

ARTICLE

Effectiveness and safety of Danmu extract syrup for acute upper respiratory tract infection in children: A real-world, prospective cohort study

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Abstract

Aim: To evaluate the effectiveness and safety of Danmu Extract Syrup for the treatment of acute upper respiratory tract infection (AURI) in children.

Methods: In this prospective cohort study, we enrolled children with AURI in the pediatric outpatient department and emergency department of West China Second Hospital. According to the treatment, they were divided into two groups: Danmu Extract Syrup Group (Danmu Group) and Xiaoer Chiqiao Granule Group (Chiqiao Group). The primary outcome was time to symptom remission, and the secondary outcomes were defervescence time, relief time, admission rate, and adherence. We used restricted mean survival time (RMST) to quantify the treatment effects and test noninferiority for primary outcome. Propensity score matching (PSM) was used to adjust confounding. Subgroup analysis and sensitivity analysis were used to verify the robustness of results.

Results: We enrolled 1036 children with AURI, including 516 in Danmu Group and 520 in Chiqiao Group. After PSM, no significant difference was observed in the baseline characteristics of the two groups. The primary results showed that the RMST differ-

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ence was -3 h (95% CI: -15.1 to 9.1) and the upper limit of the 95% CI was less than the noninferiority margin of 11 h. There was no statistical difference in the secondary outcomes except for defervescence between the two groups. The results of safety analysis showed that the incidence of adverse events occurred is 4.1% in Danmu Group, which was lower than the incidence of Chiqiao Group (6.9%).

Conclusion: This study indicated that Danmu extract syrup is noninferiority to Chiqiao Granule for AURI in children.

KEYWORDS

acute upper respiratory tract infection, cohort study, Danmu extract syrup, real-world study, traditional Chinese medicine

1 | INTRODUCTION

The World Health Organization (WHO) reports that 36% of the total global disease and injury burden involves children under 15 years of age.¹ In particular, acute upper respiratory tract infection (AURI) is a common disease in children. The global burden of disease survey showed that AURI ranked first among all diseases.² If not treated promptly and effectively, AURI can develop into serious diseases, such as lower respiratory tract infections.³⁻⁵ Medicine is the most important intervention for diseases; however, there are serious challenges associated with medications, such as off-label drug use and poor drug accessibility.⁶⁻⁸ The current treatments for upper respiratory tract infections are primarily drugs that decrease symptoms but do not shorten the course of the disease and carry the risk of adverse effects due to repeated dosing in children.³ Traditional Chinese Medicine (TCM) has been used to treat AURI (wind-cold or wind-heat) for more than 1800 years in China and has played a significant role in the control and prevention of infectious diseases, including influenza, SARS, and COVID-19.⁹⁻¹⁴ However, many TCMs have weak evidence of efficacy. In turn, they fail to meet the criteria for addition to the list of essential medicines and the policy formulation-related TCM, which has become a bottleneck hindering the development of TCM.¹¹

Danmu extract syrup is one of the TCMs used for AURI and its main ingredient is Danmu extract.¹⁵ Danmu is produced from *Nauclea officinalis* (Pierre ex Pitard) belonging to the *Rubiaceae* family, which is also known as Wutan, Xiongdan tree, etc., and is a characteristic Li medicine in the Hainan Province of China. This plant is only grown in China. Danmu extract syrup is a new preparation of Danmu and has been used to treat children for 16 years since it was marketed in 2007. Its attending functions include fever reduction, detoxification, reducing swelling, and relieving pain. Therefore, it is suitable for children with acute tonsillitis, acute pharyngitis, acute conjunctivitis, and upper respiratory infection. Clinical studies showed that the effectiveness and safety of Danmu in the treatment of children with AURI might be superior to that of ribavirin granules; however, the quality of these original studies are poor, and the dosage of Danmu for children was not stated.¹⁶⁻¹⁸ Thus, the current study aimed to provide high-quality evidence for the clinical use of Danmu.

Similar to Danmu extract syrup, Xiaoer Chiqiao Qingre granules are also suitable for children with wind-heat cold and food stagnation and have been widely used to treat children with AURI.¹⁹⁻²¹ The Xiaoer Chiqiao Qingre granule is composed of 14 herbs:¹⁹ lian-qiao (*Forsythiae Fructus*), dandouchi (*Sojae Semen Praeparatum*), bohe (*Menthae Haplocalycis Herba*), jingjie (*Schizonepetae Herba*), chaozhizi (fried *Gardeniae Fructus*), danhuang (*Rhei Radix Et Rhizoma*), qinghao (*Artemisiae Annuae Herba*), chishao (*Paeoniae Radix Rubra*), binglang (*Arecae Semen*), houpou (*Magnoliae Officinalis Cortex*), huangqin (*Scutellariae Radix*), banxia (*Pinelliae Rhizoma*), chaihui (*Bupleuri Radix*), and gancao (*Glycyrrhizae Radix Et Rhizoma*). The package inserts of Xiaoer Chiqiao Qingre granules describe its indications, such as dispelling wind, inducing sweat, reducing fever, and resolving food stagnation, and indicate the specific directions and dosage for children. Several systematic reviews and clinical studies of medium quality have proven that compared with ribavirin granules, Xiaoer Chiqiao granules have better effectiveness and safety in the treatment of pediatric AURI.^{20,21} In brief, Danmu extract syrup lacks high-quality evidence of its effectiveness and safety in the treatment of AURI in children. Therefore, we conducted a real-world, prospective cohort study, using Xiaoer Chiqiao Qingre granules as a control to evaluate the effectiveness and safety of Danmu extract syrup for children with AURI.

