

Emergency Management of Anaphylaxis in Chinese Primary Care Units: Systematic Analysis of 77 Cases

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Research

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Abstract

Background Anaphylaxis is a potentially fatal medical emergency and prompt, appropriate administration of epinephrine is critical. However, the actual clinical practices of emergency management of anaphylaxis in Chinese primary care remain unclear.

Objective To evaluate the actual emergency management of anaphylaxis in Chinese primary care units compared to current guidelines.

Methods Systematic analysis of published case reports of anaphylaxis initially treated in Chinese primary care units from January 2014 through December 2018.

Results A total of 77 cases were included in this analysis. The patients came from 22 provinces of China. Mean age was 42 years, and 49 (64.5%) were male. All the patients developed severe anaphylactic reactions, with mortality rate of 5.2%. Only 21 (27.3%) patients received epinephrine as first-line intervention. The first dose of epinephrine ranged from 0.0625 mg to 0.5 mg in children and 0.1 mg to 1.0 mg in adults. The percentage of adult patients who received initial epinephrine dose of 1.0 mg (73.7%) was significantly higher than that of 0.5 mg (19.3%; $p < 0.001$). The percentage of patients who received subcutaneous (SC), intramuscular (IM), or intravenous (IV) bolus injection was 44.3%, 36.1%, and 19.7%, respectively. Among patients who received epinephrine, 80.3% received an overdose. All the 5 patients who developed serious adverse effects associated with epinephrine had received an overdose, and 4 of these had received route of IV bolus injection.

Conclusion and Clinical Relevance The actual emergency management of anaphylaxis in Chinese primary care is not consistent with current guidelines. Under-use, overdose and inappropriate route of epinephrine administration are the major problems. Targeted training is therefore strongly suggested for Chinese general practitioners.

Introduction

Anaphylaxis is a life-threatening medical emergency and prompt appropriate emergency management is critical. International guidelines published by the World Allergy Organization (WAO), the European Academy of Allergy and Clinical Immunology (EAACI), the American Academy of Allergy, Asthma and Immunology (AAAAI), and the American College of Allergy, Asthma and Immunology (ACAAI) concur with the recommendations of intramuscular (IM) injection of epinephrine in the mid-outer thigh as first-line treatment for anaphylaxis, whereas inhaled β 2-adrenergic agonists, H1- and H2-antihistamines, and glucocorticoids are regarded as second or third-line medications^[1-3].

General practitioners play an important role in the management of anaphylaxis. However, prevalent clinical practices with respect to emergency treatment of anaphylaxis in Chinese primary care units are not well identified. Limited studies found under-use and/or inappropriate use of epinephrine during treatment of anaphylaxis in China^[4-6], but all these studies were investigated in large hospitals in Beijing

before the year of 2014; in addition, these reports did not provide specific information about the critical initial treatment of anaphylaxis.

Accordingly, we evaluated the actual emergency treatment of anaphylaxis initially treated in Chinese primary care units by analyzing published cases during period of 2014 to 2018. The objective was to identify the gaps between current clinical practices of initial treatment of anaphylaxis in Chinese primary care units and current guidelines, so as to provide further suggestions for improvement of anaphylaxis management in primary care in China.

Materials And Methods

Search strategy

According to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines, we searched online literature through several international and Chinese databases including PubMed, ScienceDirect, Web of Science, Wanfang database ([http:// med.wanfangdata.com.cn](http://med.wanfangdata.com.cn)), China National Knowledge Internet database (<http://www.cnki.net>), and VIP database ([http://www. cqvip.com](http://www.cqvip.com)). The following key words were used for the literature search: “anaphylaxis”, “anaphylactic reaction”, “anaphylactic reactions”, “reaction, anaphylactic”, “reactions, anaphylactic”, “anaphylactic shock”, “shock, anaphylactic”, “kounis syndrome”, “kounis” and “china”. In addition, the reference lists of the retrieved articles were manually screened to identify additional eligible studies.

Selection criteria

Case reports pertaining to anaphylaxis that qualified the following criteria were included: (a) with definite diagnosis of anaphylaxis based on the anaphylaxis guidelines^[1-3, 7]; (b) initially treated in Chinese primary care units; (c) availability of complete records of the trigger, symptoms and signs, initial treatment, specific dosage and route of epinephrine if used, and outcome; (d) published between January 1, 2014 to December 31, 2018; (e) published in Chinese or English. The exclusion criteria were as the following: (a) duplicate publication; (b) with insufficient data for diagnosis and/or specific emergency medical therapy for anaphylaxis; (c) cardiac arrest occurred before the first administration of epinephrine.

