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REVIEW

Prevalence, Clinical Manifestations, Treatment, and Clinical Course of Chronic Urticaria in Elderly: A Systematic Review

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Purpose: Data specific to the epidemiology, clinical features, and management of chronic urticaria (CU) in the geriatric population remain limited and not well understood. We aim to systematically review the prevalence, clinical manifestations, treatment, and clinical course of elderly patients with CU.

Patients and methods: Original articles that included data of elderly (aged >60 years) with CU that were published until February 2021 were searched in PubMed, Scopus, and Embase using predfefined search terms. Related articles were evaluated according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations.

Results: Among the included 85 studies and 1,112,066 elderly CU patients, most (57.4%) were women. The prevalence of elderly CU in the general population ranged from 0.2–2.8%, and from 0.7–33.3% among all CU patients. Compared to adult CU, elderly CU patients had a higher percentage of wheal alone (73.9%), and lower rate of positive autologous serum skin test and atopy. Gastrointestinal diseases were the most common comorbidity (71.9%), and there was a high rate of malignancies and autoimmune diseases. Second generation H_1-antihistamines were commonly used, and achievement of complete control was most often reported. Omalizumab was prescribed in 59 refractory patients, and a significant response to treatment was reported in most patients. The treatment of comorbidities also yielded significant improvement in CU.

Conclusion: Elderly CU was found to be different from adult CU in both clinical and laboratory aspects. H_1- antihistamines are effective as first-line therapy with minimal side-effects at licensed doses. Treatment of secondary causes is important since the elderly usually have age-related comorbidities.

Keywords: prevalence, clinical manifestations, treatment, chronic urticaria, elderly, systematic review

Introduction

People are now living longer due to new innovations in both technology and modern medicine.[1] The result has been a doubling of global life expectancy over the past century, and an increase in the aging population worldwide.[2] The World Health Organization and the United Nations define elderly as age ≥60 years and age ≥65 years, respectively.[3,4] Thus, elderly-specific medical care has become and will continue to be a top priority of global public health.

Chronic urticaria (CU) is one of the most common pruritic conditions in the older population.[5,6] CU is characterized by the presence of recurrent wheal, with or without angioedema, occurring at least twice a week for longer than 6 weeks.[7] CU can be classified into two subtypes: chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU).[7] The pathogenesis of CU is still unclear, but it is thought to be related to histamine, other mediators, and cytokines that are released from activated mast cells by degranulation.[7–9] Among all patient with CU, 4.1–5.5% are elderly.[10–12] Moreover, several systemic and autoimmune diseases have been reported to be associated with CU in the elderly population, including

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hypertension, chronic kidney disease, diabetes mellitus, thyroid disease, atopic dermatitis and other allergic diseases, cardiac and cerebral vascular disease, and cancer.[11,13–20] CU can also affect various aspects of patient quality of personal and social life, including sleep disorders, anxiety and depression, sexual dysfunction, and decreased work performance.[21–23]

Our current understanding of CU in the elderly is still limited since the number of studies describing the clinical manifestations and responses to treatment of CU in the geriatric population with CU remains comparatively small. The International EAACI/GA[2] LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria recommends second generation H_1-antihistamine ($sgAH_1$) as the first-line treatment for CU.[7] If disease control is inadequate after 2–4 weeks of treatment, increasing the dose up to 4-fold of the standard dose of $sgAH_1$ s is recommended. For antihistamine-refractory patients, omalizumab and cyclosporine (CsA) are the treatments of choice.[7] However, the use of some antihistamines and other medications to treat older patients with CU can be limited due to several factors. In recalcitrant cases, other differential diagnoses related to underlying medical conditions should be considered. In an effort to bridge this knowledge gap, this systematic review was conducted to investigate the reported epidemiology, clinical features, treatments, and clinical course in elderly CU from all available studies.

Methods

Protocol and Registration

The protocol of this systematic review has been reviewed and approved by the Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand with SIRB Protocol No. 107/2564 (Exempt), and followed the standard protocol of Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA).[24] Studies published until February 2021 were searched in the PubMed, Scopus, and Embase databases. The search terms were "urticaria and elderly", "urticaria and aging", and "urticaria and geriatric".

Eligibility Criteria for Systematic Review

Case reports, case series, randomized controlled trials (RCTs), prospective cohort, retrospective cohort, and other types of studies that reported the epidemiology and clinical manifestation of CU in patients aged equal to or greater than 60 years were included. Due to the relatively limited number of studies of CU in the elderly, we included the studies performed in patients aged equal to or greater than 60 years, case reports and case series, aiming to collect data from available published evidence as much as possible. Treatment data was also extracted, but it was not part of the inclusion criteria (ie, studies that described only epidemiology and clinical manifestation without a description of treatment were eligible). Five investigators (KK, CR, KM, ST, and SP) independently screened all titles and abstracts of all retrieved articles. Potentially eligible articles were reviewed in full-text to determine their final eligibility. That process was also independently conducted by the same five reviewers. Any disagreement was resolved by discussion and consensus among the five reviewers.

Data Extraction

The following data were independently extracted by the same five investigators (KK, CR, KM, ST, and SP): 1) first author's name and the year of publication; 2) number of reported patients; 3) epidemiology; 4) clinical manifestations; 5) laboratory investigations; and 6) treatment and clinical course. Response to treatment was classified into four groups, as follows: i) complete control was defined as free of symptoms on continuation of treatment; ii) marked improvement was defined as symptoms having improved considerably, but that some symptoms were still present during treatment; iii) partial improvement was defined as partial reduction of severity of symptoms during treatment; and iv) no improvement was defined as no improvement of symptoms while on medications.

Statistical Analysis

Descriptive statistics, including mean plus/minus standard deviation and number and percentage, were used to describe demographic data, clinical manifestation, prevalence, laboratory findings, treatment, and clinical course. All data were analyzed using PASW Statistics for Windows (version 18.0; SPSS, Inc., Chicago, IL).

Results

From the three databases that were searched, 17,645 articles were identified (6,079 from PubMed, 5,579 from Scopus, and 5,987 from Embase). Of those, 3,369 duplicate articles were excluded. The remaining 14,276 articles underwent title and abstract review. This process eliminated 14,127 articles that did not meet the inclusion criteria. The remaining 149 articles underwent full-text review. Of those, 85 articles (three randomized controlled trials, 12 prospective cohort studies, 34 retrospective cohort studies, one case control study, 16 cross-sectional studies, eight cases series, and 11 case reports) fulfilled the inclusion criteria and were included for systematic review (Figure 1).

Proportion of the Elderly Among All Patients with CU, and the Prevalence of CU Among the Elderly

As shown in Table 1, the percentage of elderly among all CU patients from a single-center cohort ranged from 0.7% to 18.0%,[10,12,20,25–28] while the reported percentage in general population ranged from 14.1% to 33.3%.[19,29–34] Only two studies reported the percentage of elderly among all CSU patients in the general population (15.6% and 31.5%),[34,35] while the percentage of elderly among CSU patients from single-center studies ranged from 6.7% to 21.7%.[20,36–42] The percentage of elderly CIndU patients was reported in five studies.[32,34,43–45] The highest proportion was described in a general population study (16.3%).[32] The prevalence of elderly CU in the general population was reported to range from 0.2% to 2.8%[29,33,35,46] (Table 2).

Epidemiological Data

Clinical features and demographic data of the elderly with CU are summarized in Table 3. Women accounted for 57.4%, 63.9%, and 57.9% of elderly CU, CSU, and CIndU, respectively. The mean age at presentation among all CU patients was 70.4±6.2 years. Most presented with wheal alone (73.9%), followed by wheal with angioedema (25.9%). Only 0.2% presented with wheal and anaphylaxis. The average duration of disease prior to diagnosis was 1.9±3.6 years. Allergic rhinitis, asthma, and allergic dermatitis were the three most common associated atopic diseases. Cold urticaria, symptomatic dermographism, and cholinergic urticaria were found in 10.9%, 7.3%, and 3.5% of elderly CU patients, respectively.

