABR.
14	Huangqiduot powder for injection	ASTRAGALUS POLYSACCHARIDES FROM ASTRAGALI RADIX.
15	Chaixinganmao injection	BUPLEURI RADIX, ASARI RADIX ET RHIZOMA.
16	Wutou injection	ACONITI RADIX, ACONITI KUSNEZOFFII RADIX.
17	Dangguijisheng injection	ANGELICAE SINENSIS RADIX, VISCIHERBA.
18	Rekeping injection	BUPLEURUM CHINENSE, CENTIPEDAE HERBA.
19	Qinggan injection	ISATIDIS RADIX, ARTEMISIAE SCOPARIAE HERBA, GLYCYRRHIZAE RADIX ET RHIZOMA.
20	Fantengzhi injection	ALUMEN, FIBRIURETININ, HALLOYSITUM RUBRUM.
21	Shaobei injection	CITRIC ACID, GALLIC ACID, TOTAL GLUCOSIDES OF PAEONIA.
22	Tongan injection	SINOMENII CAULIS, CHELIDONII HERBA, MACROPANAX ROSTHORNII.
23	Yinxingertieneizhipuan injection	GINKGOLIDES A, B AND K.
24	Quganre injection	ARUNDO DONAX, ARTEMISIAE ANNUAE HERBA, BUPLEURUM MARGINATUM, GYPSUM FIBROSUM.
25	Chuanshentong injection	SALVIAE MILTIORRHIZAE RADIX ET RHIZOMA, OPHIOPOGONIS RADIX, ANGELICAE SINENSIS RADIX, CHUANXIONG RHIZOMA.
26	Fufang daqingye injection	LONICERAE JAPONICAE FLOS, NOTOPTERYGII RHIZOMA ET RADIX, BISTORTAE RHIZOMA, RHEI RADIX ET RHIZOMA.
27	Gulaodi injection	NOTOGINSENG RADIX ET RHIZOMA, ASTRAGALI RADIX, DRYNARIAE RHIZOMA, OLIBANUM, MYRRHA.
28	Ruxiankang injection	SPATHOLOBI CAULIS, PHERETIMA, SALVIAE MILTIORRHIZAE RADIX ET RHIZOMA, BISTORTAE RHIZOMA, CURCUMAE RHIZOMA, TRICHOSANTHIS FRUCTUS.
29	Qingrejiedu injection	LONICERAE JAPONICAE FLOS, SCUTELLARIAE RADIX, FORSYTHIAE FRUCTUS, GENTIANAE RADIX ET RHIZOMA, GYPSUM FIBROSUM, ANEMARRHENAE RHIZOMA, GARDENIAE FRUCTUS, ISATIDIS RADIX, REHMANNIAE RADIX, OPHIOPOGONIS RADIX, HERBA GUELLENSTAEADTIAE, SCROPHULARIAE RADIX.
30	Yuangqinzhitong injection	CORYDALIS, RADIX ACONITI PREPARATA, GENTIANA MACROPHYLLA, STEPHANIA TETRANTRA, CHELIDONIUM MAJUS.
31	Fufang Haqing injection	TOAD, ASTRAGALUS, GINKGO BILOBA, ARMENIACAE SEMEN AMARUM, ASTER TATARICUS, PEUCEDANUM PRAERUPTORUM DUNN, SCHISANDRA CHINENSIS, ACONITUM NAPELLUS, BLACK PEPPER.

Supplementary Table 3 Annual number of ADR reports and corresponding percentages for conventional injections and TCM injections

Year	No. of total cases	Conventional medicine		TCM	
		No. of total cases	No. of injection (%)	No. of total cases	No. of injection (%)
2003	415	344	249 (72.38)	71	57 (80.28)
2004	3,508	2,972	2,417 (81.33)	536	476 (88.81)
2005	5,166	4,469	3,744 (83.78)	697	588 (84.36)
2006	14,807	12,790	10,760 (84.13)	2,017	1,692 (83.89)
2007	22,425	19,351	16,213 (83.78)	3,074	2,515 (81.82)
2008	32,217	27,780	22,823 (82.16)	4,437	3,740 (84.29)
2009	35,267	30,676	25,108 (81.85)	4,591	3,631 (79.09)
2010	35,840	31,529	25,861 (82.02)	4,311	3,493 (81.03)
2011	34,150	29,854	23,654 (79.23)	4,296	3,440 (80.07)
2012	34,586	29,839	24,651 (82.61)	4,747	3,951 (83.23)
2013	38,300	33,300	27,387 (82.24)	5,000	4,249 (84.98)
2014	44,127	38,401	31,613 (82.32)	5,726	4,883 (85.28)
2015	49,098	42,675	35,440 (83.05)	6,423	5,511 (85.80)
2016	55,679	48,456	39,703 (81.94)	7,223	5,925 (82.03)
2017	60,337	52,628	41,307 (78.49)	7,709	6,092 (79.02)

Supplementary Table 4 Most frequently reported ADRs for conventional injections (top 12)

