

Severe cutaneous adverse drug reactions of Chinese inpatients: a meta-analysis*

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Abstract: **BACKGROUND:** The rate of severe cutaneous adverse drug reactions is low, and these reactions can result in death or disability. An evidence-based epidemiological study of severe cutaneous adverse drug reactions in China has not been reported. **OBJECTIVE:** The aim of this study was to analyze epidemiology and characteristics of severe cutaneous adverse drug reactions of Chinese inpatients during the recent 15 years with meta-analysis.

METHODS: We retrospectively reviewed Chinese literature reporting severe cutaneous adverse drug reactions and collecting data from 2000 to 2015, which were in accordance with our inclusion criteria. All included data were analyzed with the Launch Open Meta-Analyst software.

RESULTS: Twenty-five articles involving 928 cases with severe cutaneous adverse drug reactions were included. Men to women ratio was 1.14:1. Twenty-one per cent of the patients had drug allergy history. Antibiotics (26.0%), sedative hypnotics and anticonvulsants (21.6%), and antipyretic analgesics (17.1%) were the most common causative drugs. The most frequent clinical subtype was Stevens-Johnson syndrome (50.1%), followed by toxic epidermal necrolysis (25.4%), exfoliative dermatitis (21.0%) and drug-induced hypersensitivity syndrome (1.6%). In addition to skin rashes, patients with severe cutaneous adverse drug reactions suffered mostly from fever (73%), and blood routine abnormality (66.7%).

STUDY LIMITATIONS: This meta-analysis is limited by its retrospective design and by its methodological variation.

CONCLUSION: The most common causative drugs were antibiotics and sedative hypnotics and anticonvulsants. Stevens-Johnson syndrome was the most frequent clinical subtype of severe cutaneous adverse drug reactions. In addition to skin rashes, patients with severe cutaneous adverse drug reactions suffered mostly from fever, mucosal lesion, and hematologic abnormalities.

Keywords: Drug eruptions; Meta-analysis; Dermatitis

INTRODUCTION

Adverse cutaneous drug reactions (ACDRs) are the most frequent adverse events resulting from drug treatment. Studies have shown that up to 6.7% of hospitalized patients present some degree of ACDR, with severe forms ranging from 0.33% to 3%.¹⁻³ Although the rate of severe cutaneous adverse drug reaction (SCADR) is low, these reactions can affect anyone who takes medications and can result in death or disability.⁴

The World Health Organization defines SCADRs are those requiring hospitalization or that extend the length of hospital stay, resulting in persistent or significant disability or life-threatening.³ The spectrum of SCADRs includes Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-induced hypersensitivity syndrome (DIHS)/ Drug rash with eosinophilia and systemic symptoms (DRESS).⁵ DIHS is a new type of adverse drug reaction (ADR) and is considered a SCADR. In China, exfoliative dermatitis (ED) is also classified as SCADR.⁶

During the past 15 years, numerous studies regarding SCADRs have been reported in China. However, there were incon-

sistent results and insufficient statistical power. Moreover, it is very important to acquire knowledge on SCADRs for their great impact on morbidity and mortality rates, and on hospital costs. These reasons motivated us to carry out this study to explore the characteristics of SCADRs of Chinese inpatients.

METHODS

Selection

Electronic databases were searched using the following key words: severe cutaneous adverse drug reactions / severe drug eruptions / severe dermatitis medicamentosa, causative drugs, clinical subtypes, meta-analysis. Databases used were Chinese National Knowledge Infrastructure, Wan Fang Med Online, Chinese Biology Medical Literature Database and VIP Database. The reference sections of all retrieved articles were manually searched for additional studies.

Inclusion criteria

The following criteria were used: (1) The study objects were the Chinese inpatients with severe drug eruptions; (2) All the arti-

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cles were included from the Chinese core journals, the Chinese core journals of science and technology, or the dissertations; (3) Data sources between 2000-2015 were included; (4) The latest article was selected on condition that the identical data sets were published in different journals; (5) The data of gender, history of drug allergy, causative drugs, clinical subtypes, physical examinations, or laboratory examinations were complete. According to inclusion criteria, two investigators independently scrutinized all articles and screened standard articles.