Data extraction

The retrieved articles were screened by 4 investigators. Data pertaining to the following variables were collected: (1) patient characteristics: age, sex, region, allergic history, and risk factors; (2) trigger details: type, route, and time to onset; (3) anaphylactic symptoms: skin-mucosal manifestations, cardiovascular complications, respiratory compromise, gastrointestinal symptoms, etc.; (4) first-line intervention: posture, removal of trigger, medication (epinephrine or non-epinephrine, e.g. glucocorticoids, β 2-adrenergic agonists, H1-antihistamine, H2-antihistamine, vasopressors other than epinephrine, or other medications), supplemental oxygen, intravenous fluids, or other treatments; (5) dosage, administration route, and adverse effects of epinephrine; (6) outcomes.

Adjudication

The physician adjudicators (H.L. and C.J.) independently reviewed each case to validate the diagnosis of anaphylaxis and evaluate the dose and route of epinephrine administration and associated incidence of adverse effects. Disagreements, if any, were resolved by consensus.

The diagnosis of anaphylaxis was validated using the international guidelines^[1-3,7]. Overdose of epinephrine for anaphylaxis was defined as a dose that exceeded the dose recommended by anaphylaxis guidelines, i.e., 0.01 mg/kg of 1:1000 solution with a maximal dose of 0.5 mg in adults or 0.3 mg in children for IM and SC routes, or 0.001 mg/kg of 1:10000 solution or 1:100000 solution with a maximal dose of 0.1 mg for slow IV injection^[1,3,7,8].

Cardiovascular adverse effects were defined according to Campbell et al^[8]. Hypertension was defined as systolic blood pressure \geq 180 mm Hg and/or diastolic blood pressure \geq 120 mm Hg. Cardiac ischemia was determined based on both elevated troponin T level and symptoms of cardiac ischemia. Angina pectoris was defined as chest pressure, tightness or pain without elevation of troponin T level. Stroke was defined as onset of new neurologic deficit. The criteria for evaluation of adverse effects associated with epinephrine were: (1) cases for whom both the administered dose of epinephrine and the route of administration was reported; (2) the onset of cardiovascular complications developed after epinephrine administration; and (3) without concurrent use of epinephrine-like agents (e.g., ephedrine, norepinephrine, hydroxylamine, or dopamine).

Statistical analysis

Statistical analyses were performed with SPSS version 20.0 (SPSS Chicago, IL). Normality of distribution of continuous variables was assessed using single-sample Kolmogorov-Smirnov test. Comparisons between continuous variables were performed by the independent sample *t* test or nonparametric rank test (Mann-Whitney U-test); Comparisons between categorical variables were performed by the Chi-squared test or the Fisher's exact test. Statistical significance was set as $P < .05$ and all tests were 2-sided.

Results

Clinical characteristics

A total of 7,579 articles were reviewed and 77 patients were eligible for the present analysis (Fig. 1). The patients came from 22/31 (71.0%) provinces of China (Table 1). Shandong, Jiangsu, Henan, Anhui and Hubei were the top 5 provinces that accounted for the most number of patients (12, 9, 7, 5, and 5, respectively).

Table 2 listed patient characteristics. Median age was 42 years, and 49 (64.5%) were male. Only 24.7% patients had a history of allergy. The primary triggers of anaphylaxis were antibiotics (44.2%), vaccines

(9.1%), traditional Chinese medicine (7.8%), insect venom (6.5%), foods (5.2%), and antiviral agents (5.2%). With respect to the mode of trigger, IV infusion (59.7%) was the most common route, followed by IM injection (14.3%), oral administration (9.1%), sting (6.5) and SC injection (6.2%). The median time from exposure to the onset of anaphylaxis was 14.3 minutes. All the 77 patients developed severe anaphylactic reactions (hypotension and/or respiratory distress) and 4 of them (5.2%) died.