Rank	Total reports		Serious reports	
	ADRs (WHO-ART Preferred Term)	No. (%) of reports (n=574,610) ^a	ADRs (WHO-ART Preferred Term)	No. (%) of reports (n=48,008) ^b
1	Rash	111,026 (19.32)	Anaphylactic shock	4,501 (9.38)
2	Pruritus	97,642 (16.99)	Rigors	4,107 (8.55)
3	Rigors	37,524 (6.53)	Dyspnoea	2,730 (5.69)
4	Nausea	29,022 (5.05)	Chest pain	2,306 (4.80)
5	Chest pain	24,871 (4.33)	Hyperthermia	1,983 (4.13)
6	Vomiting	23,743 (4.13)	Rash	1,858 (3.87)
7	Dizziness	21,817 (3.80)	Anaphylactoid reaction	1,770 (3.69)
8	Fever	18,639 (3.24)	Pruritus	1,630 (3.40)
9	Anaphylactoid reaction	17,534 (3.05)	Fever	1,430 (2.98)
10	Flushing	17,511 (3.05)	Dizziness	1,346 (2.80)
11	Palpitations	13,666 (2.38)	Palpitations	1,203 (2.51)
12	Rash maculo-papular	12,043 (2.10)	Vomiting	991 (2.06)

^a 574,610 drug-ADR combinations obtained from the split of the adverse reactions of the total 330,930 original reports.

^b 48,008 drug-ADR combinations contained from the split of the adverse reactions of the 22,258 original serious reports.

Supplementary Table 5 Most frequently reported ADRs for blood circulation promoting TCM injections (top 12)

Rank	Total reports		Serious reports	
	ADRs (WHO-ART Preferred Term)	No. (%) of reports (n=48,754) ^a	ADRs (WHO-ART Preferred Term)	No. (%) of reports (n=4,407) ^b
1	Rigors	7,024 (14.41)	Rigors	630 (14.30)
2	Pruritus	6,270 (12.86)	Dyspnoea	573 (13.00)
3	Rash	5,925 (12.15)	Hyperpyrexia	330 (7.49)
4	Chest pain	3,709 (7.61)	Chest pain	278 (6.31)
5	Fever	3,116 (6.39)	Fever	235 (5.33)
6	Dyspnoea	2,621 (5.38)	Anaphylactic shock	176 (3.99)
7	Palpitations	2,440 (5.00)	Palpitations	173 (3.93)
8	Dizziness	2,277 (4.67)	Dizziness	135 (3.06)
9	Flushing	1,995 (4.09)	Pruritus	131 (2.97)
10	Nausea	1,542 (3.16)	Anaphylactoid reaction	123 (2.79)
11	Anaphylactoid reaction	1,121 (2.30)	Rash	111 (2.52)
12	Vomiting	1,066 (2.19)	Flushing	96 (2.18)

^a 48,754 drug-ADR combinations obtained from the split of the adverse reactions of the total 25,536 original reports.

^b 4,407 drug-ADR combinations obtained from the split of the adverse reactions of the total 1,663 original reports.

Supplementary Table 6 Most frequently reported ADRs for antipyretic TCM injections (top 12)

Rank	Total reports		Serious reports	
	ADRs (WHO-ART Preferred Term)	No. (%) of reports (n=26,991) ^a	ADRs (WHO-ART Preferred Term)	No. (%) of reports (n=1,846) ^b
1	Rash	6,291 (23.31)	Rigors	286 (15.49)
2	Pruritus	5,060 (18.75)	Dyspnoea	212 (11.48)
3	Rigors	2,132 (7.90)	Hyperpyrexia	166 (8.99)
4	Anaphylactoid reaction	1,174 (4.35)	Anaphylactic shock	147 (7.96)
5	Chest pain	1,029 (3.81)	Chest pain	85 (4.60)
6	Fever	984 (3.65)	Dizziness	75 (4.06)
7	Flushing	960 (3.56)	Anaphylactoid reaction	73 (3.95)
8	Dyspnoea	958 (3.55)	Fever	72 (3.90)
9	Rash maculo-papular	919 (3.40)	Rash	68 (3.68)
10	Dizziness	910 (3.37)	Muscle contractions involuntary	54 (2.93)
11	Nausea	723 (2.68)	Cyanosis	52 (2.82)
12	Vomiting	620 (2.30)	Pruritus	51 (2.76)

^a 26,991 drug-ADR combinations obtained from the split of the adverse reactions of the total 15,553 original reports.

^b 1,846 drug-ADR combinations obtained from the split of the adverse reactions of the total 809 original reports.