Data extraction

To test for reliability of our extraction process, two investigators independently extracted data of the included articles. We extracted data of total number of the patients, the number of men and women, history of drug allergy, causative drugs, clinical subtypes, relation between causative drugs and clinical subtypes, physical and laboratory examinations. Other information extracted included first author, publication year of the articles, name of standard journal or dissertations in each study.

Statistical analysis

The Launch Open Meta Analyst was used to analyze all included studies. The effect size (ES), 95% confidence intervals (CI), and P value were calculated. Heterogeneity of studies was examined by the inconsistency index (I²) test. According to the inconsistency index, the random-effect model and the fixed-effect model were chosen. If a statistical difference existed in terms of heteroge-

neity (I²>50%), a random effect model was adopted as the analysis method. Otherwise, a fixed-effect model was used.

RESULTS

Literature retrieval

According to our criteria, 2425 articles were retrieved. Five hundred articles of obvious irrelevance were excluded. There were 1825 excluded articles that were reviewed, but were not included because they were case report, single clinical subtype, single causative drug study or duplicated publication after screening the articles. In addition, 75 articles were excluded (not published in the last 15 years and data sources before 2000, not core journals, or had insufficient data). Finally, 25 articles were included in our meta-analysis. Features of these 25 studies are presented in table 1.⁷⁻³¹

Results of meta-analysis

Gender proportion

Twenty-five studies reported the gender of patients. There were 928 patients, comprising 495 men and 433 women. The proportion of men was 53.2% [I²=56%, 95%CI (0.484 to 0.581), P<0.001]. The proportion of women was 46.8% [I²=56%, 95%CI (0.419 to 0.516), P<0.001]. The man to woman ratio was 1.14:1.

History of drug allergy

There were 13 articles analyzing drug allergy history. The proportion of drug allergy history was 21.3% [I²=79%, 95%CI (0.136 to 0.290), P<0.001] (Figure 1).

TABLE 1: Basic features of the included 25 articles for meta-analysis

Study	Year	Cases	Gender		Age (Year)	Region	CD	CS	R	PLE
			Male	Female						
Li ⁷	2014	23	11	12	4-82	East	D	D	N	N
Yang ⁸	2013	32	15	17	1.5-80	Central China	D	D	N	N
Li ⁹	2013	42	29	13	6-74	South	D	D	Y	Y
Sun ¹⁰	2013	29	17	12	5-12	East	D	D	N	Y
Fang ¹¹	2012	51	32	19	3m-14.5	Southwest	D	D	N	N
Ji ¹²	2012	46	22	24	13-81	East	D	D	Y	Y
Su ¹³	2012	28	16	12	5-68	North	D	D	N	Y
Wei ¹⁴	2012	76	45	31	6-73	North	D	D	Y	Y
Liu ¹⁵	2012	82	38	44	15-68	North	D	D	N	Y
Chen ¹⁶	2011	62	21	41	11-70	North	D	D	Y	Y
Wang ¹⁷	2010	38	27	11	20-79	Central China	D	D	Y	Y
Liu ¹⁸	2010	44	23	21	11-76	North	D	D	N	Y
Kang ¹⁹	2009	25	14	11	6m-16	Northwest	D	D	Y	Y
Luo ²⁰	2009	33	12	21	60-83	South	D	D	N	Y
Zhang ²¹	2008	24	8	16	5-67	Central China	D	D	N	Y
Zhu ²²	2008	74	48	26	12-87	East	D	D	N	Y
Luo ²³	2008	24	10	14	6m-8	South	D	D	N	Y
Wang ²⁴	2007	19	13	6	9-78	Central China	D	D	N	Y
Zou ²⁵	2007	31	19	12	1-71	Central China	D	D	N	Y
Miao ²⁶	2006	22	15	7	4-91	Central China	D	D	Y	Y
Hu ²⁷	2006	24	8	16	33-82	East	D	D	Y	Y
Xu ²⁸	2006	29	17	12	15-79	East	D	D	Y	Y
Chen ²⁹	2005	24	9	15	15-54	Northeast	D	D	Y	Y
Xiao ³⁰	2004	22	13	9	1-17	Southwest	D	D	Y	Y
Fang ³¹	2004	24	13	11	12-84	Southwest	D	D	Y	N

