

ORIGINAL ARTICLE

Patients with urticaria are at a higher risk of anaphylaxis: A nationwide population-based retrospective cohort study in Taiwan

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ABSTRACT

The clinical features of urticaria and anaphylaxis are similar, and they share common causal immune-mediated pathways. We aimed to investigate the risk of anaphylaxis among patients with urticaria. A 12-year population-based retrospective cohort study was conducted. Investigated subjects were identified from the Taiwan National Health Insurance Research Database by the International Classification of Disease, Ninth Revision, Clinical Modification. We included 126 031 subjects with newly diagnosed urticaria and 252 062 matched controls between 2000 and 2013. Risk of anaphylaxis among patients with urticaria was calculated by calculating adjusted hazards ratios (HR) after matching for confounding comorbidities. Urticaria was more common in women than it was in men (58% vs 42%), with a peak onset age of 20–40 years. The number of comorbidities including asthma, allergic rhinitis, herpes zoster, hepatitis B and C, rheumatoid arthritis and gout were higher in patients with urticaria than that in age- and sex-matched controls. The crude HR for anaphylaxis among urticaria subjects was 2.883 (95% confidence interval [CI], 2.787–2.982; $P < 0.001$). After adjustment for potential confounders which have been proposed to increase the risk of anaphylaxis, patients with urticaria were found to be at a significantly high risk of anaphylaxis with an adjusted HR of 2.529 (95% CI, 2.442–2.619; $P < 0.001$). We conclude that the incidence rate of anaphylaxis is significantly high in patients with urticaria in Taiwan.

Key words: allergy, anaphylaxis, autoimmune diseases, the national health insurance research database, urticaria.

INTRODUCTION

Urticaria is a vascular disorder of the skin, and its pathology is mediated by various immune-response pathways. Causal agents include food, pollutants, drugs, animal bites or specific chemical and physical stimulants (e.g. sun, pressure, extreme temperatures [high or low]).^{1–3} The causative immunogens or other stimulants primarily induce the production of immunoglobulin (Ig)E, which can bind to receptors on the membranes of mast cells; such activated mast cells in turn release vasoactive mediators to cause symptoms.^{1,2} Most cases of urticaria are acute and self-limiting. The clinical manifestations usually do not persist beyond 24 or 48 h. In most subtypes of urticaria, the characteristic wheals often appear within 6–8 h and rarely last for more than several days, though the probability of recurrence several weeks later is high.^{1–3} Chronic urticaria is defined as urticaria with recurrent episodes lasting longer than 6 weeks. Chronic urticaria occurs with

higher frequencies in children, adolescents and atopic adult patients, and significantly reduces the quality of life in these patient populations.^{1–3} The development of urticaria is often a localized event and does not involve a systemic reaction. Rarely, however, manifestation of urticaria may be a prelude to the development of an anaphylactic reaction. If any features of anaphylaxis (e.g. hypotension, respiratory distress, stridor, gastrointestinal distress, difficulty in swallowing, joint swelling and joint pain) are observed, medical providers should institute immediate medical interventions to prevent serious consequences.

Anaphylaxis shares common etiologies and activation pathways (involving mast cell process) with urticaria, and basophils are involved in the systemic allergic reaction as well. After degranulation, the mast cells generate copious amounts of mediators, which initiate immune signaling cascades.^{2,3} Anaphylaxis is a serious allergic reaction with a rapid onset and can be fatal.⁴ Epidemiological studies of anaphylaxis-related

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conditions, such as food allergies and asthma, have demonstrated concerning increases in prevalence. Studies of anaphylaxis also suggest that the incidence of this condition may be increasing. A majority of the mechanisms of pathogenesis of anaphylaxis overlap with those of urticaria. Anaphylaxis is also an acute, life-threatening systemic reaction that results from the sudden release of mediators from mast cells and basophils. Prompt recognition of the signs and symptoms of anaphylaxis is critical to providing rapid and effective treatment. Epinephrine is the most important medication for treating anaphylaxis, and earlier administration prognosticates better prognosis. The diagnosis of anaphylaxis is based on the recognition of clinical symptoms and requires a detailed evaluation of the episode, including that of activities and events occurring within hours preceding the episode. Patients typically present with a combination of respiratory, dermatological, gastrointestinal and cardiovascular symptoms. The most common triggers for anaphylactic shock are medications, insect stings and food. Medication-related anaphylaxis accounts for most deaths resulting from anaphylaxis.