2 | MATERIALS AND METHODS

2.1 | Study design

From July 2018 to June 2020, we conducted a real-world, prospective cohort study at the pediatric outpatient and emergency department of West China Second Hospital of Sichuan University.

2.2 | Study patients

The inclusion criteria^{22,23} were as follows: ① patients who met the diagnostic criteria for upper respiratory tract infections, including acute tonsillitis, acute pharyngitis, and herpetic angina; ② patients aged 1-14

years in the outpatient or emergency department; ③ patients whose symptoms had begun within the previous 48 h; ④ patients using Danmu syrup or Chiqiao Qingre granule.

The exclusion criteria included the following: ① patients with lower respiratory tract infection; ② patients with possible bacterial infections; ③ patients with allergic rhinitis; ④ patients with complications from severe malnutrition, rickets, or serious diseases involving other systems; ⑤ patients who were allergic to the research medicines; ⑥ patients who had used antiviral or similar medicines before enrollment.

2.3 | Grouping situation

According to doctors' prescriptions, patients were divided into treatment and control groups. The treatment group (Danmu group) received Danmu extract syrup (1–3 years old, 5 ml each time, 3 times a day; 4–7 years old, 10 ml each time, 3 times a day; 8–13 years old, 10 ml each time, 4 times a day) and basic treatment; the control group (Chiqiao group) received Chiqiao Qingre granules 3 times a day (1–3 years old, 2–3 g; 4–6 years old, 3–4 g; 7–9 years old, 4–5 g; >10 years old, 6 g) and basic treatment. Basic treatment consisted of routine clinical symptomatic treatment, including but not limited to antipyretic analgesics, antihistamines, expectorants, antitussives, and decongestants. The treatment course for the two groups was 3–5 days.

2.4 | Outcome measures

2.4.1 | Effectiveness outcome measures

The primary outcome was the time to symptom remission, which is the time required for all symptoms to disappear (symptom score is 0). The symptom scoring standards were formulated following the Guideline on Evaluation of Chinese Materia Medica Research for Treatment of AURI in Children.²³

The secondary outcomes included: ① time to defervescence, when the body temperature was less than 37.3°C and maintained for at least 24 h; ② time to symptom relief, when any symptoms began to decrease; ③ medication compliance, calculated as the total number of cases in this group minus the number of patients who stopped, replaced research medicines, or used other TCM, the sum of which was divided by the total number of cases in this group; and ④ admission rate, number of hospitalized cases due to aggravation of illness divided by total number of cases in this group.

2.4.2 | Safety outcome measures

The safety outcome measures included the number of adverse events and the incidence rate. We referred to Good Clinical Practice and the evaluation standards of the National Center for ADR Monitoring for the definition of adverse events and evaluation of the causal relationship between adverse events and study medicines.^{24,25}

2.5 | Sample size

In this study, a noninferiority design was used. Based on the results of similar studies, the pediatric clinical specialty considers a difference of 12 h (0.5 days) in the time to healing of symptoms in children with acute upper respiratory tract infection to be clinically significant, so the noninferiority margin of this study was prespecified as 11 h. The literature reports that the time to symptomatic recovery of Chiqiao is 98 ± 46 h. We used one-sided $\alpha = 0.025$, $\beta = 0.2$ for noninferiority hypothesis. The number of cases in each group was calculated as 116 cases, and the number of cases in each group was 145 cases considering 20% of lost visits, and the actual implementation was based on 150 cases in each group, with a total of 300 cases in both groups, and the total sample size was about 1200 cases by multiplying the number of cases by 4 times considering the propensity score matching.

2.6 | Research registration, ethics review, and informed consent

This trial was registered at the China Clinical Research Registration Center (a first-level registration member of the WHO clinical trial registration platform). The registration number is ChiCTR1800016745. Ethics approval was obtained from the Ethics Committee of West China Second Hospital of Sichuan University. Prior to involvement in the trial, subjects, or their legal guardians fully understood the content of the study, agreed to participate, and signed informed consent forms.²⁵

2.7 | Data collection and follow-up

We collected data on the basic characteristics of patients, medication usage (both research medicines and other medicines), symptom scores, and occurrence of adverse events. We conducted follow-up by telephone to collect data on medication, symptoms, and adverse events. The longest follow-up time was 14 days after enrollment. The staff in charge of follow-up were uniformly trained, and the follow-up data were recorded on a paper version of the case report form, which was inputted into the electronic data capture (EDC) system. After input, the data were automatically checked by the EDC system and reviewed by professional researcher.