CD=Causative drug, CS=clinical sub-types, R=Relationship between causative drug and clinical sub-types, PLE= Physical and laboratory examinations, D=Detailed data, Y = Mentioned, N = Not mentioned.

Causative drugs

Twenty-five articles described causative drugs in detail. As presented in Figure 2, antibiotics (29.2%), sedative hypnotics and anticonvulsants (SHA) (26.0%), and antipyretic analgesics (AA) 17.1% were the most common causative drug groups. Gout suppressants (GS) were responsible for 11.0%. Chinese medicine and Chinese patent medicine (CMCPM) was implicated in 2.2%, others in 2.1%, unknown drugs (UD) in 1.7%, unconfirmed drugs (UCD) in 1.5% and biological agents (BA) in 1.4%.

Clinical subtypes

Clinical subtypes of SCADRs were analyzed in 25 articles. As shown in Figure 3, the most frequent clinical type of SCADRs was SJS (50.1%), followed by TEN 25.4% and ED 21.0%. However, the proportion of DIHS was only 1.6%.

Relation between causative drugs and clinical subtypes

There were 12 studies exposing the relation between causative drugs and clinical subtypes. Causative drugs of SCADRs and their major clinical subtypes are presented in table 2. Clinical subtypes of SCADRs and their most frequent causative drugs are shown in Table 3.

Physical and laboratory examinations

As shown in Figure 4, fever was implicated in 73.0% of cases; 63.8% of the patients had mucosal lesions (ML) (given the insufficiency of other data of physical examinations, such as edema, lymphadenomegaly, etc., only fever and ML were analyzed). Blood routine abnormality (BRA) was presented in 66.7%. The incidence of liver dysfunction (LD) was 41.8%, urinalysis abnormality (UA) 32.5%. Electrolyte imbalance (EI) was presented in 29.5% of the patients, renal dysfunction (RD) in 16.8%, cardiac enzymes abnormality (CEA) in 15.2% and stool routine abnormality (SRA) in 8.4%.

Publication bias

In this meta-analysis, there was no significant publication bias for gender proportion, history of drug allergy, physical and laboratory examinations. However, possible publication bias may exist for causative drugs, clinical subtypes, relation between causative drugs and clinical subtypes. Publication bias is derived from exclu-

sion of results that were not published. We specifically acknowledge the limitations and expect more studies. Nevertheless, a possible publication bias does not affect the main results.

Influence analysis

Influence analysis was performed to investigate the influence of a single study on the overall analysis. The heterogeneities were not changed significantly after exclusion of any single study. Furthermore, the corresponding pooled standardized mean difference (SMD) and 95% CI were not conspicuously altered with any single study excluded. Therefore, the reliability of the results was enhanced by the influence analysis.