Emergency management of anaphylaxis

Supplemental oxygen (49.4%) was the most commonly administered initial treatment (Table 3). 74.7% of the patients received oxygen therapy via nasal catheter; 12.7% were administered via face mask. Only 27.3% of the patients received epinephrine as first-line intervention. Glucocorticoids were most commonly administered drugs during the course of anaphylaxis. Out of 77 patients, 73 (94.8%) were administered glucocorticoids, of which dexamethasone accounted for 97.3%; whereas 64 (83.1%) received epinephrine during the course of anaphylaxis.

Dose and route of epinephrine administration

The dose of epinephrine ranged from 0.0625 mg to 0.5 mg among children (age <18 years) and 0.1 mg to 1.0 mg among adults (age ≥65 years) (Table 4)^[9-12]. Among 4 children with available data on dose and route of epinephrine administration, 3 received an overdose of epinephrine, and only 1 received epinephrine intramuscularly. Among 57 adult patients with available data on epinephrine dose and route, 46 (80.7%) received an overdose of epinephrine, of them 42 (73.7%) received an initial dose of 1.0 mg; only 11 adult patients (19.3%; $p < 0.001$) received a recommended initial dose of 0.5 mg. The number of adult patients who received epinephrine by the route of SC, IM, and IV bolus injection was 25 (43.9%), 21 (36.8%), and 11 (19.3%), respectively.

Adverse effects of epinephrine

Among the 64 patients who received epinephrine, 5 developed serious adverse effects associated with epinephrine (Table 5), including 2 cases of hypertension, 1 case of ventricular arrhythmias, 1 case of myocardial ischemia, and 1 case of pulmonary edema. All of them had received an overdose of epinephrine; and 4 of them had received epinephrine by IV bolus injection.

Discussion

To our knowledge, this is the first study that assessed the actual emergency management of anaphylaxis in Chinese primary care by analyzing treatment details in reported cases. To evaluate the appropriateness of clinical practice in Chinese primary care against the guidelines, we analyzed the use of epinephrine as first-line intervention, as first-line medication, and during the whole course of anaphylaxis.

Epinephrine is life-saving for anaphylaxis because of its alpha-1 adrenergic effects on preventing and relieving anaphylactic shock as well as airway obstruction. Failure to use it promptly may lead to fatality,

hypoxic ischemic encephalopathy, or biphasic anaphylaxis^[13, 14]. International guidelines concur with recommendation of epinephrine as first-line drug for treatment of patients with confirmed or suspected anaphylaxis^[15]. However, as shown in our data, there are considerable under-use of epinephrine as first-line treatment in anaphylaxis in Chinese primary care. Moreover, compared to epinephrine, glucocorticoids seem to be more frequently used in Chinese anaphylactic cases. This may imply a general lack of awareness of the appropriate emergency treatment in anaphylaxis among Chinese primary care providers.

According to international guidelines, as the first-line medication choice in anaphylaxis, epinephrine should be injected intramuscularly in the mid-outer thigh at a dose of 0.01 mg/kg of a 1:1000 (1 mg/mL) solution, up to a maximum of 0.5 mg in adults and 0.3 mg in children^[1-3]. However, the first dose of epinephrine showed in this analysis ranged from 0.0625 mg to 1.0 mg, and 80.3% patients had received an overdose of epinephrine. In China, epinephrine is only available in the form of 1 mg: 1 mL (1:1000) ampules, while other concentrations or epinephrine auto-injectors are not available. Another possible reason may be the lack of clarity about appropriate dosage and route of epinephrine administration for different indications, e.g., a first IV bolus dosage of 1 mg (1:10000) is recommended for cardiac arrest^[16-18].

Two pharmacokinetic studies conducted in children and adults demonstrated that, compared to SC injection in the arm, IM injection of epinephrine into the mid-outer thigh is more effective and is therefore recommended by guidelines as the preferred route of epinephrine administration in anaphylaxis^[19, 20]. The SC or inhalational routes for epinephrine are not recommended owing to the lower efficacy. However, most of the patients in this study were treated with epinephrine via SC injection (44.3%), and 19.7% of the patients received IV bolus injection. Data pertaining to the site of injection was available only for 2 patients, and neither of them received epinephrine in accordance with the recommended site of injection.