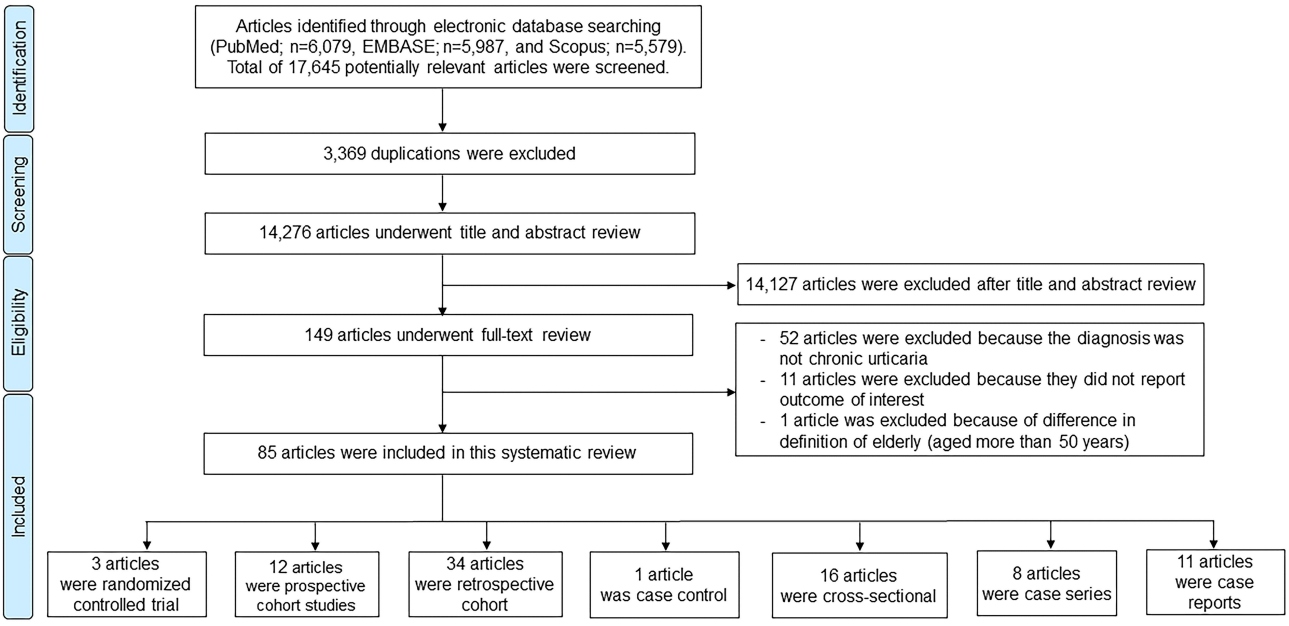

Figure 1 Flow diagram of the literature review process in this systematic review. Eighty-five articles were suitable for the inclusion criteria and were included in our systemic review. There were three randomized controlled trials, 12 prospective cohorts, 34 retrospective cohorts, one case-control, 16 cross-sectional, eight case series, and 11 case reports.

Table 1 The Reported Prevalence of Chronic Urticaria, Chronic Spontaneous Urticaria, and Chronic Inducible Urticaria in Elderly Patients Relative to All Reported Cases of These Disorders

Study (year)	Study design	Country	Population	Elderly patients among all reported patients N/Total (%)
Chronic urticaria				
Juhlin (1981)[12]	Retrospective cohort	Sweden	University Hospital	18/330 (5.5)
Greene et al (1985)[244]	Prospective cohort	USA	Department of Dermatology Mayo Clinic	9/50 (18.0)
Mekkes et al (1986)[25]	Retrospective cohort	Netherland	Dermatology clinic University Hospital	3/109 (2.8)
Barlow et al (1993)[26]	Retrospective cohort	UK	Urticaria clinic St John's Dermatology Centre	1/135 (0.7)
Hashiro et al (1994)[27]	Cross-sectional	Japan	Outpatient clinic Hospital	5/30 (16.7)
Gaig et al [a] (2004)[29]	Cross-sectional	Spain	Spanish population National telephone directory survey	10/30 (33.3)
Chen et al [b] (2012)[19]	Retrospective cohort	Taiwan	Taiwan population National Health Insurance Research Database	3,615/12,720 (28.4)
Krupashankar et al (2012)[28]	Prospective cohort	India	University Hospital	5/80 (6.3)
Magen et al (2013)[63]	Retrospective cohort	Israel	Allergy consultation Secondary and tertiary care	124/1,319 (9.4)
Ban et al (2014)[11]	Retrospective cohort	South Korea	Allergy clinic University Hospital	37/837 (4.4)
Chuamanochan et al (2016)[10]	Retrospective cohort	Thailand	Urticaria clinic University Hospital	67/1,622 (4.1)
Chu [b] (2017)[30]	Retrospective cohort	Taiwan	Taiwan population National Health Insurance Research Database	40,816/177,879 (23.0)
Eun et al (2018)[31]	Prospective cohort	Korea	Korean Population National Health Insurance Service - National Sample Cohort	447/2,980 (15.0)
Seo et al [c] (2019)[32]	Retrospective cohort	Korea	Korean Population Health Insurance Review and Assessment Service database	41,882/174,579 (24.0)
Wertenteil et al [d] (2019)[33]	Cross-sectional	USA	Multihealth system data analytics and research platform	22,900/69,570 (32.9)
Jankowska-Konsur et al[e] (2019)[34]	Cross-sectional	Poland	Poland Population Recruitment from multi centers all over the country	154/1,091 (14.1)
Chung et al (2020)[74]	Retrospective cohort	Korea	Outpatient clinic University Hospital	26/329 (7.9)
Napolitano et al (2021)[45]	Retrospective cohort	Italy	Dermatology unit University Hospital	153/1,970 (7.8)
Chronic spontaneous urticaria				
Yang et al (2005)[41]	Cross-sectional	Taiwan	Dermatological Clinics University Hospital	5/75 (6.7)
Hiragun et al (2013)[38]	Retrospective cohort	Japan	University Hospital	22/117 (18.8)
Magen et al (2013)[63]	Retrospective cohort	Israel	Allergy consultation secondary and tertiary care	92/1,051 (8.8)
Vikramkumar et al (2014)[42]	Cross-sectional	India	Department of Dermatology	5/48 (10.4)
Lapi et al [f] (2016)[35]	Retrospective cohort	Italy	Italian population The Health Search IMS Health Longitudinal Patient Database	4,242/13,479 (31.5)
Curto-Barredo et al (2018)[36]	Retrospective cohort	Spain	Urticaria unit Hospital	119/549 (21.7)
Nettis et al (2018)[40]	Retrospective cohort	Italy	Secondary care centers	32/322 (9.9)

(*Continued*)

Table 1 (Continued).