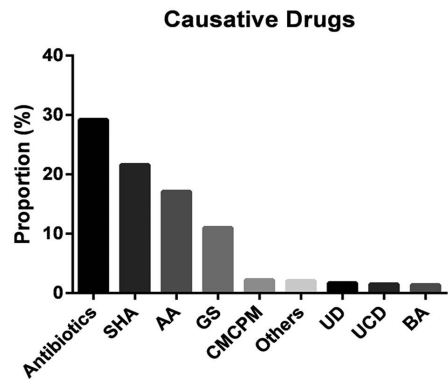


FIGURE 2: Proportions of causative drugs of severe cutaneous adverse drug reactions. The meta-analysis included 928 patients. As the figure shows, the proportion of antibiotics was 29.2% [I²=76%, 95%CI (0.235 to 0.348), P<0.001], sedative hypnotics and anticonvulsants (SHA) 21.6% [I²=81%, 95%CI (0.163 to 0.268), P<0.001], antipyretic analgesics (AA) 17.1% [I²=65%, 95%CI (0.171 to 0.210), P<0.001], gout suppressants (GS) 11.0% [I²=81%, 95%CI (0.077 to 0.143), P<0.001], Chinese medicine and Chinese patent medicine (CMCPM) 2.2% [I²=0%, 95%CI (0.013 to 0.032), P=0.663], others 2.1% [I²=0%, 95%CI (0.012 to 0.030), P=0.607], unknown drugs (UD) 1.7% [I²=4%, 95%CI (0.009 to 0.025), P=0.411], unconfirmed drugs (UCD) 1.5% [I²=3%, 95%CI (0.009 to 0.025), P=0.411] and biological agents (BA) 1.4% [I²=19%, 95%CI (0.007 to 0.143), P=0.201]

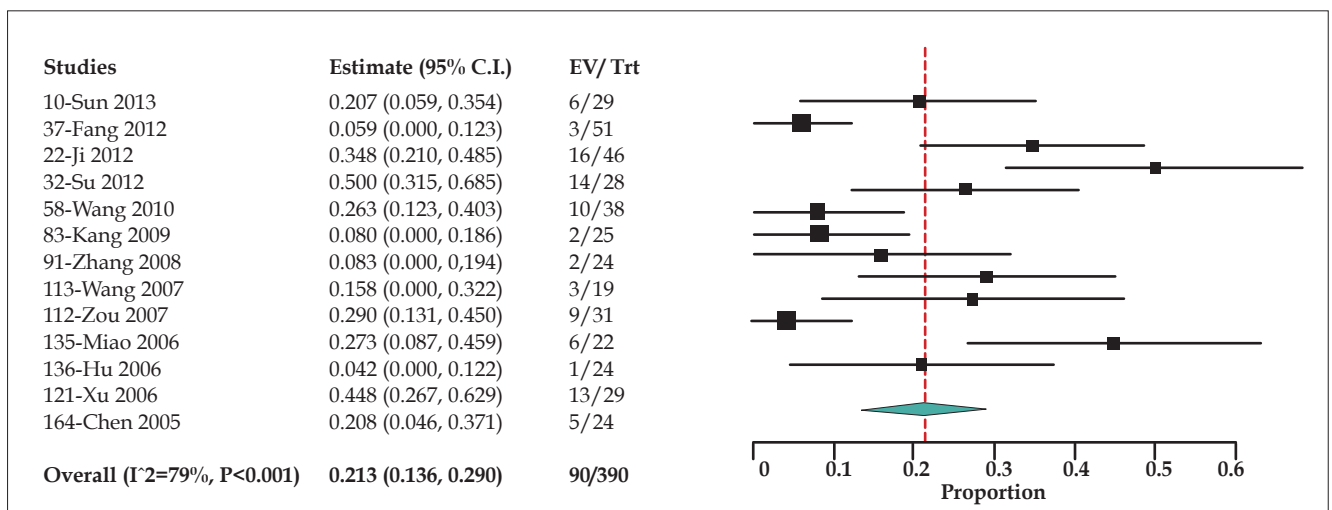


FIGURE 1: Forest plot of drug allergy history. The meta-analysis showed 21.3% of the patients had drug allergy history. [I²=79%, 95%CI (0.136 to 0.290), P<0.001].

DISCUSSION

Epidemiology of SCADRs has been reported in multiple countries and regions.³²⁻³⁴ However, to our knowledge, an epidemiological study of Chinese inpatients with SCADRs has not been reported. This meta-analysis is the first to respectively analyze epidemiology and clinical characteristics of SCADRs among Chinese inpatients during the recent 15 years.