2.8 | Statistical analysis methods

Statistical analyses mainly included baseline comparability analysis between groups, analysis of medicine effectiveness, and safety analysis. In statistical descriptive analysis, quantitative data were described by means, standard deviations, medians, and quartiles; nominal data were described by absolute numbers and constituent ratios. In statistical inference analysis, if the quantitative data conformed to normal distribution and homogeneity of variance, the data were analyzed by

Student's *t*-test; otherwise, the data were analyzed by a nonparametric rank sum test. The nominal data were analyzed by chi-square test or Fisher's exact test, and the survival analysis of survival data were analyzed by univariate or multivariate Cox regression, with a test level α of 0.05.

Covariates in the multivariable model included age, sex, normal health, type of diagnosis, concomitant medication, symptom score at enrollment. Propensity score matching (PSM) was performed to control for confounding variables and improve comparability between groups. We used nearest-neighbor matching on a propensity score derived from a logistic regression model within 0.25 caliper width on the standard deviations scale. We provided the standardized mean differences and histogram of PS to describe the differences between two groups in the unmatched and matched cohort. Restricted mean survival time (RMST) and Cox regression was applied to quantify the treatment effects, including time to symptom remission, time to symptom relief and complete fever reduction. And RMST after PSM was used as primary analysis to test noninferiority for primary outcome (time to symptom remission). The noninferiority margin was set at 11 h. If the 95% CI upper limit of the difference between the two groups (Danmu group and Chiqiao group) was less than 11 h, the Danmu group was not inferior to the Chiqiao group. We used one-sided $\alpha = 0.025$ for noninferiority hypothesis. Adherence analysis was performed using the Z test between two groups. Hospitalization rate was tested by chi-square test. Safety outcomes such as adverse events were tested by chi-square test. Subgroup and sensitivity analyses were performed to verify the robustness of the results. Sensitivity analyses included crude analysis method, multivariable Cox regression, and multivariable analysis adjusted for propensity score.

Data processing and statistical analyses were performed using R software (version: 3.5.1) and SAS version 9.4 (SAS Institute, Cary, NC).

3 | RESULTS

3.1 | Patient screening

From July 2018 to June 2020, a total of 1518 children with AURI were enrolled, including 673 patients in the Danmu group and 684 patients in the Chiqiao group. The Danmu and Chiqiao groups ultimately included 516 cases and 520 cases, respectively. The screening flow of patients is shown in Figure 1.

3.2 | Baseline characteristics of patients

Baseline characteristics of the Danmu and Chiqiao groups, including age, sex, health status of the patient, type of diagnosis, concomitant medication, and symptom scores at enrollment, were compared before and after PSM. The results showed that age, health status of the patient, type of diagnosis, concomitant medication between

the two groups indicated significant differences ($p < 0.05$) before PSM. After PSM, there were no statistically significant differences in all baseline characteristics (Table 1). Figure 2 is the histograms of the density of propensity scores for cohort before and after matching.

3.3 | Efficacy evaluation

3.3.1 | Survival analysis of symptom remission time

The primary results showed that the RMST of both groups were 116.8 (95% CI: 108.4–125.3) h and 113.8 (95% CI: 105.1–122.5) h, with no statistical difference ($p = 0.627$) in the matched cohort (Table 2). The observed RMST difference was -3 h (95% CI: -15.1 – 9.1 , $p_{\text{noninferiority}} = 0.032$), the upper limit of the two-sided 95% confidence interval was less than the noninferiority margin of 11 h. This result indicated that Danmu Extract Syrup is noninferiority to that of Xiaoe Chiqiao Qingre Granule in decreasing healing time of AURI in children.

3.3.2 | Survival analysis of symptom relief time

Before PSM, the results of RMST and univariate Cox regression analyses showed that there was no significant difference in symptom relief time between the two groups ($p > 0.05$). The results of RMST and multivariate Cox regression analyses after PSM were similar to those before PSM, as shown in Table 3.

3.3.3 | Survival analysis of time to defervescence

Before PSM, the results of RMST and univariate Cox regression analyses showed that there was no significant difference in time to defervescence between the two groups ($p > 0.05$), as shown in Table 4. After PSM, both analyses showed time to defervescence were significantly shorter in Danmu group ($p < 0.05$).

3.3.4 | Adherence and admission rate

The average adherence index of the Danmu and Chiqiao groups was 95.0 ± 14.0 (%) and 95.0 ± 15.0 (%) respectively, and the difference was not significant ($p > 0.05$). Nonadherence was mainly due to changing medicines in 29 (5.6%) and 33 (6.4%) patients in the Danmu and Chiqiao groups, respectively. The results of the chi-square test showed that there was no significant difference in the distribution of nonadherence between the two groups ($p > 0.05$). For admission rate, 0.2% (0.1%, 2.4%) in the Danmu group and 0.2% (0.1%, 2.4%) in the Chiqiao group, there was no significant difference between the two groups ($p = 1.000$).