Study (year)	Study design	Country	Population	Elderly patients among all reported patients N/Total (%)
Curto-Barredo et al (2019)[37]	Retrospective cohort	Spain	Urticaria unit Hospital	99/549 (18.0)
Jankowska-Konsur et al [e] (2019)[34]	Cross-sectional	Poland	Poland Population Recruitment from multi centers all over the country	104/667 (15.6)
Jo et al (2019)[39]	Retrospective cohort	South Korea	University Hospital	79/970 (8.1)
Chronic inducible urticaria				
Dover et al [c] (1988)[43]	Retrospective cohort	England	Dermatology Hospital	1/44 (2.3)
Katsarou-Katsari et al (2008)[44]	Retrospective cohort	Greece	Skin allergy division Hospital	10/62 (16.1)
Seo et al [g] (2019)[32]	Retrospective cohort	Korea	Korean Population Health Insurance Review and Assessment Service database	3,290/20,191 (16.3)
Jankowska-Konsur et al [e] (2019)[34]	Cross-sectional	Poland	Poland Population Recruitment from multi centers all over the country	46/383 (12.0)
Napolitano et al (2021)[45]	Retrospective cohort	Italy	Dermatology Unit University Hospital	26/451 (5.8)

Notes: [a]Gaig et al conducted a population-based study among adults in Spain. Population sample was randomly selected from a national telephone directory. The phone survey was performed with each individual employing the Computer-assisted Telephone Interview technique. [b]The database from National Health Insurance Research of Taiwan represented approximately 99.9% of Taiwan's population. [c]Dover et al reported the prevalence of delayed pressure urticaria in hospital for diseases of the skin and the dermatology institute. [d]Electronic health records data for a demographically heterogenous population-based sample of >55 million patients. The database is from 27 participating integrated health care organizations, representing over 55 million unique persons (17% of the population across all four census regions of the United States). [e]This nationwide, multi-center, cross-sectional questionnaire-based study was performed under the auspices of the Polish Dermatological Society. Ten chronic urticaria patients were recruited by each of 102 dermatologists and allergists from different regions of Poland to achieve a good representation of patients from the whole country. [f]The database from the Health Search IMS Health Longitudinal Patient Database (HSD) contained the computer-based patient records from about 1,000 general practitioners (GPs) throughout Italy. Included in this study were almost 1 million electronic patient records which met standard quality criteria. They were selected on a geographical basis to represent the whole Italian population. [g]The database from Health Insurance Review and Assessment Service covers 97.0% of the Korean population. Not all types of urticaria were included in the study of Seo et al. The reported subtypes of chronic inducible urticaria were cholinergic urticaria and cold/heat urticaria, as shown in this table. Prevalence of dermographism was also reported but not included in this current study, as it was not symptomatic dermographism, which is chronic inducible urticaria subtypes.

Severity of CU was reported in 19 studies, mostly moderate-to-severe disease activity.[11,20,40,47–62] Urticaria activity score (weekly total score 42) was used in 13 studies, and the average score among all studies was 22.1±12.2.[20,40,48,53–55,57–63] The other scores used to report severity were Visual Analog Scale (VAS; total score 10),[54] Urticaria Activity Score (UAS; total score 9),[50] Urticaria Activity Score (UAS; total score 15),[11] Urticaria Severity Score (USS; total score 93),[51] and Treatment Score (TS; total score 5).[49,53] Twelve CSU studies reported severity using Urticaria Activity Score (UAS; weekly total score 42) with an average score among studies of 26.1±12.2.[40,53–55,57–60,62] Severity of CIndU was reported in heat urticaria, which showed a temperature threshold of 38°C, and in cold urticaria which showed 22 mm for the wheal and 40 mm for the flare by cold stimulation test.[52,56]

Elderly CU Patients Suffer from Various Age-Related Comorbidities

The reported comorbidities of study patients are shown in Table 3. Unspecified gastrointestinal (GI) disease was the most commonly reported comorbidity among elderly CU patients (71.9%), with the majority of cases collected from a large national database (Korean Health Insurance Review and Assessment Service: HIRA).[64] The reported prevalence of coronary and cerebral vascular disease were also high at 36.7%. The prevalence of dyslipidemia, hypertension, obesity, and diabetes mellitus in elderly CU patients was 42.9%, 18.6%, 16.7%, and 12.6%, respectively. Thyroid diseases were reported in 20 studies,[10,20,37,45,49–51,53,61,62,65–74] and some of them were related to autoimmune disorders. For example, Grave's disease and Hashimoto's disease was reported in 44.4% and 20.8% of aging CU, respectively. Other common comorbidities were

Table 2 The Reported Prevalence of Chronic Urticaria in the Elderly Population

Study (year)	Study design	Country	Population	Reported chronic urticaria among all elderly patients N/Total (%)
Chronic urticaria				
Gaig et al[a] (2004)[29]	Cross-sectional	Spain	Spanish population National telephone directory survey	10/1,047 (1.0)
Lapi et al[b] (2016)[35]	Retrospective cohort	Italy	Italian population The Health Search IMS Health Longitudinal Patient Database	13,476/488,145 (2.8)
Wertenteil et al[c] (2019)[33]	Cross-sectional study	USA	Multihealth system data analytics and research platform	22,900/9,757,210 (0.2)
Gaber et al (2020)[46]	Prospective cohort	Egypt	Outpatient clinic University Hospital	2/260 (0.8)

Notes: [a]Gaig et al conducted a population-based study among adults in Spain. Population sample was randomly selected from a national telephone directory. The phone survey was performed with each individual employing the Computer-assisted Telephone Interview technique. [b]The database from the Health Search IMS Health Longitudinal Patient Database (HSD) contained the computer-based patient records from about 1,000 general practitioners (GPs) throughout Italy. Included in this study were almost 1 million electronic patient records which met standard quality criteria. They were selected on a geographical basis to represent the whole Italian population. [c]Electronic health records data for a demographically heterogenous population-based sample of >55 million patients. The database is from 27 participating integrated health care organizations, representing over 55 million unique persons (17% of the population across all four census regions of the United States).

osteoporosis (42.9%), Raynaud phenomena (33.3%), gout (20.0%), avascular hip necrosis (20.0%), systemic lupus erythematosus (20.0%), and anemia (20.0%). Malignancies were also reported at a high rate. Most malignancies were unspecified but, among those that were specified, GI cancer was the most prevalent (60.0%). Other possible causes or aggravating factors of CU were paronychia (100.0%), stress (27.3%), unspecified drug allergy (9.1%), parasitic infection (4.7%), collagen vascular disease (3.2%), unspecified food allergy (3.0%), insect bite (2.4%), and aspirin intolerance (2.0%).

Laboratory results in Elderly with CU

As shown in Table 3, a positive autologous serum skin test (ASST) was found in 47.5% of elderly CU patients, which was less than in elderly CSU patients (54.9%). A Basophil histamine release test was reported in six studies,[50,61,75–78] and the result was positive in five of 13 tested patients (38.5%). There were 22 studies that reported the level of total serum IgE, and 16 of those studies reported the IgE value. The average level among those 16 studies was higher than the normal upper limit.[11,20,37,40,49,50,52,55,57,61,62,76,79–82] The other six studies reported only whether the level was elevated or not. The value was elevated in 42.1% of patients,[58,69,75,83–85] and this rate was similar to the 43.8% rate reported in elderly CSU. Erythrocyte sedimentation rate (ESR) was increased in 26.8% and 25.4% of elderly CU and CSU, respectively. Positive D-dimer was found in 50.0% of elderly CU patients, and elevated prothrombin fragment was found in 75.0%.[86] Antinuclear antibody (ANA) was reported in 13 studies[10,45,51,56,58,63,65,69,79,82,83,85,87] with an average positivity rate of 16.0% among those studies. Anti-FcεRI antibody was reported in one study (66.7% positive).[72] Abnormal thyroid hormone was common since it was reported in five of 21 studies.[65,71–73,77] No study reported abnormal free T3, but 13.0% of elderly CU patients had abnormal free T4 hormone, and 18.2% had abnormal thyroid stimulating hormone. Twenty-four studies reported thyroid autoantibodies with a positivity rate of antithyroid peroxidase antibodies of 26.4%, and a positivity rate of antithyroglobulin antibodies of 15.6%.[10,11,40,50,51,55,56,60,63,65–67,69–73,77,78,82,83,85,88,89]