In patients with adequate circulation, IV injection of epinephrine may cause serious, life-threatening adverse effects. Slow IV infusion, but not IV bolus injection, is considered only when anaphylaxis is refractory to IM injection of regular doses or anaphylactic shock is imminent or has developed. Currently, there is no established dosage for IV infusion of epinephrine in anaphylaxis^[3]. A prospective study demonstrated the efficacy of a 1:100000 solution of epinephrine administered intravenously by infusion pump at the initial rate of 2–10 mg/min and titrated according to the clinical response or side effects^[21, 22]. It is suggested that IV epinephrine for anaphylaxis should be administered under the guidance of those experienced in the use of vasopressors (anesthetists, emergency physicians, etc.) and under close hemodynamic monitoring^[23]. In the present study, 4 of the 5 patients who developed life-threatening adverse effects received epinephrine by IV bolus injection, indicating which is a potentially harmful route of epinephrine administration in anaphylaxis.

Our study indicates that the actual emergency treatment of anaphylaxis in Chinese primary care does not comply with current guidelines. Consistent with the previous study including more inpatients^[24], under-

use, overdose, and inappropriate administration route of epinephrine were identified as the major problems. Notably, none of these problems was noticed or discussed in these publications. This may imply a general lack of awareness about the appropriate dose and route of epinephrine for anaphylaxis in many Chinese primary care providers. Our findings call for more efforts to change this situation. In 2017, Chinese expert consensus of penicillin skin test developed by the Expert Committee on Clinical Application of Antibiotics and Evaluation of Bacterial Resistance of the National Health and Family Planning Commission recommended IM or SC injection of epinephrine for treatment of anaphylactic shock^[25]. Meanwhile, the guidelines for clinical drug use in the Pharmacopoeia of the People's Republic of China (2015 Edition) also recommend SC or IM route of epinephrine administration for treatment of anaphylaxis in adults. Therefore, we strongly underline the need to update the Chinese guidelines for treatment of anaphylaxis in accordance with the international guidelines. In addition, a targeted nationwide educational program about the international anaphylaxis management guidelines should be implemented to facilitate optimal patient care. Moreover, as recommended, written emergency protocol for diagnosis and management of anaphylaxis may be posted in primary care facilities and rehearsed regularly just like cardio-pulmonary resuscitation (CPR).

Limitations

Although reported cases may not be entirely representative of the actual clinical practices, systematic analysis of published case reports was the only feasible way for us to determine emergency treatment details in these patients nationwide. To minimize the risk of bias, we have established rigorous inclusion/exclusion criteria and performed a thorough literature search to include more cases of anaphylaxis initially treated in Chinese primary care units. Moreover, we searched Chinese literature to increase the yield of cases and to improve the representativeness of our findings.

Conclusion

There are some critical gaps between actual emergency management of anaphylaxis in Chinese primary care and international anaphylaxis guidelines. Under-use, overdose and inappropriate route of epinephrine administration are the major problems identified in this analysis. Targeted training in this respect is strongly suggested for Chinese primary care providers.

Declarations

Authors' contributions: C.J. and H.L. designed study; C.J., L.W., C.L., and X.H performed study; C.J. analyzed data; and C.J. wrote the paper.

Conflict of Interest Disclosures: There are no conflicts of interest to declare.

Availability of data and materials: Yes, they are available.

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Tables

Table 1. Geographic distribution of the included patients with anaphylaxis

Province/autonomous regions /municipality, n (%)	Patients with available data, n	Value
Shandong	77	12 (15.6)
Jiangsu	77	9 (11.7)
Henan	77	7 (9.1)
Anhui	77	5 (6.5)
Hubei	77	5 (6.5)
Liaoning	77	4 (5.2)
Xinjiang	77	4 (5.2)
Fujian	77	3 (3.9)
Guangdong	77	3 (3.9)
Guangxi	77	3 (3.9)
Guizhou	77	3 (3.9)
Hebei	77	3 (3.9)
Jilin	77	3 (3.9)
Shanghai	77	3 (3.9)
Beijing	77	2 (2.6)
Heilongjiang	77	2 (2.6)
Hunan	77	1 (1.3)
Inner Mongolia	77	1 (1.3)
Qinghai	77	1 (1.3)
Shaanxi	77	1 (1.3)
Yunnan	77	1 (1.3)
Zhejiang	77	1 (1.3)

The patients were widely distributed across 22 provinces/autonomous regions /municipalities in mainland China. Shandong, Jiangsu, Henan, Anhui and Hubei were the top 5 provinces where the most number of patients with anaphylaxis (12, 9, 7, 5, and 5, respectively) were included in this study.