There is a wide variation in the reported prevalence and incidence of anaphylaxis. The incidence rate of anaphylaxis is difficult to estimate accurately due to its varying definitions, lack of confirmatory laboratory tests, as well as underrecognition and underdiagnosis by clinicians. An incidence rate of 3.2–20 episodes per 100 000 person-years has been reported, with an estimated prevalence of 0.3–5.1%, depending on the rigor of the definitions used. Population-based studies in the USA, the UK and in other developed countries have estimated the incidence rate of anaphylactic shock to be 40–500 per million person-years.

The vast majority of episodes of acute urticaria/anaphylaxis are idiopathic in adults and adolescents without a history of atopic diseases. However, the relationship between urticaria and anaphylaxis has not been previously investigated. We therefore assessed the risk of anaphylaxis in a large, nationally representative, population-based cohort of patients with urticaria in Taiwan. Based on our analysis, we conclude that patients with a history of urticaria are at a significant risk of developing anaphylaxis, and thus adequate monitoring and patient education are indicated.

METHODS

Data source

All data were accessed from The National Health Insurance Research Database (NHIRD), maintained by the National Health Research Institutes. This database is population-based and contains all claims data pertaining to participants within the program. This program is a mandatory-enrollment, single-payment system created in 1995, with coverage encompassing over 99% of Taiwan's population. The NHIRD contains all medical claims pertaining to the National Health Insurance program as well as patients' basic data; this database is thus a unique and valuable resource providing data with a sufficient sample size to pursue the objectives addressed in this study. To ensure the accuracy of disease diagnosis, the

National Health Insurance Bureau of Taiwan has randomly reviewed medical charts of one in 100 ambulatory and one in 20 inpatient claims. The high validity of the diagnostic data from the NHIRD has been reported previously.⁵ The 2000 Longitudinal Health Insurance Research Dataset (LHIRD) comprises 1 million randomly sampled beneficiaries from the NHIRD in 2000. Based on data from the NHIRD, there were no significant differences in sex, age or health-care costs between cohorts in the 2000 LHIRD and all insurance enrollees. We used the 2000 LHIRD to analyze claims data filed from 2000 to 2013. The 2000 LHIRD is a secondary database which provides researchers with de-identified data in accordance with privacy laws, and therefore informed consent was not required in this study. This study also received approval from the institutional review board of Chung Shan Medical University Hospital (CS15134).

Selection of study cases and controls

We first selected all patients who had received a first-time diagnosis of urticaria (International Classification of Disease, Ninth Revision, Clinical Modification [ICD-9-CM] code 708.X), and whose clinical history included at least two outpatient visits and one hospital admission between 1 January 2000 and 31 December 2013 ($n = 168\,057$). Because administrative datasets are usually criticized for their poor diagnosis validity, this study only included patients with at least two principal diagnoses of urticaria coded in their medical claims, in addition to at least one instance of hospital admission, in order to increase the validity of the diagnoses. We excluded 42 026 patients diagnosed with urticaria before 2002 and those with a first episode of urticaria combined with anaphylaxis. Ultimately, 12 031 patients with urticaria were included in the study. We assigned the first ambulatory care visit for receiving a diagnosis of urticaria as the index date.

Case definition of urticaria and anaphylaxis

The identification of patients with urticaria and anaphylaxis was based on hospital records. Patients with urticaria were selected based on ICD-9-CM code 708.X, and those with anaphylaxis were selected based on ICD-9-CM codes 995.0, 995.2, 995.3, 995.4 and 995.6. The clinical history of patients with urticaria and anaphylaxis needed to include at least one instance of hospital admission and two instances of outpatient visits to fulfill the case definition.