Supplementary Table 7 Most frequently reported ADRs for anticancer TCM injections (top 12)

Rank	Total reports		Serious reports	
	ADRs (WHO-ART Preferred Term)	No. (%) of reports (n=14,554) ^a	ADRs (WHO-ART Preferred Term)	No. (%) of reports (n=1,026) ^b
1	Chest pain	1,779 (12.22)	Dyspnoea	180 (17.54)
2	Rigors	1,712 (11.76)	Rigors	112 (10.92)
3	Dyspnoea	1,265 (8.59)	Chest pain	81 (7.89)
4	Rash	1,184 (8.14)	Anaphylactic shock	53 (5.17)
5	Pruritus	1,113 (7.65)	Dizziness	44 (4.29)
6	Palpitations	1,010 (6.94)	Hyperpyrexia	43 (4.19)
7	Flushing	916 (6.29)	Fever	41 (4.00)
8	Fever	807 (5.54)	Palpitations	40 (3.90)
9	Dizziness	750 (5.15)	Flushing	39 (3.80)
10	Nausea	474 (3.26)	Anaphylactoid reaction	36 (3.51)
11	Anaphylactoid reaction	457 (3.14)	Muscle contractions involuntary	28 (2.73)
12	Vomiting	318 (2.18)	Cyanosis	24 (2.34)

^a 14,554 drug-ADR combinations obtained from the split of the adverse reactions of the total 7,415 original reports.

^b 1,026 drug-ADR combinations obtained from the split of the adverse reactions of the total 405 original reports.

Supplementary Table 8 Most frequently reported ADRs for pain-alleviating TCM injections (top 12)

Rank	Total reports		Serious reports	
	ADRs (WHO-ART Preferred Term)	No. (%) of reports (n=411) ^a	ADRs (WHO-ART Preferred Term)	No. (%) of reports (n=24) ^b
1	Pruritus	139 (33.82)	Quadriplegia	3 (12.50)
2	Rash	73 (17.76)	Dizziness	3 (12.50)
3	Flushing	37 (9.00)	Anaphylactic shock	2 (8.33)
4	Dizziness	26 (6.33)	Hypoaesthesia	2 (8.33)
5	Anaphylactoid reaction	17 (4.14)	Vomiting	2 (8.33)
6	Injection site pruritus	14 (3.41)	Rigors	2 (8.33)
7	Chest pain	10 (2.43)	Palpitations	2 (8.33)
8	Rash maculo-papular	9 (2.19)	Flushing	1 (4.17)
9	Hypoaesthesia	8 (1.95)	Muscle contractions involuntary	1 (4.17)
10	Pain	7 (1.70)	Anaphylactoid reaction	1 (4.17)
11	Fever	6 (1.46)	Dyspnoea	1 (4.17)
12	Rash erythematous	6 (1.46)	Vision abnormal	1 (4.17)

^a 411 drug-ADR combinations obtained from the split of the adverse reactions of the total 239 original reports.

^b 24 drug-ADR combinations obtained from the split of the adverse reactions of the total 9 original reports.

Supplementary Table 9 Most frequently reported ADRs for other TCM injections ^c (top 12)

Rank	Total reports		Serious reports	
	ADRs (WHO-ART Preferred Term)	No. (%) of reports (n=2,956) ^a	ADRs (WHO-ART Preferred Term)	No. (%) of reports (n=380) ^b
1	Rigors	504 (17.05)	Rigors	71 (18.68)
2	Chest pain	287 (9.71)	Dyspnoea	66 (17.37)
3	Rash	264 (8.93)	Hyperpyrexia	29 (7.63)
4	Pruritus	254 (8.59)	Chest pain	28 (7.37)
5	Fever	236 (7.98)	Fever	23 (6.05)
6	Dyspnoea	211 (7.14)	Palpitations	20 (5.26)
7	Dizziness	148 (5.01)	Anaphylactic shock	13 (3.42)
8	Palpitations	145 (4.91)	Dizziness	13 (3.42)
9	Flushing	110 (3.72)	Flushing	12 (3.16)
10	Nausea	102 (3.45)	Tachycardia	11 (2.89)
11	Vomiting	77 (2.60)	Cyanosis	10 (2.63)
12	Hyperpyrexia	63 (2.13)	Hypertension	9 (2.37)

^a 2,956 drug-ADR combinations obtained from the split of the adverse reactions of the total 1,500 original reports.

^b 380 drug-ADR combinations obtained from the split of the adverse reactions of the total 140 original reports.

^c TCM injections with therapeutic functions other than blood circulation promoting, antipyretic, anticancer or pain-alleviating, including injections for diseases of the skin, haemorrhoids, parasites and so on.

Supplementary Table 10 Main routes of administration and the corresponding number of ADR reports for conventional injections

Routes of administration	No. of reports	Percentage (%)
Intravenous drip	288,930	87.31
Intravenous push	20,802	6.29
Intramuscular injection	11,872	3.59
Special route ^a	9,326	2.81
Total	330,930	100.00

^a Special route: subcutaneous injection, intracutaneous injection, intraperitoneal injection, intra-arterial injection, intrathecal injection, and so on.

Supplementary Table 11 Sources of ADR reports for conventional injections

Sources of reports	N	%
Profession of the reporter		
Physician	222,961	67.37
Nurse	72,034	21.77
Pharmacist	32,294	9.76
Consumer or unknown reporter	3641	1.10
Type of reporting body		
Medical institution	328,072	99.14
Distributor	2,034	0.61
Manufacturer	389	0.12
Consumer or unknown institution	435	0.13

Supplementary Fig. 1 Age-specific ADR reporting rates for conventional injections (per million inhabitants)