Table 2. Characteristics of the included patients with anaphylaxis

	Patients with available data, n	Value
Age, median (minimum-maximum), years	74	42 (2-84)
<18, n (%)	74	5 (6.8)
18-44, n (%)	74	32 (43.2)
45-64, n (%)	74	22 (29.7)
≥65, n (%)	74	15 (20.3)
Male, n (%)	76	49 (64.5)
Positive allergic history, n (%)	77	19 (24.7)
Risk factors, n (%)		
Acute infection	77	41 (53.2)
CVD	77	3 (3.9)
Asthma	77	1 (1.3)
Triggers		
Type, n (%)		
Antibiotics	77	34 (44.2)
Vaccines	77	7 (9.1)
TCM (injection)	77	6 (7.8)
Venom	77	5 (6.5)
Foods	77	4 (5.2)
Antiviral agents	77	4 (5.2)
NSAIDs	77	3 (4.5)
Antispasmodic agents	77	2 (3.3)
Others	77	12 (15.6)
Route, n (%)		
IV infusion	77	46 (59.7)
IM	77	11 (14.3)
PO	77	7 (9.1)
Sting	77	5 (6.5)
SC	77	4 (5.2)
IV injection	77	2 (2.6)
ID	77	2 (2.6)
Time of exposure to onset, median (minimum - maximum), min	65	14.3 (1-180)
Severity of the anaphylaxis, n (%)		
Severe	77	77 (100.0)
Moderate	77	0 (0)
Mild	77	0 (0)
Outcome, n (%)		
Recovery	77	73 (94.8)
Death	77	4 (5.2)

Data presented as frequency (%) unless indicated otherwise. Data for the analysis of age, gender, allergic history, risk factors, triggers, time of exposure to onset, severity of the anaphylaxis, and outcomes were available for 74, 76, 77, 77, 77, 65, 77, and 77 patients, respectively. CVD, cardiovascular disease; TCM, traditional Chinese medicine; NSAIDs, nonsteroidal anti-inflammatory drugs non-steroid anti-inflammatory drugs; IV, intravenous; IM, intramuscular; PO, per oral; SC, subcutaneous; ID, intradermal.

] Table 3. Treatment of the included patients with anaphylaxis

	Patients with Available Data, n	Value
First-line treatment, n (%)		
Oxygen	77	38 (49.4)
Epinephrine	77	21 (27.3)
Glucocorticoid	77	10 (13.0)
Fluid	77	5 (6.5)
H1-antihistamine	77	2 (2.6)
Aminophylline	77	1 (1.3)
First-line medication, n (%)		
Epinephrine	77	46 (59.7)
Glucocorticoid	77	21 (27.3)
H1-antihistamine	77	8 (10.4)
Vasopressor	77	1 (1.3)
Aminophylline	77	1 (1.3)
Treatment during the course of anaphylaxis, n (%)		
Glucocorticoids	77	73 (94.8)
Dexamethasone	73	71 (97.3)
Methylprednisolone	73	2 (2.7)
Epinephrine	77	64 (83.1)
Oxygen	77	58 (75.3)
Oral catheter	58	56 (96.6)
Oxygen mask	58	2 (3.4)
Fluid support	77	52 (71.2)
Glucose solution	52	22 (42.3)
Normal saline	52	18 (34.6)
Balanced solution	52	3 (5.8)
Colloid solution	52	3 (5.8)
Glucose saline	52	1 (1.9)
Unspecified	52	5 (9.6)
H1-antihistamines	77	37 (48.1)
Vasopressors	77	11 (14.3)
H2-antihistamines	77	2 (2.6)
Inhaled beta-2 agonists	77	0 (0)

Data presented as frequency (%) unless indicated otherwise. Oxygen (49.4%), epinephrine (27.3%), and glucocorticoid (13.0%) were the top 3 most commonly administered first-line interventions. In the analysis of first-line medications, 46 patients (59.7%) were administered epinephrine, followed by glucocorticoids (27.3%) and Hi-antihistamine agents (10.4%). Glucocorticoids were the most commonly administered drugs during the course of anaphylaxis (94.8%).