Treatments for CU

Among the elderly who achieved complete control with the use of AH_1, $sgAH_1$ was most often used at a regular dose (24 of 34 patients), whereas first generation H_1-antihistamine ($fgAH_1$) was prescribed at a high dose (2 of 2 patients). Side-effects of antihistamines were reported in one study. A combination of multiple high-dose $fgAH_1$, which were hydroxyzine (dose: 25–200 mg/day), diphenhydramine (dose: 25–200 mg/day), and doxepin (dose: 25–125 mg/day), showed

Table 3 The Reported Demographic and Clinical Characteristics of Elderly Patients with Chronic Urticaria (CU), and Compared Between the Two Subtypes of CU – Chronic Spontaneous Urticaria and Chronic Inducible Urticaria

Clinical features: N/Total (%)	CU[a] (N=1,112,066)	CSU (N=891)	CIndU (N=1,568)
Gender			
Female	61,170/106,669 (57.4)	276/432 (63.9)	873/1,509 (57.9)
Age at presentation, mean±SD, years	70.4±6.2	71.6±6.7	69.9±3.8
Symptoms			
Wheal alone	305/413 (73.9)	236/312 (75.6)	NA
Wheal with angioedema	107/413 (25.9)	76/312 (24.4)	NA
Wheal with anaphylaxis	1/413 (0.2)	0/312 (0.0)	1/1 (100.0)
Duration of disease prior diagnosis, mean±SD, years	1.9±3.6	1.9±3.7	NA
Personal history of atopy[b]			
Allergic rhinitis	44/233 (18.9)	9/100 (9.0)	9/27 (33.3)
Asthma	84,519/982,862 (8.6)	4/101 (4.0)	2/27 (7.4)
Atopic Dermatitis	57,163/985,228 (5.8)	15/162 (9.3)	4/27 (14.8)
Allergic conjunctivitis	2/73 (2.7)	0/7 (0.0)	1/27 (3.7)
Unspecified atopy	18/144 (12.5)	8/105 (7.6)	0/1 (0.0)
Family history of atopy			
Allergic rhinitis	5/74 (6.8)	0/1 (0.0)	0/2 (0.0)
Asthma	2/74 (2.7)	0/1 (0.0)	0/2 (0.0)
Atopic Dermatitis	1/74 (1.4)	0/1 (0.0)	0/2 (0.0)
Types of chronic inducible urticaria			
Cold urticaria	18/165 (10.9)	NA	7/154 (4.6)
Symptomatic dermographism	25/344 (7.3)	NA	25/344 (7.3)
Cholinergic urticaria	1,468/42,006 (3.5)	NA	3/124 (2.4)
Delayed pressure urticaria	4/126 (3.2)	NA	2/124 (1.6)
Heat urticaria	3/154 (2.0)	NA	2/153 (1.3)
Solar urticaria	2/125 (1.6)	NA	1/124 (0.8)
Aquagenic urticaria	1/153 (0.7)	NA	1/153 (0.7)
Comorbidity[b,c]			
Gastrointestinal diseases	708,417/985,284 (71.9)	1/5 (20.0)	NA
Coronary and other vascular diseases			
Cardiac/cerebral vascular diseases	72/196 (36.7)	52/169 (30.8)	19/26 (73.1)
Atrial fibrillation	1/5 (20.0)	1/5 (20.0)	NA
Metabolic diseases			
Dyslipidemia	3/7 (42.9)	2/6 (33.3)	1/1 (100.0)
Hypertension	183,473/986,035 (18.6)	103/264 (39.0)	20/27 (74.1)
Obesity	5/30 (16.7)	0/4 (0.0)	5/26 (19.2)
Diabetes Mellitus	34/271 (12.6)	34/271 (12.6)	NA
Unspecified metabolic syndrome	21/67 (31.3)	21/67 (31.3)	NA
Musculoskeletal diseases			
Osteoporosis	3/7 (42.9)	3/7 (42.9)	NA
Gout	1/5 (20.0)	0/4 (0.0)	NA
Avascular hip necrosis	1/5 (20.0)	1/5 (20.0)	NA
Thyroid diseases			
Hyperthyroidism	1/1 (100.0)	NA	NA
Hypothyroidism	5/9 (55.6)	1/5 (20.0)	NA
Grave's disease	4/9 (44.4)	2/6 (33.3)	NA
Hashimoto's thyroid diseases	22/106 (20.8)	21/105 (20.0)	NA
Parathyroid adenoma	1/5 (20.0)	1/5 (20.0)	NA
Unspecified thyroid diseases	28/142 (19.7)	24/116 (20.7)	4/26 (15.4)

(*Continued*)

Table 3 (Continued).

Clinical features: N/Total (%)	CU[a] (N=1,112,066)	CSU (N=891)	CIndU (N=1,568)
Systemic diseases			
Raynaud phenomena	2/6 (33.3)	0/4 (0.0)	NA
Systemic lupus erythematosus	1/5 (20.0)	1/5 (20.0)	NA
Anemia	1/5 (20.0)	0/4 (0.0)	NA
Unspecified autoimmune diseases	8/70 (11.4)	8/69 (11.6)	0/1 (0.0)
High myopia	1/5 (20.0)	0/4 (0.0)	NA
Genitourinary disorders			
Benign prostate hyperplasia	3/30 (10.0)	3/30 (10.0)	3/26 (11.5)
Chronic kidney diseases	6/96 (6.3)	6/96 (6.3)	NA
Chronic obstructive pulmonary diseases	2/31 (6.5)	1/5 (20.0)	1/26 (3.8)
Psychiatric problems			
Dementia	4/67 (6.0)	4/67 (6.0)	NA
Unspecified psychiatric problems	5/130 (3.9)	2/103 (1.9)	2/26 (7.7)
Dermatologic diseases			
Psoriasis	4/96 (4.2)	4/96 (4.2)	NA
Contact dermatitis	3/96 (3.1)	3/96 (3.1)	NA
Malignancy			
Gastrointestinal cancer	6/10 (60.0)	0/4 (0.0)	NA
Genitourinary cancer	2/6 (33.3)	0/4 (0.0)	NA
Bronchioalveolar cancer	2/6 (33.3)	0/4 (0.0)	NA
Thyroid cancer	2/6 (33.3)	2/6 (33.3)	NA
Malignant melanoma	1/5 (20.0)	0/4 (0.0)	NA
Hematologic malignancy	35/3,625 (1.0)	0/8 (0.0)	NA
Unspecified malignancy	459/3,714 (12.4)	11/99 (11.1)	NA
Possible causes of urticaria			
Stress	27/99 (27.3)	27/99 (27.3)	NA
Aspirin intolerance	8/42 (2.0)	1/5 (20.0)	0/4 (0.0)
Parasitic infection	6/129 (4.7)	0/4 (0.0)	NA
Collagen vascular disease	4/124 (3.2)	NA	NA
Insect bite	3/126 (2.4)	1/1 (100.0)	1/27 (3.7)
Paronychia	1/1 (100.0)	NA	NA
Unspecified drug allergy	12/132 (9.1)	1/8 (12.5)	NA
Unspecified food allergy	1/33 (3.0)	0/7 (0.0)	1/26 (3.9)
Laboratory investigations			
Positive ASST	125/263 (47.5)	107/195 (54.9)	1/3 (33.3)
Positive SPT	1/9 (11.1)	0/4 (0.0)	1/1 (100.0)
Positive Basophil histamine release test	5/13 (38.5)	4/9 (44.4)	NA
Leukocytosis	4/82 (4.9)	4/70 (5.7)	0/1 (0.0)
Positive HBsAg	8/75 (10.7)	8/68 (11.8)	0/1 (0.0)
Positive anti-HCV	0/70 (0.0)	0/68 (0.0)	0/2 (0.0)
Total serum IgE			
Elevated IgE	8/19 (42.1)	7/16 (43.8)	1/1 (100.0)
IgE level, mean±SD, kU/L			
ImmunoCAP method (normal range 0–119 kU/L) [d]	477.3±288.8	477.3±288.8	NA
Pharmacia CAP System IgE FEIA method[e] (normal range 0–100 kU/L)	164.9±210.4	194.5±269.7	NA
Nephelometry method[f] (normal range 0–100 kU/L)	125	125	NA
Elevated erythrocyte sedimentation rate	22/82 (26.8)	18/71 (25.4)	0/1 (0.0)
Elevated D-dimer	2/4 (50.0)	NA	NA
Elevated prothrombin fragment	3/4 (75.0)	NA	NA

(*Continued*)

Table 3 (Continued).