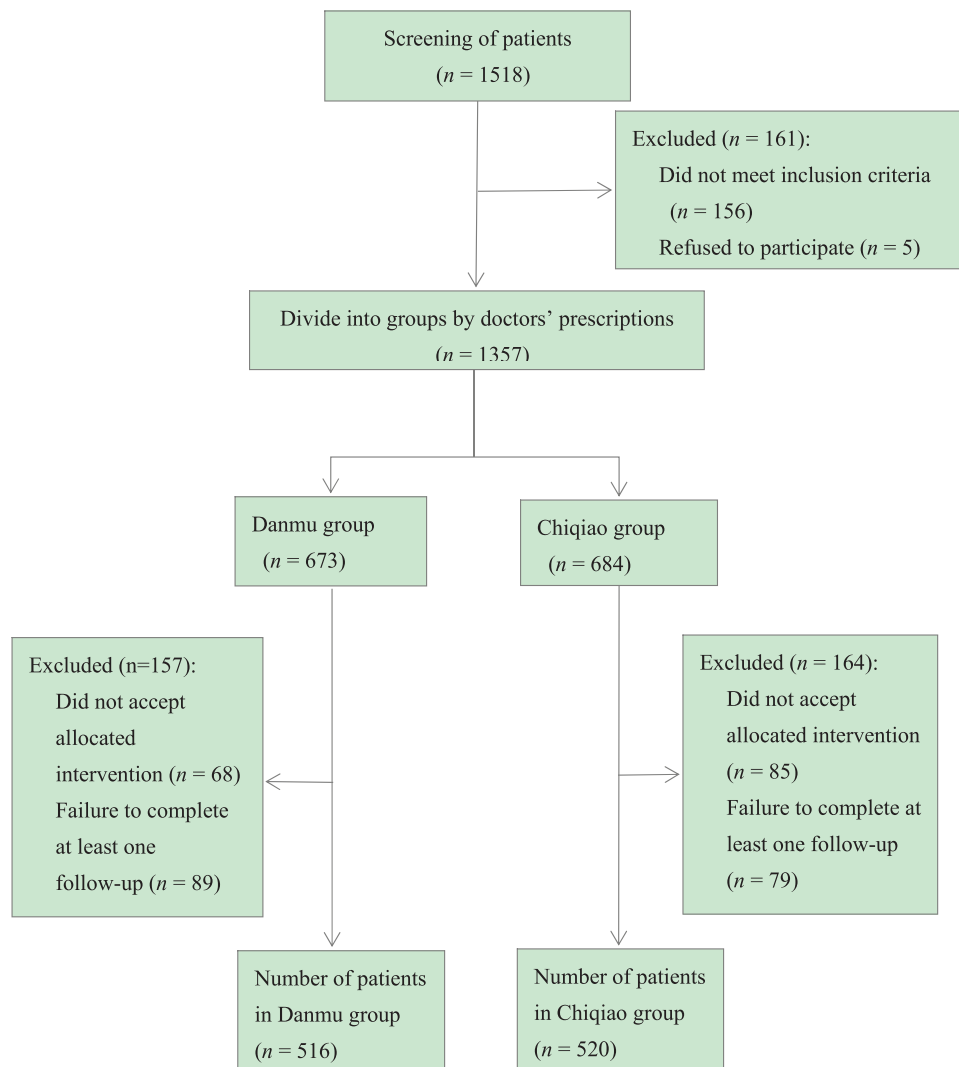


FIGURE 1 Screening flow of patients in the study

3.4 | Safety evaluation

The results of the safety evaluation showed that the number of adverse events in the Danmu group was 28 (5.4%), which was lower than that in the Chiqiao group (57 (11.0%)). Common adverse events in both groups included diarrhea, vomiting, rash, poor appetite, and nausea. The incidence of serious adverse events was 0.2% (1/516) in the Danmu group and 0.2% (1/520) in the Chiqiao, and none was related to Danmu or Chiqiao (Table 5).

3.5 | Subgroup analysis and sensitivity analysis

The results of subgroup analysis showed no significant difference in symptom recovery time between the Danmu and Chiqiao groups by gender, age, diagnosis, health status, or year of enrollment, indicating no interaction, as shown in Figure 3. In the sensitivity analysis, excluding cases with poor adherence, RMST showed that the RMST of both groups were 92.6 (95% CI: 86.3–98.9) h and 97.2 (95% CI:

90.8–103.6) h, with no statistical difference ($p = 0.327$) in the matched cohort. The observed RMST difference was -4.6 h (95% CI: -13.6 to 4.4 , $p_{\text{noninferiority}} = 0.013$). The upper limit of the two-sided 95% confidence interval was less than the noninferiority margin of 11 h, which was consistent with the primary result. And it suggested that the result of the primary efficacy outcome was robust. The results of multivariable Cox model and Cox model adjusted for PS were consistent with the result of PSM univariate Cox model (Table 6).