Table 4. Initial Dosage and route of administration of Epinephrine

Initial Administration of Epinephrine in Patients with Available Data							
Group (n)	Dosage (mg)	Route (n)					Overdose (n)
		IM	SC	IV injection	Unspecified	Total	
Children (5)	0.5	0	1	0	0	1	1
	0.3	1	0	0	0	1	1
	0.1	0	0	1	0	1	1
	0.0625	0	1	0	1	2	0
	Total	1	2	1	1	5	3
Adults (59)	1.0	13	22	7	0	42*	42
	0.7	0	0	1	0	1	1
	0.5	6	3	2	0	11	2
	0.3	0	0	1	0	1	1
	0.2	1	0	0	0	1	0
	0.1	1	0	0	0	1	0
	Unspecified	0	0	0	2	2	NA
	Total	21	25	11	2	59	46
Total		22	27	12	3	64	49

Data presented as frequency (n) unless indicated otherwise. In adults, the percentage of patients who received a dose of 1.0 mg (73.7%) was significantly higher than that of 0.5 mg (19.3%; $\chi^2=33.886$, $p<0.001$). The number of patients who received IM, SC and IV bolus injection was 22 (36.1%), 27 (44.3%), and 12 (19.7%), respectively. Among the 61 patients with record of both the epinephrine dose and the route, 49 (80.3%) patients received an overdose of epinephrine. IM, Intramuscular; SC, Subcutaneous; IV, intravenous; NA, not available.

* $p<0.01$ versus 0.5 mg.

Table 5. Serious adverse effects associated with epinephrine administration

Serious Adverse effects, n (%)	IM injection (n=1)		IV bolus injection (n=4)		Total (n=54)
	overdose	non-overdose	overdose	non-overdose	
Ventricular arrhythmia	0	0	1 (25.0)	0	1 (20.0)
Hypertension	1 (100.0)	0	1 (25.0)	0	2 (40.0)
Pulmonary edema	0	0	1 (25.0)	0	1 (20.0)
Myocardial ischemia	0	0	1 (25.0)	0	1 (20.0)

Data presented as frequency (%) unless indicated otherwise. Out of a total of 64 patients who received epinephrine, 5 patients (7.8%) developed serious adverse effects associated with epinephrine. All the 5 patients received an overdose, and 4 of them were administered by IV bolus injection. IM, Intramuscular; SC, Subcutaneous; IV, intravenous; NA, not available.

Figures

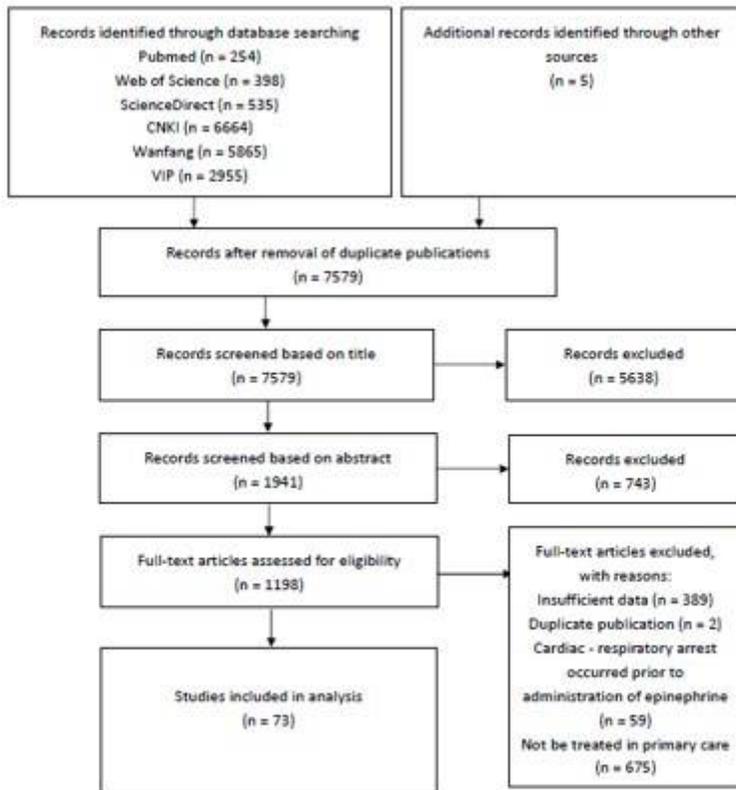


Figure 1

PRISMA flow diagram of the selection of studies.