Clinical features: N/Total (%)	CU[a] (N=1,112,066)	CSU (N=891)	CIndU (N=1,568)
Abnormal C3	0/18 (0.0)	0/7 (0.0)	0/1 (0.0)
Abnormal C4	2/18 (11.1)	0/7 (0.0)	0/1 (0.0)
Abnormal CH50	1/11 (0.0)	0/5 (0.0)	NA
Abnormal C1-INH	0/13 (0.0)	0/7 (0.0)	NA
Positive antinuclear antibodies	13/81 (16.0)	13/69 (18.8)	0/2 (0.0)
Positive anticentromere antibodies	2/2 (100.0)	NA	NA
Positive Anti-FcεRI antibodies	2/3 (66.7)	2/3 (66.7)	NA
Abnormal free T3	0/22 (0.0)	0/9 (0.0)	0/1 (0.0)
Abnormal free T4	4/31 (12.9)	3/20 (15.0)	0/1 (0.0)
Abnormal TSH	6/33 (18.2)	3/19 (15.8)	0/2 (0.0)
Positive antithyroid peroxidase antibodies	40/150 (26.7)	25/110 (22.7)	1/2 (50.0)
Positive antithyroglobulin antibodies	42/124 (33.9)	31/86 (36.1)	0/1 (0.0)
Abnormal urinalysis	10/64 (15.6)	10/63 (15.9)	NA
Abnormal stool examination	6/85 (7.1)	4/77 (5.2)	NA

Notes: [a]It should be noted that the CU group included all CU patients aged above 60 years. Studies that reported specifically for CSU or CIndU subtypes were also included in the subgroups of CSU and CIndU. [b]One patient could have more than one personal history of atopy or one comorbidity. Comorbidity and history of atopy were only showed information from papers which mentioned about each disease. [c]It should be noted that the studies of Urbach, Lindelof et al, and Chen et al reported only the number of patients with malignancy, other comorbidities were not identified. [d]Total IgE level measured by ImmunoCAP method were reported in three studies, Ban et al (n=37), Romano et al (n=1), and Nettis et al (n=32), which reported about CU, CSU, and CSU, respectively. Referring to the National Center for Health Statistics, Centers for Disease Control and Prevention, the normal range of total IgE based on ImmunoCAP method is 0–119 kU/L. [e]Total IgE level measured by Pharmacia CAP method was reported in only one study, Staubach et al (n=4), which reported about CSU. [f]Total IgE level measured by Nephelometry method was reported in only one study, Kulthanan et al (n=1), which reported about CSU.

Abbreviations: Anti-FcεRI, anti-FcepsilonRI; ASST, autologous serum skin test; C3, complement C3; C4, complement C4; CH50, total hemolytic complement; C1-INH, complement 1 esterase inhibitor; CIndU, chronic inducible urticaria; CSU, chronic spontaneous urticaria; CU, chronic urticaria; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; Ig, immunoglobulin; NA, not available/not applicable; SD, standard deviation; SPT, skin prick test; TSH, thyroid stimulating hormone.

no additional benefit and caused severe sedation. Treatment in those cases was later changed to omalizumab.[60] Omalizumab was prescribed in 15 studies. Complete control was observed in 59 of 89 patients, and the prescribed dose ranged from 150 to 300 mg every 2–4 weeks. Fifty patients from five studies received omalizumab alone.[48,76,81,90,91] Others received omalizumab in combination with other treatments, including with H_1-antihistamine (AH_1) in seven patients from five studies,[49,50,57,58,61] and systemic corticosteroid in two patients from one study.[55,60] Side-effects of omalizumab were reported in three studies.[62,81,90] Two patients experienced nausea, two patients reported asthenia that spontaneously resolved within 48 hours, and one patient had pain at the injection site.

Treatment of Secondary Causes Should Be Considered a Strategy for Controlling CU

Treatment of secondary causes was also effective for controlling CU in the elderly. Thirty-nine studies described the treatment of secondary causes and the outcomes of treatment (Figure 2 and Table 4). More specifically, the following treatments, prescriptions, or procedures improved CU symptoms in the elderly: treatment for *Helicobacter pylori* (*H. pylori*) infection,[63] treatment for *Strongyloides* infection,[92] treatment for thyroid diseases,[73,88] prescription of immunosuppressants for malignancies,[79,83,93] prescription of intravenous immunoglobulin (IVIG)[53,54,60] or sulfasalazine to treat recalcitrant CSU,[94] and surgical removal of adenoma/neoplasms.[69,84,85,89,95–97]

Follow-Up Time, Tapering, Relapse, and Mean Duration of Treatment

The follow-up time after completion of treatment was mentioned in 16 studies,[51,53,54,58,62,69,73,82–85,88,89,92,94,95] and the average follow-up time was 17.5 months. Some patients who had already achieved complete control continued their previous medication during the follow-up period, such as sulfasalazine and $sgAH_1$, until they could be tapered off.[94] Methotrexate (MTX) was tapered off in two patients, but one of them relapsed.[83] Four patients continued to receive omalizumab maintenance at the same dose with an attempt to increase the interval between doses.[55,60,91] One patient was prescribed $fgAH_1$ as needed, but there was no report of the actual frequency of use.[88] Another patient continued

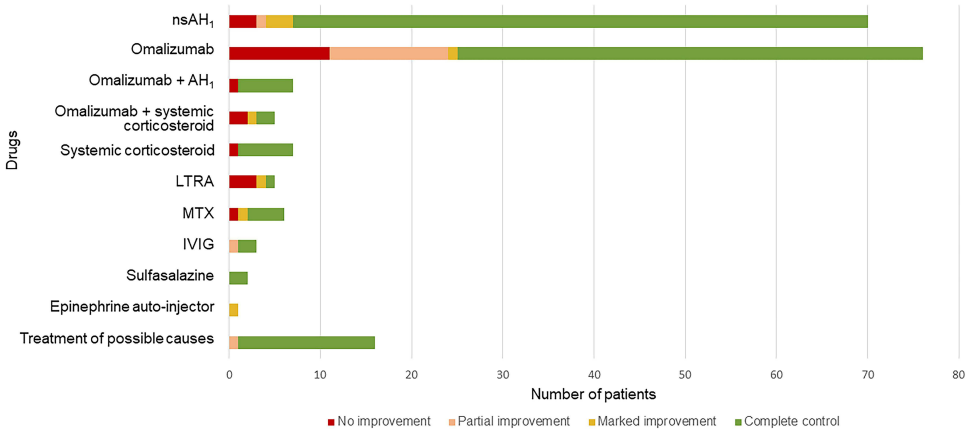

Figure 2 Treatments and responses to treatment among elderly with chronic urticaria.
Notes: Some patients received more than one type of treatment.
Abbreviations: AH_1,H_1-antihistamine; $fgAH_1$, first generation H_1-antihistamine; IVIG, intravenous immunoglobulin; LTRA, leukotriene receptor antagonist; MTX, methotrexate; NA, not available/not applicable; $sgAH_1$, second generation H_1-antihistamine.

levothyroxine for 2 years before tapering, but relapse occurred. The dose was increased back to the initial dose and complete control was re-established.[51] The average duration of treatment in this study was 205.8 days (6.9 months).