4 | DISCUSSION

In this study, RMST analysis after PSM was selected as the primary analysis, and noninferiority analysis was performed using the 95% CI. The primary results indicated that Danmu Extract Syrup was noninferior to Xiaer Chiqiao Qingre Granules in decreasing the time to symptom remission of AURI in children. Before PSM, the baseline characteristics of the two groups were unbalanced, and therefore, the time to symptom recovery could not be directly compared between

TABLE 1 Distribution and comparisons of baseline characteristics before and after PSM

Characteristic	Before PSM			After PSM			
	Chiqiao (n = 520)	Danmu (n = 516)	p	Chiqiao (n = 254)	Danmu (n = 254)	p	SMD
Age (years)			<0.001			0.213	0.157
1~	120 (23.1)	71 (13.8)		37 (14.6)	34 (13.4)		
2~	355 (68.3)	321 (62.2)		173 (68.1)	160 (63.0)		
6~	45 (8.7)	124 (24.0)		44 (17.3)	60 (23.6)		
Sex			0.107			0.477	0.071
Male	295 (56.7)	266 (51.6)		129 (50.8)	138 (54.3)		
Female	225 (43.3)	250 (48.4)		125 (49.2)	116 (45.7)		
Health status of the patient			<0.001			0.384	0.090
Healthy	484 (93.1)	444 (86.0)		231 (90.9)	224 (88.2)		
Moderate/bad	36 (6.9)	72 (14.0)		23 (9.1)	30 (11.8)		
Type of diagnosis			0.067			1.000	0.001
Acute tonsillitis/pharyngitis	186 (35.8)	156 (30.2)		80 (31.5)	80 (31.5)		
Acute upper respiratory infection	334 (64.2)	360 (69.8)		174 (68.5)	174 (68.5)		
Number of combined medicines			0.829			0.593	0.123
1	164 (31.5)	154 (29.8)		73 (28.7)	80 (31.5)		
2	179 (34.4)	173 (33.5)		90 (35.4)	81 (31.9)		
3~	150 (28.8)	158 (30.6)		80 (31.5)	86 (33.9)		
Medicines for symptoms	486 (93.5)	475 (92.1)	0.451	237 (93.3)	242 (95.3)	0.444	0.085
Antibacterial agents	72 (13.8)	66 (12.8)	0.683	34 (13.4)	33 (13.0)	1.000	0.012
Chinese traditional medicines	73 (14.0)	106 (20.5)	0.007	51 (20.1)	51 (20.1)	1.000	0.001
Other medicines	108 (20.8)	96 (18.6)	0.425	57 (22.4)	53 (20.9)	0.747	0.038
Compound preparations	407 (78.3)	441 (85.5)	0.003	209 (82.3)	220 (86.6)	0.221	0.120
Analgesic-antipyretic	238 (45.8)	108 (20.9)	<0.001	84 (33.1)	75 (29.5)	0.444	0.076
Antihistamine agents	74 (14.2)	98 (19.0)	0.048	53 (20.9)	45 (17.7)	0.431	0.080
Antitussive and expectorant agents	10 (1.9)	19 (3.7)	0.127	9 (3.5)	11 (4.3)	0.820	0.040
First-day symptom score	4.0	5.0	0.078	5.0	5.0	0.589	0.001
Median [Q1, Q3]	[4.0, 6.0]	[4.0, 6.0]		[4.0, 7.0]	[4.0, 6.0]		