Statistical analysis

We used the χ^2 -test and Student's *t*-test to compare the demographic data of the urticaria and non-urticaria groups; multivariate Cox regression models were used to calculate the hazard ratios (HR) and 95% confidence intervals (CI) of associations between pre-existing urticaria and anaphylaxis after adjusting for age, sex and urbanization. All data analyses were performed using SAS version 9.4 (SAS Institute, Carey, NC, USA) and $P < 0.05$ was considered to be statistically significant.

In addition to this, we analyzed potential risk factors for urticaria including atopic disorders (asthma, ICD-9-CM code 493; allergic rhinitis, ICD-9-CM code 477; and atopic dermatitis,

ICD-9-CM codes 69) and autoimmune diseases (rheumatoid arthritis, ICD-9-CM code 714.0).

RESULTS

Study population

Of the sampled urticaria patients, 57.87% were women and 42.13% were men. After matching for sex, age and index date, there was a significant difference in geographic region, monthly income, urbanization level, atopic disorders and autoimmune diseases between study cases and controls (all $P < 0.001$) (Table 1). The study population comprised 126 031 urticaria patients in Taiwan between 2000 and 2013 (Fig. 1).

Baseline characteristics of patients with urticaria

The baseline demographic and clinical data from 126 031 patients with urticaria are shown in Table 1. Patients with urticaria were more likely to be female, and displayed significant differences in income levels and occupation ($P = 0.0002$). Living in urban areas increased the likelihood of being diagnosed with urticaria (59.35%).

Frequency of outpatient visits

Most of the patients with urticaria (83.83%) did not require hospital admission. However, 9.58% of these patients required hospital stays for between 1 and 6 days. The three most common comorbidities observed were allergic rhinitis (18.37%), diabetes mellitus (8.38%) and asthma (6.90%). Patients with

Table 1. Baseline characteristics of study groups

	Control ($n = 252\ 062$)	Exposure of urticaria ($n = 126\ 031$)	P
Sex			
Female	145 870 (57.87%)	72 935 (57.87%)	1.0000
Male	106 192 (42.13%)	53 096 (42.13%)	
Age, years			
<20	46 092 (18.29%)	23 046 (18.29%)	1.0000
20–39	84 382 (33.48%)	42 191 (33.48%)	
40–59	77 078 (30.58%)	38 539 (30.58%)	
≥60	44 510 (17.66%)	22 255 (17.66%)	
Urbanization			
Urban	15 3436 (60.87%)	74 795 (59.35%)	<0.0001
Suburban	74 572 (29.58%)	38 373 (30.45%)	
Rural	24 054 (9.54%)	12 863 (10.21%)	
Low income	1384 (0.55%)	816 (0.65%)	0.0002
Frequency of outpatient visits (within 2 years before index date)			
0	16 304 (6.47%)	691 (0.55%)	<0.0001
1–6	34 757 (13.79%)	7977 (6.33%)	
7–13	43 356 (17.2%)	15 647 (12.42%)	
14–27	64 036 (25.4%)	32 226 (25.57%)	
≥28	93 609 (37.14%)	69 490 (55.14%)	
Length of hospital stays (Within 2 years before index date)			
No admission	22 0315 (87.41%)	10 5651 (83.83%)	<0.0001
1–6 days	19 292 (7.65%)	12 080 (9.58%)	
7–13 days	6364 (2.52%)	4299 (3.41%)	
≥14 days	6091 (2.42%)	4001 (3.17%)	
Comorbidity			
Asthma	11 231 (4.46%)	8691 (6.90%)	<0.0001
Allergic rhinitis	31 785 (12.61%)	23 156 (18.37%)	<0.0001
Herpes zoster	7233 (2.87%)	5775 (4.58%)	<0.0001
Hepatitis B virus infection	4200 (1.67%)	2592 (2.06%)	<0.0001
Hepatitis C virus infection	1524 (0.60%)	1167 (0.93%)	<0.0001
Diabetes mellitus	17 155 (6.81%)	10 558 (8.38%)	<0.0001
Gout	577 (0.23%)	479 (0.38%)	<0.0001
Rheumatoid arthritis	78 (0.03%)	79 (0.06%)	<0.0001
Cancer	1954 (0.78%)	1107 (0.88%)	0.0008
Medication			
Corticosteroids	8008 (3.18%)	12 207 (9.69%)	<0.0001
NSAID	17 343 (6.88%)	14 384 (11.41%)	<0.0001
Antihistamines	23 644 (9.38%)	30 977 (24.58%)	<0.0001

NSAID, non-steroidal anti-inflammatory drug.