Discussion

The results of this systematic review revealed some similarities and differences between adult CU and elderly CU. Previously reported prevalence of CU in adult population ranges from 0.1% to 3.4%, which is relatively similar to the 0.2% to 2.8% prevalence of CU in the elderly.[33,98] Our review also showed variation between prevalence in various geographic areas. As shown in Table 1, large population and nationwide studies showed a relatively higher prevalence of elderly in the CU population than smaller studies. However, larger studies and smaller studies reported a similar prevalence of CU in the overall elderly population (Table 2).

Even if women formed the majority of this study, which was similar to previous elderly and adult CU reports,[10,11,23,99,100] some clinical presentations of elderly patients differed from adult CU. Comparison of the reported demographic and clinical characteristics of elderly patients with CU and those of non-elderly is shown in Table 5. Although the majority of both groups presented with wheal alone, its proportions in the elderly were higher than in adults, ranging from 33% to 87% across the studies, while the prevalence of concurrent angioedema was less.[9,10,12,20,37,40,90] Wheal with anaphylaxis in our review was found only in one case report of the elderly with cold urticaria, which was the type that could have concurrent anaphylaxis up to 3.7–38.0%.[44,101–107] CSU was the most common subtype among the elderly, similar to adult CU.[10,20,26,45,108–111] Concerning CIndU, symptomatic dermographism (SD) was reported as the most common CIndU in both groups.[10,20,45,74,108,112] Similar to the report of Ban et al,[11] history of atopy, which is known to be associated with CU, was found at a relatively lower rate in this study than adult CU,[10,11,20,37,45,64,74,90] in contrast with some previous studies.[10,11,18] Regarding comorbidities, Lapi et al[35] reported the risk of developing CU to be related to numerous factors. Gastrointestinal diseases, being the most common concomitant disease, together with coronary heart diseases, cerebrovascular diseases, metabolic syndrome, autoimmune diseases, thyroid diseases, psychological problems, and malignancies, were all reported at high rates in elderly CU. These findings were consistent with previous studies that reported CU to be associated with increased risk of having metabolic syndrome in both adults and the elderly.[20,113–115] Moreover, the risk of developing metabolic syndrome was also found to increase with age.[116,117] As reported by Zbiciak-Nylec et al[118] that later onset of urticaria symptoms can result from obesity. Similar to previous studies, autoimmune diseases including autoimmune thyroid diseases, rheumatoid arthritis, and systemic lupus erythematosus had been reported in high rates in all age groups of CU patients, but much more in the elderly.[17,70,90,119–123] This can be a result from increasing production of autoantibodies with aging, as Ramos-Casals et al[124] proposed. In addition, a previous nationwide study reported

Table 4 The Reported Treatment for and Clinical Course of Chronic Urticaria in the Elderly

Study (year)	N = Elderly CU/ Total	Treatment									Duration of treatment	Treatment response	Follow-up after treatment and outcome	Side-effects after treatment
		AH_1			Corticosteroids		LTRA	Omalizumab	Immunosuppressant	Others				
		$fgAH_1$	$sgAH_1$	Unspecified AH_1	Systemic	Topical								
Prospective Cohort Studies														
Leznoff et al (1983)[67]	N = 1 of 17	NA	NA	NA	NA	NA	NA	NA	NA	- Levothyroxine (dose: 0.2 mg/d) for euthyroid patient who had autoimmune thyroiditis	NA	Partial improvement	NA	NA
Rumbyrt et al (1995)[88]	N = 1 of 7	NA	NA	NA	Previous use of - Prednisolone (dose: NA) with no improvement	NA	NA	NA	NA	Previous use of - Famotidine (dose: NA) with no improvement - Doxepin (dose: NA) with no improvement -Thyroxine (0.05 mg/d) for euthyroid patient who had autoimmune thyroiditis	At least 4 weeks	Complete control then discontinued thyroxine	Longer than 1 year of rare hive, with use of Hydroxyzine (dose: NA, as needed)	NA
O'Donnell et al (1998)[54]	N = 1 of 10	NA	- Cetirizine (dose: 10 mg twice daily)	Previous use of 0 (dose: NA) with no improvement	NA	NA	NA	NA	No	- IVIG (dose: 0.4 g/kg/d for 5 days)	5 days	Partial improvement	6 months	Headache

(*Continued*)

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Table 4 (Continued).

Study (year)	N = Elderly CU/ Total	Treatment									Duration of treatment	Treatment response	Follow-up after treatment and outcome	Side-effects after treatment
		AH_1			Corticosteroids		LTRA	Omalizumab	Immunosuppressant	Others				
		$fgAH_1$	$sgAH_1$	Unspecified AH_1	Systemic	Topical								
Sanada et al (2005)[242]	N = 5 of 25	NA	Previous use of - Ebastine (dose: 20 mg/d) with no improvement - Ebastine (dose: 20 mg/d)	NA	NA	NA	- All cases: Montelukast (dose: 10 mg/d)	NA	NA	NA	NA	Complete control	NA	NA
		NA	Previous use of - Ebastine (dose: 20 mg/d) with no improvement - Ebastine (dose: 20 mg/d)		Previous use of - Betamethasone (dose: 0.5 mg/d orally) with no improvement							Marked improvement		
		Previous use of - Hydroxyzine (dose: 50 mg/d) with no improvement	Previous use of - Homochlorcyclizine (dose: 30 mg/d) with no improvement - Homochlorcyclizine (dose: 30 mg/d)		NA							No improvement		
		NA	Previous use of - Olopatadine (dose: 20 mg/d) with no improvement - Olopatadine (dose: 20 mg/d)		Previous use of - Betamethasone (dose: 0.5 mg/d orally) with no improvement							No improvement		
		NA	Previous use of - Loratadine (dose: 10 mg/d) - Ebastine (dose: 10 mg/d) with no improvement - Loratadine (dose: 10 mg/d) - Ebastine (dose: 10 mg/d)		NA							No improvement		

Kaplan et al [a] (2008)[50]	N = 2 of 12	- Hydroxyzine (dose: 25–50 mg every 6 hours as needed, total 100–175 mg/d) - Hydroxyzine (dose: 25–50 mg every 6 hours as needed, total 175 mg/d in the first 4 week then tapered dose until stop at week 8)	NA	NA	NA	NA	NA	- All cases: Omalizumab 150 mg sc every 2 weeks or every 4 weeks	No	NA	4 months	No improvement Complete control	NA	NA
Uysal et al (2014)[61]	N = 3 of 27	NA	All cases: - Desloratadine or fexofenadine; (dose: recommended dose for 3–4 times)	NA	NA	NA	NA	- Omalizumab 150 mg sc every 2 weeks then extend to 5 weeks - Omalizumab 150 mg sc every 2 weeks then extend to 7 weeks - Omalizumab 150 mg sc every 2 weeks then extend to 7 weeks	Previous use of - MTX (dose: NA) with no improvement Previous use of - AZA (dose: NA) with no improvement Previous use of - AZA (dose: NA) with no improvement	NA	112 days 78 days 62 days	Complete control then discontinued omalizumab	NA	NA
Retrospective cohort studies														
McGirt et al (2006)[94]	N = 2 of 19	Previous use of - Hydroxyzine (dose: maximum 25 mg nightly) with no improvement	Previous use of - Cetirizine (dose: maximum 10 mg/d) with no improvement	NA	Previous use of - Prednisolone (dose: 10 mg/d for 3 days; 2–3 times) with no improvement - Prednisolone (dose: 10 mg/d once for 5 months)	NA	NA	NA	NA	- Sulfasalazine (dose: start at 500 mg/d then increased by 500 mg each week until 2 g/d) for total 12 months	12 months	Complete control then tapered off of sulfasalazine, $sgAH_1$	3 months	NA
		NA	Previous use of - Cetirizine (dose: 10 mg/d) with no improvement		Previous use of - Prednisolone dose pack (dose: NA) for 5 courses with no improvement					- Sulfasalazine (dose: start at 500 mg/d then increased by 500 mg each week until 2 g/d) for total 11 months	11 months	Complete control then discontinued sulfasalazine	NA	

(*Continued*)

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Table 4 (Continued).