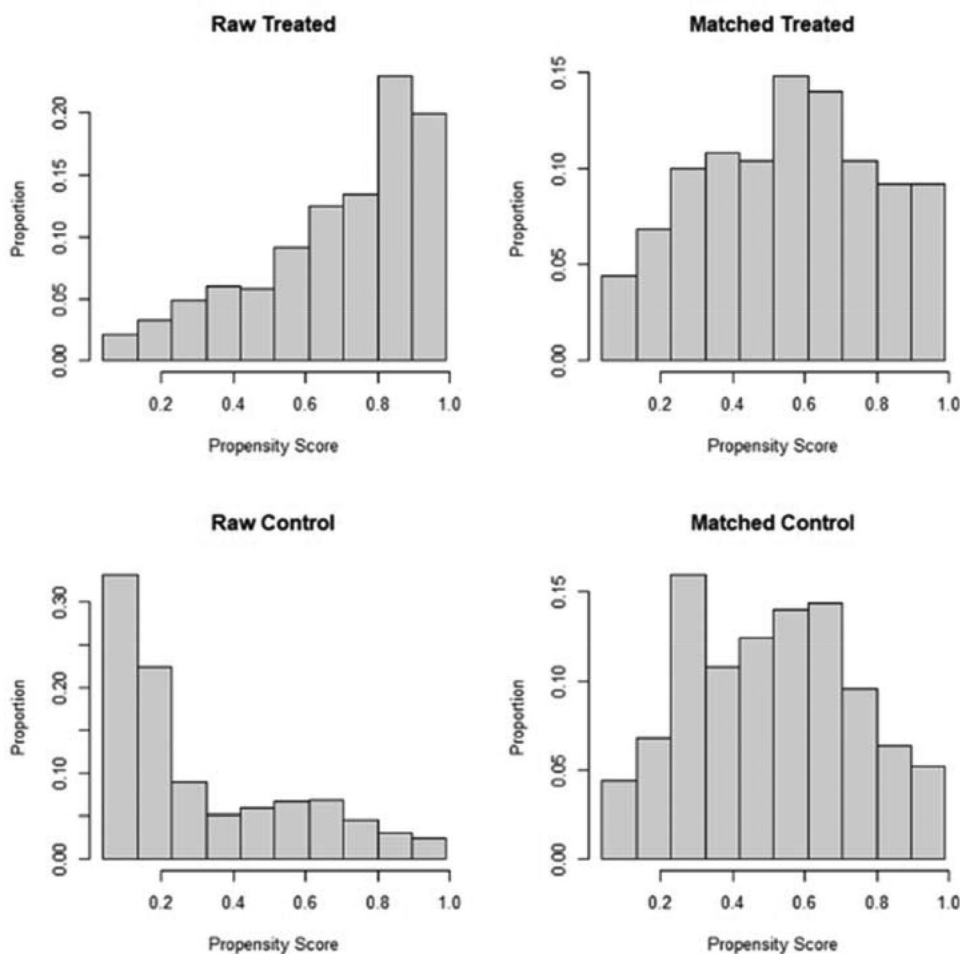


FIGURE 2 The histograms of the density of propensity scores for cohort before and after matching

TABLE 2 RMST and Cox model to compare symptom remission time of Chiqiao and Danmu for AURI before and after PSM

Time of symptoms remission (h)	RMST			<i>p</i>	Univariate Cox	
	Chiqiao (<i>n</i> = 254)	Danmu (<i>n</i> = 254)	difference (95% CI)		HR (95% CI)	<i>p</i>
Before PSM	115.2 (107.8, 122.6)	132.5 (123.9, 141.2)	17.3 (5.9, 28.7)	0.003	0.8 (0.7, 0.9)	0.003
After PSM	116.8 (108.4, 125.3)	113.8 (105.1, 122.5)	-3 (-15.1, 9.1)	0.627	1.0 (0.9, 1.2)	0.692

TABLE 3 RMST and Cox model to compare symptom relief time of Chiqiao and Danmu for AURI before and after PSM

Time of symptoms relief (h)	RMST			<i>p</i>	Univariate Cox	
	Chiqiao (<i>n</i> = 254)	Danmu (<i>n</i> = 254)	difference (95% CI)		HR (95% CI)	<i>p</i>
Before PSM	34.7 (31.0, 38.3)	36.5 (32.7, 40.3)	-1.8 (-7.1, 3.5)	0.500	1.0 (0.9, 1.2)	0.753
After PSM	32.1 (29.2, 35.1)	33.4 (30.3, 36.5)	-1.2 (-5.5, 3.0)	0.568	1.1 (0.9, 1.3)	0.333

TABLE 4 RMST and Cox model to compare symptom time to defervescence of Chiqiao and Danmu for AURI before and after PSM

Time to defervescence (h)	RMST		Univariate Cox	
	Chiqiao (n = 155)	Danmu (n = 155)	HR (95% CI)	p
Before PSM	76.0 (72.9, 79.3)	71.5 (67.6, 75.5)	1.1 (0.9, 1.3)	0.176
After PSM	94.2 (81.2, 107.1)	75.3 (67.4, 83.3)	1.3 (1.0, 1.6)	0.039
			difference (95% CI)	p
			-4.6 (-9.6, 0.6)	0.500
			-18.8 (-34.0, -3.7)	0.015

the two groups. The shorter recovery times in the Chiqiao group before PSM may be due to the better health status, lower first-day symptom scores, and higher use of antipyretic and analgesic drugs compared with those in the Danmu group (Table 1). After PSM, only cases with matching baseline characteristics in both groups were retained, and the rest were excluded (Table 1 and Figure 2). We used RMST results after PSM as the primary result because the two groups were unbalanced at baseline, before PSM, and there was confounding bias affecting the outcome estimates.²⁶ After PSM, however, the matched cohorts were subjected to a post hoc randomization, which balanced the baseline characteristics of the two groups and ensured the accuracy of the effect estimates.

Danmu has a long history of use in preventing and treating infectious diseases. This date back to the 1920s to the 1940s, when the Qiongya Column and Red Detachment of Women were blocked by armed forces and medicines were in short supply. Danmu was widely used to treat fevers, upper respiratory tract infections, and women's diseases and was known as the "Red Revolutionary Herb." In 1962, the Department of Logistics and Health of Guangzhou Army developed a single preparation of "Danmu tablet." In contrast, Danmu extract syrup has only been marketed and widely used in the treatment of AURI in children since 2007. However, there is no indication for use in children on the label, and there is still a lack of high-quality evidence supporting the use of Danmu in children. In short, the application of Danmu has a long history and its new preparation, Danmu extract syrup, has been widely used in clinical practice but is associated with a lack of high-quality evidence-based studies. Thus, this study aimed to explore the effectiveness and safety of Danmu in children with AURI and provide evidence for the rational clinical use of Danmu.