In this meta-analysis, men predominance was found in Chinese inpatients with SCADRs, coincident with previous studies.^{5,35,36} This study also demonstrated that 21.3% of the patients had a history of drug allergy. People with a history of drug allergy may present a defect of detoxification function, which makes them more vulnerable to suffer drug eruptions.

Similar to previous studies, this meta-analysis manifested antibiotics (29.2%) were the most frequent causative drugs for SCADRs, followed by SHA (26.0%).^{5,36-38} AA were implicated in 17.1% of the patients. Inconsistently, some studies reported antibiotics and allopurinol were the most common culprit drugs.^{32,39} It is

noteworthy that CMCPM accounted for 2.2%. CMCPM is commonly used in China. Given that CMCPM are very complex, it is difficult to identify the culprit ingredient in the medicine.

Our study showed SJS (50.1%) was the most common clinical subtype for SCADRs, followed by TEN (25.4%), which was consistent with most studies.^{1,5,32} Interestingly, Grando *et al.* analyzed SCADRs and pointed to the predominance of DIHS. DIHS is a new type of SCADRs that accounted for 1.6% in this study.³ This result may be associated with the insufficient knowledge on DIHS for many Chinese dermatologists.

Antibiotics, the prominent causative drugs, were responsible for 40.7% of SJS, 25.7% of ED and 25.4% of TEN cases. SHA, another common culprit drugs, were implicated in 38.4% of SJS, 35.6% of TEN, 24.3% of DIHS. (Table 2) Besides, our study demonstrated that antibiotics and AA were major causes of SJS. In addition to antibiotics, SHA were the main culprit drugs for TEN (Table 3).

SCADRs may affect multiple organs and present with other systemic symptoms. In a previous study, 85.7% of patients developed hepatitis, 65.7% fever, 54.3% leukocytosis, and 31.4% developed acute renal insufficiency. Su *et al.* reported that transaminitis (37.5%) and gastrointestinal manifestations (25%) were the most common complications.³² This pooled estimate revealed 73.0% and 63.8% of the patients suffered from fever and mucosal lesions, respectively. Blood routine abnormality (66.7%) and liver dysfunction (41.8%) were most frequent abnormal examinations in laboratory investigations.

CONCLUSION

This meta-analysis is the first to retrospectively analyze the epidemiology and characteristics of SCADRs among Chinese inpatients during the recent 15 years. Men were slightly more af-

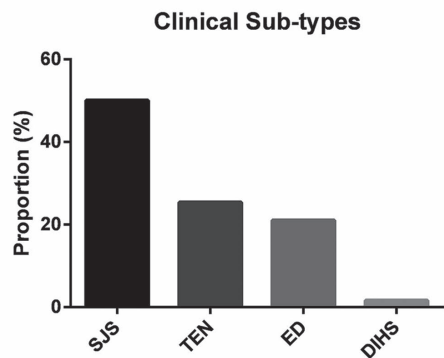


FIGURE 3: Proportions of clinical sub-types of severe cutaneous adverse drug reactions. The meta-analysis included 928 patients. As the figure shows, the most frequent clinical sub-type was Stevens-Johnson syndrome (SJS) (50.1%) [I2=84%, 95%CI (0.425 to 0.577), P<0.001], followed by toxic epidermal necrolysis (TEN) (25.4%) [I2=74%, 95%CI (0.202 to 0.306), P<0.001], then exfoliative dermatitis (ED) (21.0%) [I2=82%, 95%CI (0.156 to 0.264), P<0.001]. The proportion of drug-induced hypersensitivity syndrome (DIHS) was 1.6% [I2=0%, 95%CI (0.008 to 0.024), P=0.799]