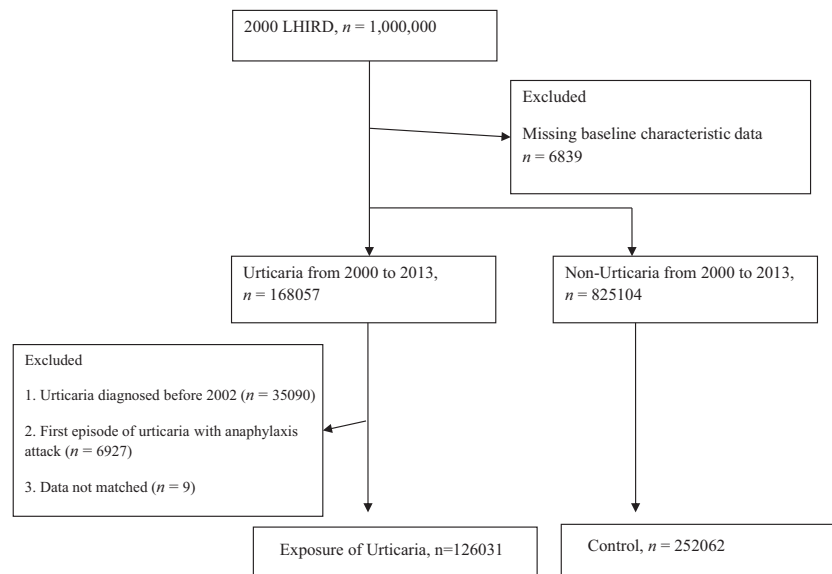


Figure 1. Flowchart of the case-control study. LHIRD, Longitudinal Health Insurance Research Dataset.

urticaria received medications including antihistamines (24.58%) and corticosteroids (9.69%).

Incidence of anaphylaxis in patients with urticaria

There were 8211 new anaphylaxis patients with a history of urticaria (Table 2). The incidence rate of urticaria with anaphylaxis was 8.92 (per 10 000 person-months) between 2000 and 2013 in Taiwan, with a relative risk of 2.89 (95% CI, 2.79–2.99).

HR of anaphylaxis

The crude HR for urticaria among subjects with anaphylaxis was 2.883 (95% CI, 2.787–2.982; $P < 0.001$) (Table 3). After adjustment for potential confounders, which have been proposed to increase the risk of anaphylaxis, urticaria was found to be significantly associated with the risk of anaphylaxis with an adjusted HR of 2.529 (95% CI, 2.442–2.619; $P < 0.001$).

Table 2. Incidence of anaphylaxis in the study group

	Control (n = 252 062)	Exposure of urticaria (n = 126 031)
Follow-up person-months	18 889 488	9 201 944
New anaphylaxis cases	5836	8211
Incidence rate [†]	3.09	8.92
Relative risk (95% CI)	Reference	2.89 (2.79–2.99)

[†]Incidence rate, per 10 000 person-months. CI, confidence interval.

DISCUSSION

In this study, urticaria was proposed as a risk factor for the development of anaphylaxis. To the best of our knowledge, this is the first study to apply a nationwide longitudinal population-based database to evaluate the relationship between urticaria and anaphylaxis. Our analysis of data from the NHIRD in Taiwan pertaining to the period between 2000 and 2013 suggested that urticaria confers a significant risk for the development of anaphylaxis.