Due to ethical issues, recruitment difficulties, and low profits of drug development, clinical trials studying drugs for use in children are often difficult to carry out or progress. This results in insufficient evidence to evaluate the effectiveness and safety of drugs for use in children, which affects the accessibility and the standardization of pediatric clinical drug use.²⁷ With the emergence of TCM for use in clinical practice, increased health decision-making, and internationalization, higher requirements have been put forward for the quality of TCM research. Internationally agreed-upon clinical research methods was used to produce clinical evidence of effectiveness and safety of TCM. It will be conducive to promoting rational drug use and improving medical quality, patient safety, and resource use efficiency. This will be a key approach to solve the existing challenges faced by TCM.

Compared with traditional randomized controlled trials, real-world studies can effectively solve problems such as ethical issues, recruitment difficulties, high cost, and poor population representativeness.²⁸ These studies also have unique advantages in the evaluation of TCM and children's medication. As a new approach, real-world studies have been gradually used to support the research, development, and evaluation of TCM and other medications. They can be used to evaluate the applications of new drugs, extensions of indications, and improvements of dosage protocols.²⁹ Real-world studies can also provide evidence specifically for children's medication, such as the clinical use of TCM and the formulation of relevant medical policies.³⁰

TABLE 5 Distribution and comparison of adverse events between the two groups

Adverse events	Chiqiao (n = 520)		Danmu (n = 516)	
	N	%	N	%
Patients occurs adverse events	36	6.9	21	4.1
Diarrhea	18	50	9	42.9
Vomiting	8	22.2	5	23.8
Rash	8	22.2	2	9.5
Poor appetite	3	8.3	3	14.3
Nausea	3	8.3	2	9.5
Adverse events	57	11.0	28	5.4
Severity				
Mild	49	9.4	27	5.2
Moderate	4	0.8	0	0.0
Severe	4	0.8	1	0.2
Prognosis				
Disappear, without sequelae	47	9.0	21	4.0
Disappear, with sequelae	0	0.0	0	0.0
Remission	0	0.0	0	0.0
Nonremission	0	0.0	1	0.2
Death	0	0.0	0	0.0
Unclear	10	1.9	6	1.2
Relevance				
Definitely relevant	0	0.0	0	0.0
Probably relevant	3	0.6	1	0.2
Possibly relevant	10	1.9	1	0.2
Possibly not relevant	42	8.1	26	5.0
Not relevant	2	0.4	0	0.0

Various other studies have also assessed the clinical use of Danmu extract syrup in children.^{16,17,18,19,20} These studies showed good effectiveness and safety of Danmu extract syrup in the treatment of children with upper respiratory infection, but the sample sizes of these studies were generally small. The quality of these studies are poor as they fail to report the study design, methods of follow-up, and standards of outcome measurements or fail to adopt random allocation concealment or blinding methods. Our results showed that Danmu extract syrup was noninferior to Xiaoer Chiqiao Qingre granules in the treatment of children with AURI; there was no significant difference between the two groups in terms of secondary effectiveness indicators; in terms of safety, the incidence of adverse events associated with Danmu extract syrup was lower than that associated with Xiaoer Chiqiao Qingre granules. This study provides high-quality evidence for the clinical application of Danmu extract syrup in the treatment of children with AURI.

There are several strengths in the study. First, compared with existing studies, the sample size of our study was large enough to ensure sufficient statistical efficacy. The inclusion and exclusion criteria, effectiveness and safety indicators, and implementation procedures of this study conformed to China's authoritative standards, guidelines,

and teaching materials, thus ensuring the reliability of this study.²²⁻²⁵ Second, we excluded patients with the following diseases: respiratory tract infection, bacterial infection, and allergic rhinitis. We also excluded patients who had taken antiviral or similar medication before treatment to identify the population with the indication, improve the homogeneity of the study subjects, and reduce the influence of confounding factors on the results. Third, this study recorded, in detail, the disease progression in the study subjects during the study period. These factors included modified diagnoses (including bronchitis, pneumonia, bronchopulmonary pneumonia, and febrile convulsion) and additional medication (including antibiotics, proprietary Chinese medicines, and symptomatic medicine). In the statistical analysis, multifactor analysis was used to control for the above confounding factors and reduce bias arising from them. Subgroup and sensitivity analyses were used to explore interactions and the robustness of the results. Fourth, in this study, Xiaoer Chiqiao Qingre granules were selected as the positive control, which not only has the indication for use in children on the label but is also one of the commonly used proprietary Chinese medicines for the clinical treatment of children with AURI. The taste of Danmu extract syrup is better than that of Xiaoer Chiqiao