Causative drugs	Clinical sub-types			
Antibiotics	SJS (40.7%)	ED (25.7%)	TEN (25.4%)	DIHS (9.9%)
AA	SJS (53.0%)	TEN (23.7%)	DIHS (16.4%)	ED (8.5%)
SHA	SJS (38.4%)	TEN (35.6%)	DIHS (24.3%)	ED (15.2%)
GS	SJS (42.4%)	ED (23.7%)	TEN (20.9%)	DIHS (6.7%)
CMCPM	SJS (56.3%)	ED (39.0%)	TEN (27.1%)	
BA	SJS (40.8%)	TEN (40.6%)	DIHS (20.6%)	ED (4.9%)
UD	TEN (46.1%)	SJS (46.1%)		
UCD	TEN (63.8%)	SJS (25.8%)	ED (23.1%)	DIHS (14.1%)
Others	ED (52.6%)	TEN (31.6%)	SJS (23.4%)	

SJS=Stevens Johnson syndrome, ED=Exfoliative dermatitis, TEN= Toxic epidermal necrolysis, DIHS=Drug-induced hypersensitivity syndrome, AA=antipyretic analgesics, SHA=sedative hypnotics and anticonvulsants, GS=gout suppressants, CMCPM=Chinese medicine and Chinese patent medicine, BA= biological agents, UD=unknown drugs, and UCD=unconfirmed drugs.

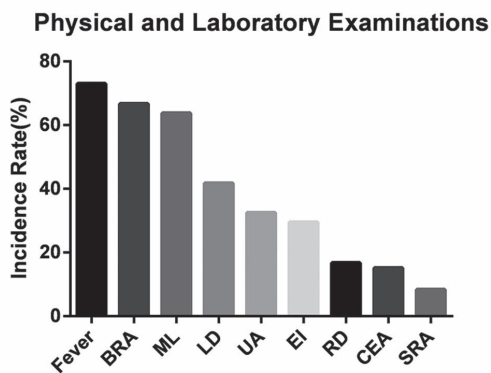


FIGURE 4: Incidence rate of physical and laboratory examinations. As shown in figure, fever (73.0%) [I2=95%, 95%CI (0.645 to 0.816), P<0.001] and blood routine abnormality (BRA) (66.7%) [I2=83%, 95%CI (0.586 to 0.748), P<0.001] were the most frequent clinical features; mucosal lesions (ML) was presented in 63.8% [I2=91%, 95%CI (0.536 to 0.740), P<0.001] of the patients and liver dysfunction (LD) in 41.8% [I2=82%, 95%CI (0.344 to 0.492), P<0.001], urinalysis abnormality (UA) in 32.5% [I2=81%, 95%CI (0.231 to 0.420), P<0.001], electrolyte imbalance (EI) in 29.5% [I2=92%, 95%CI (0.179 to 0.412), P<0.001], renal dysfunction (RD) in 16.8% [I2=70%, 95%CI (0.120 to 0.216), P<0.001], cardiac enzymes abnormality (CEA) in 15.2% [I2=85%, 95%CI (0.083 to 0.221), P<0.001], stool routine abnormality (SRA) was 8.4% [I2=22%, 95%CI (0.056 to 0.112), P=0.232]

TABLE 3: Different sub-types of severe drug eruptions and their frequent causative drugs

Clinical sub-types	Frequent causative drugs		
ED	Antibiotics (31.1%)	GS (14.8%)	SHA (10.3%)
SJS	Antibiotics (28.2%)	AA (25.9%)	SHA (11.9%)
TEN	Antibiotics (25.4%)	SHA (22.0%)	AA (18.3%)
DIHS	Antibiotics (28.1%)	SHA (24.2%)	AA (20.6%)

ED=Exfoliative dermatitis, GS=gout suppressants, SHA=sedative hypnotics and anticonvulsants, SJS=Stevens Johnson syndrome, AA=antipyretic analgesics, TEN= Toxic Epidermal Necrolysis, DIHS=Drug-induced hypersensitivity syndrome

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