Study (year)	N = Elderly CU/ Total	Treatment									Duration of treatment	Treatment response	Follow-up after treatment and outcome	Side-effects after treatment
		AH_1			Corticosteroids		LTRA	Omalizumab	Immunosuppressant	Others				
		$fgAH_1$	$sgAH_1$	Unspecified AH_1	Systemic	Topical								
Perez et al (2010)[241]	N = 1 of 16	NA	Previous use of - $sgAH_1$ (unmentioned name, dose: above the recommended dose) with no improvement	NA	Previous use of - Prednisolone (dose: 20 mg/d) with no improvement	NA	NA	NA	Previous use of - CsA (dose: NA) with no improvement - MTX (dose: 5 mg weekly)	Previous use of 0 (unmentioned name, dose: NA) with no improvement - Folic acid (dose: 5 mg weekly)	NA	Marked improvement	NA	NA
Mitzel-Kaoukhov et al (2010)[53]	N = 2 of 6	NA	Previous use of - $sgAH_1$ (unmentioned name, dose: 4-fold of the recommended dose) with no improvement	NA	NA	NA	All cases: previous use of - LTRA (unmentioned name, dose: NA) with no improvement	NA	All cases: previous use of - CsA (dose: NA) with no improvement	Previous use of - Histaglobin (dose: NA) with no improvement - IVIG (dose: 2 mg/kg every 4 weeks) for 11 cycles	10 months	Complete control then discontinued	14 months	No
			Previous use of - $sgAH_1$ (unmentioned name, dose: 8-fold of the recommended dose) with no improvement		Previous use of - Systemic corticosteroid (unmentioned name, dose: high dose) with no improvement				NA	Previous use of - Dapsone (dose: NA) with no improvement - IVIG (dose: 2 mg/kg every 4 weeks) for 4 cycles then remission but 4 months later	11 months	Complete control then discontinued	2 months then relapse occurred so IVIG was reinitiated for other 5 cycles	Impairment of pre-existing HT, disappeared after extending the treatment period of IVIG from 2 to 3 days

Sagi et al (2011)[83]	N = 5 of 8	All cases: previous use of - fgAH$_1$ (unmentioned name, high dose) with no improvement	All cases: previous use of - sgAH$_1$ (unmentioned name, high dose) with no improvement	NA	Previous use of - Systemic corticosteroid (unmentioned name, dose: NA) with no improvement - Systemic corticosteroid (dose: 30–40 mg/d) for multiple courses then tapered down (dose: NA) - Systemic corticosteroid (dose: 30–40 mg/d) for multiple courses then tapered down (dose: NA) - Systemic corticosteroid (dose: 30–40 mg/d) for multiple courses then tapered down until off	NA	NA	NA	- MTX (dose: 15 mg weekly) for 1 month then tapering down to 10 and 5 mg oral weekly for 1 and 1 month, respectively)	- Folic acid (dose: 5 mg weekly)	3 months	Complete control then discontinued MTX and folic acid	8 months	No
									- MTX (dose: 15 mg weekly) for 3 months then currently in the process of tapering down to 10 mg oral weekly for 2 months, without recurrence of urticaria)		5 months	Complete control (still in the MTX tapering process)	NA	Elevated liver enzyme (Twice the normal values) – resolved after reducing MTX dosage
									- MTX (dose: 15 mg oral weekly) for 3 months		3 months	Complete control then discontinued MTX and folic acid	2 months	No
									- MTX (dose: 7.5 mg oral weekly) for 2 months		2 months	No improvement then discontinued MTX and folic acid due to poor compliance	2 months	Fatigue
									- MTX (dose: 15 mg oral weekly) for 1 month then change to 15 mg IM weekly for 4 months		5 months	Complete control then tapering MTX down but relapse occurred and required a constant dose of MTX 15 mg/week	NA	Gastrointestinal discomfort – resolved after changing to MTX IM route
Magen et al (2013)[20]	N = 49 of 92	- fgAH$_1$ (unmentioned name; dose: NA) in 8 of 46 patients	- sgAH$_1$ (unmentioned name; dose: NA) in 49 of 49 patients	NA	- Systemic corticosteroid (unmentioned name, dose: NA) in 2 of 49 patients	NA	NA	NA	NA	NA	12 months	Complete control in 34 of 46 patients	NA	NA
Magen et al (2013)[63]	N = 1 of 9	NA	NA	NA	NA	NA	NA	NA	NA	- Amoxicillin (dose: 2 g/d) - Clarithromycin (dose: 1 g/d) - Omeprazole (dose: 40 mg/d) for treatment of *H. pylori* infection	2 weeks	Complete control then discontinued *H. pylori* infection treatment	NA	NA

(*Continued*)

Table 4 (Continued).

Study (year)	N = Elderly CU/ Total	Treatment									Duration of treatment	Treatment response	Follow-up after treatment and outcome	Side-effects after treatment
		AH_1			Corticosteroids		LTRA	Omalizumab	Immunosuppressant	Others				
		$fgAH_1$	$sgAH_1$	Unspecified AH_1	Systemic	Topical								
Song et al (2013)[55]	N = 4 of 16	NA	All cases: previous use of - Cetirizine (dose: 60–80 mg/d) with no improvement	NA	Previous use of - Prednisolone (dose: 15 mg/d) for 10 courses with no improvement - Prednisolone (dose: NA) for short courses Previous use of - Prednisolone (dose: 10 mg/d) for >20 courses with no improvement - Prednisolone (dose: NA) Previous use of - Prednisolone (dose: 5–20 mg/d) for >20 courses with no improvement - Prednisolone (dose: NA) tapered dose then off shortly after start omalizumab Previous use of - Prednisolone (dose: 5–10 mg/d) for >20 courses with no improvement - Prednisolone (dose: NA) tapered dose then off shortly after start omalizumab	NA	NA	All cases: - Omalizumab 150 mg sc every 4 weeks	NA	NA	24 months	Complete control and continued with omalizumab 150 mg sc every 4–8 weeks	NA	No
											2 months	No improvement then discontinued omalizumab and went into spontaneous remission then discontinued prednisolone		Flare of urticaria after first dose of omalizumab injection
											2 months	No improvement then discontinued omalizumab		No
											24 months	Complete control and continued with omalizumab 150 mg sc every 4–8 weeks		No