The results of our analysis highlighted the importance of careful evaluation of patients with urticaria for risk of anaphylaxis. Australia and the USA have the highest incidence rates of severe anaphylaxis among developed countries. Manivannan *et al.*⁶ found an incidence rate of 498 cases per million person-years in Rochester, MN, USA, between 1990 and 2000, while Mullins *et al.*⁷ showed that the hospital admission rate due to anaphylaxis was 10.6 per 100 000 population-years in 2011–2012 in Australia. Thus, the incidence differs according to geographic area, possibly due to differences in the distribution of races, environmental conditions, socioeconomic status of residents, quality and availability of medical resources, and the definition of anaphylaxis used. Epinephrine auto-injectors are beneficial for food-induced anaphylactic shock prior to hospitalization, though studies have found a relatively low prescription frequency for adrenaline auto-injectors. In Taiwan, epinephrine auto-injectors are not standard devices in pre-hospital situations. The incidence of food-induced anaphylactic shock (peanut and shellfish) in Asian populations is reported to be different from that observed in Western populations. However, we found an increasing rate of epinephrine administration by patients or caregivers over the study period in Taiwan.

Table 3. Hazard ratios of anaphylaxis

	Crude HR (95% CI)	P	Adjusted HR (95% CI)	P
Urticaria	2.883 (2.787–2.982)	<0.0001	2.529 (2.442–2.619)	<0.0001
Sex				
Female	Reference		Reference	
Male	0.847 (0.819–0.877)	<0.0001	0.888 (0.857–0.919)	<0.0001
Age, years				
<20	Reference		Reference	
20–39	1.161 (1.106–1.218)	<0.0001	1.223 (1.164–1.286)	<0.0001
40–59	1.115 (1.061–1.171)	<0.0001	1.124 (1.067–1.183)	<0.0001
≥60	1.345 (1.273–1.422)	<0.0001	1.158 (1.089–1.231)	<0.0001
Urbanization				
Urban	0.78 (0.738–0.824)	<0.0001	0.824 (0.779–0.871)	<0.0001
Suburban	0.767 (0.723–0.814)	<0.0001	0.791 (0.745–0.839)	<0.0001
Rural	Reference		Reference	
Low income	1.321 (1.091–1.601)	0.0044		
Frequency of outpatient visits (within 2 years before index date)				
0	Reference		Reference	
1–6	2.22 (1.869–2.638)	<0.0001	1.84 (1.548–2.187)	<0.0001
7–13	3.121 (2.644–3.685)	<0.0001	2.319 (1.963–2.74)	<0.0001
14–27	3.924 (3.336–4.616)	<0.0001	2.619 (2.224–3.084)	<0.0001
≥28	5.304 (4.518–6.228)	<0.0001	2.896 (2.459–3.411)	<0.0001
Length of hospital stays (within 2 years before index date)				
No admission	Reference		Reference	
1–6 days	1.356 (1.284–1.431)	<0.0001	1.098 (1.039–1.16)	0.001
7–13 days	1.502 (1.375–1.641)	<0.0001	1.146 (1.047–1.256)	0.0032
≥14 days	1.782 (1.626–1.952)	<0.0001	1.31 (1.187–1.445)	<0.0001
Comorbidity				
Asthma	1.553 (1.461–1.652)	<0.0001	1.142 (1.07–1.218)	<0.0001
Allergic rhinitis	1.455 (1.395–1.518)	<0.0001	1.169 (1.117–1.224)	<0.0001
Herpes zoster	1.324 (1.218–1.439)	<0.0001	1.037 (0.954–1.128)	0.3944
Hepatitis B virus infection	1.054 (0.926–1.201)	0.4247	0.88 (0.772–1.004)	0.0568
Hepatitis C virus infection	1.554 (1.3–1.857)	<0.0001	1.151 (0.961–1.379)	0.1264
Diabetes mellitus	1.318 (1.24–1.401)	<0.0001	1.005 (0.941–1.074)	0.8764
Gout	2.079 (1.623–2.662)	<0.0001	1.287 (0.999–1.658)	0.051
Rheumatoid arthritis	1.122 (0.468–2.689)	0.7959	0.52 (0.216–1.253)	0.145
Cancer	1.521 (1.26–1.837)	<0.0001	1.034 (0.849–1.258)	0.7411
Medication				
Corticosteroids	1.859 (1.752–1.973)	<0.0001	1.123 (1.053–1.197)	0.0004
NSAID	1.677 (1.596–1.763)	<0.0001	1.194 (1.131–1.262)	<0.0001
Antihistamines	1.68 (1.615–1.749)	<0.0001	1.072 (1.024–1.123)	0.003

CI, confidence interval; HR, hazard ratio; NSAID, non-steroidal anti-inflammatory drug.