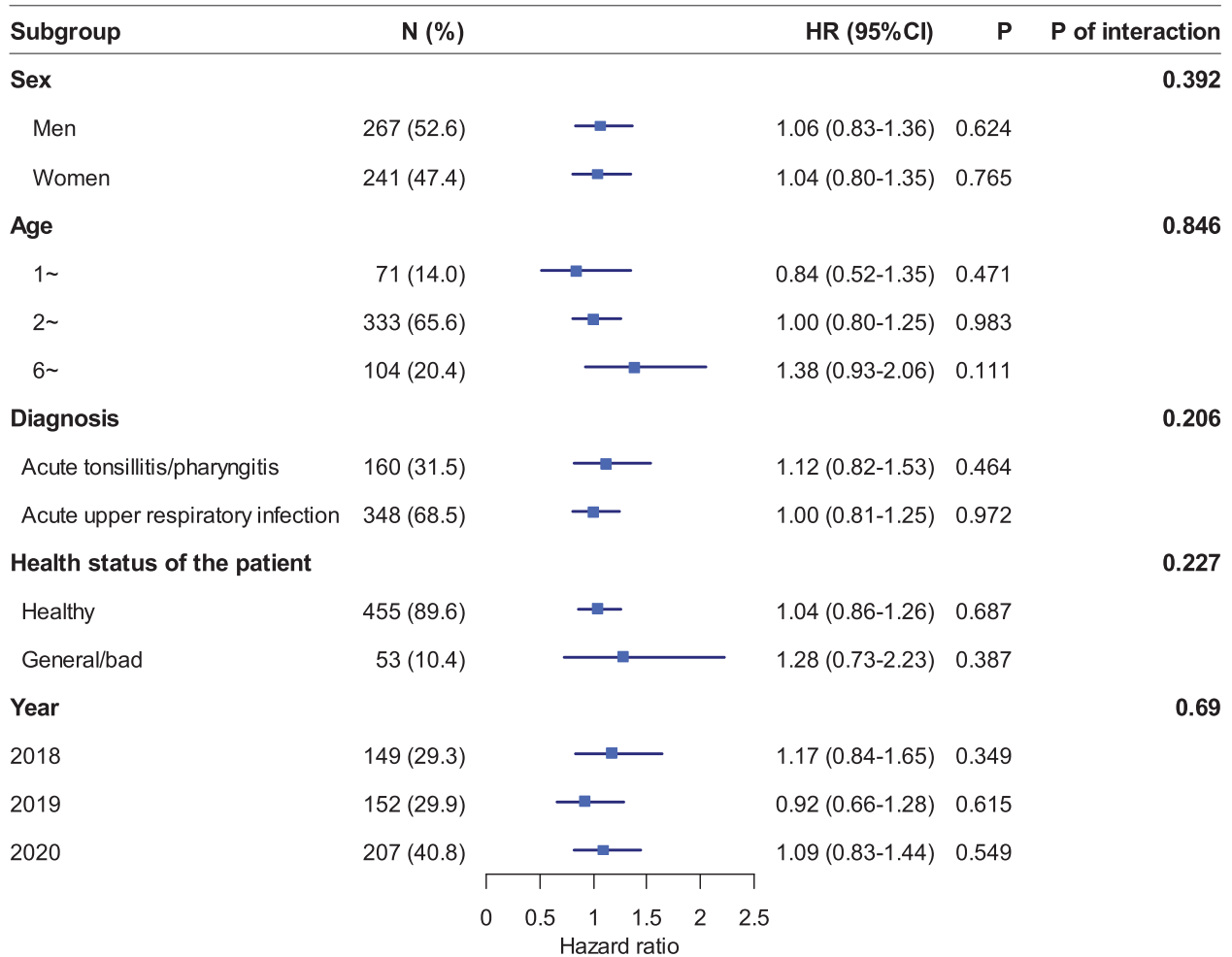


FIGURE 3 Subgroup analysis of multivariate Cox regression of symptom recovery

TABLE 6 Adjusted hazard ratios of multivariable cox model and cox model adjusted for PS

Outcomes	Multivariable Cox model		Cox model adjusted for PS	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Time of symptoms remission	1.03 (0.89, 1.19)	0.725	1.15 (0.96, 1.39)	0.130
Time of symptoms relief	1.12 (0.95, 1.31)	0.176	1.10 (0.91, 1.32)	0.317
Time to defervescence	1.22 (1.01, 1.49)	0.042	1.33 (1.04, 1.70)	0.023

Qingre granule, which is more bitter and discourages children from taking it and may reduce compliance. In addition, the cost of Danmu is lower than that of Chiqiao. Finally, the inclusion and exclusion criteria in this study were less stringent than those in randomized controlled trials, and the treatment regimen and combined medication were more consistent with clinical practice, which better reflected the efficacy and safety of the drug in the actual medical environment.

Although multivariate analysis and propensity score were used to control for confounding bias, the results might still be biased due to unknown confounders. Furthermore, consistent with all single-center

studies, there were sample representativeness limitations, and it is recommended to consider the consistency of the population and application conditions when extrapolating conclusions.

In conclusion, in terms of effectiveness of treatment for AURI, Danmu was noninferior to Chiqiao in decreasing the time to symptom remission. The time to defervescence was significantly shorter in the Danmu group, but there was no significant difference in time to symptom relief, adherence, and hospital admission rate. In terms of safety, the incidence of adverse events in the Danmu group was lower than that in the Chiqiao group.

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