Multiple previous studies have demonstrated low rates of epinephrine administration among ED patients with anaphylaxis. Thus, it is imperative that clinicians be cognizant of these trends in the epidemiology of anaphylaxis, and ensure that the patients at risk are adequately informed and educated about this condition. In addition, patients must be provided with epinephrine auto-injectors to mitigate the effects of recurrent reactions. Although not all patients may require epinephrine treatment, increased access to epinephrine in public settings will help reduce complications of anaphylaxis.

Asthma is caused by chronic inflammation of the lung. The etiology of asthma is attributed to genetic and environmental factors. Patients with associated genetic background are susceptible to allergens. Allergens including dust, pollutants, insects, animals, microorganisms and food can activate T cells

through antigen-presenting cells of the airway and then induce the secretion of interleukin (IL)-4, IL-5 from T-helper 2 cells. IL-4 continuously stimulates B cells to produce IgE, which then combine with mast cells. Mast cells combined with IgE can release cytokines, such as histamine, prostaglandins and leukotriene, to arouse inflammation. On the other hand, IL-5 can attract eosinophils and cause contraction of smooth muscle of the airway and inflammation as well.⁸ We found some reference data for several diseases associated with urticaria. The Taiwan NHIRD research found that asthma was associated with chronic urticaria (crude odds ratio [OR], 1.31; 95% CI, 1.19–1.44), allergic rhinitis was associated with chronic urticaria (crude OR, 1.59; 95% CI, 1.52–1.66) and chronic urticaria (crude OR, 1.34; 95% CI, 1.12–1.60).⁹ Hepatitis B or C can occasionally induce urticarial vasculitis, but this is probably

related more to vasculitis than to true urticaria.¹⁰ A case report conjectured that hepatitis C may induce urticaria.¹¹ A cross-sectional study showed an association between gout and urticaria that was borderline significant (OR, 1.24; 95% CI, 0.99–1.55).¹² This study also presented that metabolic syndrome was related to chronic urticaria.

Anaphylaxis is a systemic reaction. Typical features include a feeling of impending doom, hypotension (often with loss of consciousness), diarrhea, vomiting and abdominal cramps, laryngeal edema and bronchospasm. Urticaria may be present, but up to 50% of reactions may not be accompanied by this rash. Urticaria, with or without angioedema, especially when chronic, is almost never due to IgE-mediated mechanisms. Patients with underlying asthma are at a greater risk of severe reactions which may include bronchospasms. Risk factors for a fatal outcome to anaphylaxis may include age (and age-related comorbidities such as hypertension and ischemic heart disease) and drug therapy (particularly angiotensin-converting enzyme inhibitors). Summers *et al.*¹³ have examined risk factors for anaphylaxis in patients with peanut and tree nut allergies, and found that severe pharyngeal edema was more likely to be present in patients with severe rhinitis and those with low levels of angiotensin-converting enzyme (≤ 37 mmol/L). Life-threatening bronchospasm was more likely in patients with severe asthma, while altered consciousness was more likely in those with severe eczema.

Though anaphylaxis is a common and serious condition, it is rarely fatal. However, it is crucial that patients receive appropriate acute and follow-up treatment. It is also essential that anaphylaxis is distinguished from benign non-allergic urticaria and angioedema (which is at least 100-times more common), and that adrenaline is used only in those patients who truly require it.

A particular strength of this study is the use of a nationwide population-based dataset. Therefore, there is a very low probability of selection bias in this study.

There are potential limitations to this study. With the great variation in clinical manifestations and diagnostic definition, the diagnosis of anaphylaxis is frequently disregarded by clinicians. Due to a lack of alertness to identifying symptoms, patients may not seek treatment for anaphylaxis. Patients with anaphylactic symptoms treated without hospitalization were thus not included in our study.

In conclusion, this is the first epidemiological study to identify an increased risk of anaphylaxis among patients with a

prior diagnosis of urticaria. Shedding light on this link may boost an earlier awareness of anaphylaxis among patients with urticaria and promote the availability and use of epinephrine auto-injectors for high-risk patients.

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CONFLICT OF INTEREST: None declared.

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