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Romano et al (2015)[62]	N= 1 of 9	Previous use of - Cinnarizine (dose: NA) with no improvement	NA	Previous use of -AH_1 (unmentioned name, dose: NA) with no improvement	Previous use of - Systemic steroid (unmentioned name, dose: NA) with no improvement	NA	Previous use of - LTRA (unmentioned name, dose: NA) with no improvement	- Omalizumab 150 mg sc every 4 weeks	Previous use of - CsA (dose: NA) with no improvement	NA	5 months	No improvement then discontinued omalizumab	42 months	Pain at injected site
Sugiyama et al (2015)[73]	N = 2 of 40	NA	Previous use of - Olopatadine (dose: 5 mg/d) with partial improvement - Olopatadine (dose: 5 mg/d) NA	NA	NA	NA	NA	NA	NA	All cases: - Triiodothyronine (dose: 25 g/d) for Hashimoto's disease	3 months	Complete control then discontinued triiodothyronine	>10 months of complete control then recurrence occurred after triggered by upper respiratory tract infection; symptom was well-controlled with olopatadine 2.5 mg/d NA	NA
Kulthanan et al (2017)[57]	N = 1 of 13	NA	Previous use of - Desloratadine (dose: 20 mg/d) - Levocetirizine (10 mg/d) with no improvement - Desloratadine (dose: 5–10 mg/d)	NA	Previous use of - Prednisolone (5–10 mg/d) with no improvement	NA	Previous use of - Montelukast (dose: NA) with no improvement	- Omalizumab 150 mg sc every 4 weeks	Previous use of - CsA (dose: NA) - HCQ (dose: NA) with no improvement	Previous use of 0 (unmentioned name, dose: NA) with no improvement	4 months	Complete control then discontinued omalizumab	NA	No
Napolitano et al (2018)[93]	N = 1 of 1,493	NA	NA	Previous use of 0 (dose: 4 times of licensed dose) with no improvement	Previous use of - Prednisolone (dose: NA) with partial improvement	NA	NA	NA	NA	- Chemotherapy for small cell lung cancer	NA	Complete control	NA	NA

(*Continued*)

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Table 4 (Continued).

Study (year)	N = Elderly CU/ Total	Treatment									Duration of treatment	Treatment response	Follow-up after treatment and outcome	Side-effects after treatment
		AH_1			Corticosteroids		LTRA	Omalizumab	Immunosuppressant	Others				
		$fgAH_1$	$sgAH_1$	Unspecified AH_1	Systemic	Topical								
Napolitano et al (2021)[45]	N = 26 of 451	NA	- $sgAH_1$ (unmentioned name, recommended dose) in 23 of 26 patients - $sgAH_1$ (unmentioned name, double dose) in 3 of 26 patients with SD	NA	NA	NA	NA	NA	NA	NA	NA	Complete control in 26 of 26 patients	NA	No
Martina et al (2021)[90]	N = 62 of 62	NA	NA	NA	NA	NA	NA	- Omalizumab 300 mg sc every 4 weeks	NA	NA	3 months	- Complete control in 44 of 62 patients - Partial improvement in 11 of 62 patients - No improvement in 7 of 62 patients	NA	asthenia; spontaneously resolved within 48 hours (2 patients)
Case Series														
Manganoni et al (2007)[89]	N = 1 of 4	Previous use of - Oxatomide (dose: 60 mg/d) with no improvement	NA	NA	Previous use of - Betamethasone (dose: 2 mg/d orally) with no improvement	NA	NA	NA	NA	- Surgery: total thyroidectomy for papillary thyroid carcinoma	NA	Complete control	60 months	NA
Godse (2011)[48]	N = 1 of 5	NA	Previous use of - $sgAH_1$ (unmentioned name, dose: 4 times of recommended dose) with no improvement	NA	Previous use of - Systemic corticosteroid (dose: NA) with no improvement	NA	NA	- Omalizumab 300 mg sc every 4 weeks	NA	NA	4 months	Complete control then discontinued omalizumab	NA	NA
Groffik et al (2011)[49]	N = 1 of 9	NA	Previous use of - $sgAH_1$ (unmentioned name, dose: 4 times of recommended dose) with no improvement	NA	Previous use of - Systemic corticosteroid (dose: NA) for long-term with no improvement	NA	NA	- Omalizumab 300 mg sc every 2 weeks	NA	NA	2 months	Complete control then discontinued omalizumab	NA	NA

Metz et al (2011)[52]	N = 1 of 7	NA	Previous use of - Loratadine (recommended dose) - Cetirizine (recommended dose) - Desloratadine (2–6 fold of recommended dose) - Ebastine (recommended dose) - Rupatadine (2–6 fold of recommended dose) - Levocetirizine (recommended dose) with no improvement	NA	NA	NA	Previous use of - Montelukast (dose: NA)	- Omalizumab 300 mg sc every 2 weeks	NA	Previous use of - Ranitidine (dose: NA) - Antibiotics (unmentioned name, dose: NA) with no improvement	3 months	No improvement then discontinued omalizumab	NA	NA
Kirkpatrick et al (2012)[51]	N = 1 of 6	NA	NA	Previous use of 0 (dose: NA) with no improvement	Previous use of - Systemic corticosteroid (unmentioned name, dose: NA) with no improvement	NA	NA	NA	No	- Levothyroxine (dose: 150 g/d) for hypothyroidism due to post I^{131} for Grave's disease	1 month	Complete control, then continue levothyroxine same dose	24 months. After that, levothyroxine was tapered to 125 g/d but relapsed occurred within 3 weeks, so dose was increased to 150 g/d again; complete control	NA
Ivyanskiy et al (2012)[76]	N = 3 of 19	NA	NA	All cases: previous use of 0 (dose: NA) with no improvement	NA	NA	NA	All cases: - Omalizumab 150 mg sc every 2 weeks	No Previous use of - CsA (dose: NA) with no improvement Previous use of - CsA (dose: NA) - AZA (dose: NA) - MMF (dose: NA) with no improvement in all treatment	No Previous use of - TNF-α inhibitor (dose: NA) with no improvement Previous use of - TNF-α inhibitor (dose: NA) with no improvement	6 months 9 months 4 months	Complete control then discontinued omalizumab Complete control then discontinued omalizumab Partial improvement then discontinued omalizumab	NA	No

(*Continued*)

Table 4 (Continued).

Study (year)	N = Elderly CU/ Total	Treatment									Duration of treatment	Treatment response	Follow-up after treatment and outcome	Side-effects after treatment
		AH_1			Corticosteroids		LTRA	Omalizumab	Immunosuppressant	Others				
		$fgAH_1$	$sgAH_1$	Unspecified AH_1	Systemic	Topical								
Armengot-Carbo et al (2013)[81]	N = 5 of 15	NA	NA	Previous use of 0 (dose: NA) with no improvement	Previous use of - Systemic corticosteroid (unmentioned name, dose: NA) with no improvement NA Previous use of - Systemic corticosteroid (unmentioned name, dose: NA) with no improvement NA Previous use of - Systemic corticosteroid (unmentioned name, dose: NA) with no improvement	NA	NA	- Omalizumab 150 mg sc every 4 weeks for 3 months then 300 mg sc every 4 weeks for other 3 months	Previous use of - CsA (dose: NA) with no improvement	Previous use of -AH_2 (unmentioned name, dose: NA) with no improvement Previous use of -AH_2 (unmentioned name, dose: NA) with no improvement Previous use of -AH_2 (unmentioned name, dose: NA) with no improvement NA Previous use of -AH_2 (unmentioned name, dose: NA) with no improvement	6 months	Partial improvement	NA	Nausea
								- Omalizumab 150 mg sc every 4 weeks for 3 months			3 months	No improvement then discontinued omalizumab		Nausea
								- Omalizumab 150 mg sc every 2 weeks for 3 months then 150 mg sc every 4 weeks for other 3 months			6 months	Complete control		No
								- Omalizumab 300 mg sc every 4 weeks for 6 months			6 months	Complete control		No
								- Omalizumab 150 mg sc every 4 weeks for 3 months			3 months	No improvement then discontinued omalizumab		No
Zubrinich et al (2019)[92]	N = 1 of 4	NA	NA	Previous use of - unspecified AH_1 (dose: NA) with partial improvement	Previous use of - Prednisolone (dose: NA) with partial improvement	NA	NA	NA	NA	- Ivermectin (dose: NA) for treatment of *Strongyloides* infection	NA	Complete control	10 months	NA
Case reports														
Urbach (1942)[97]	N = 1 of 1	NA	NA	NA	NA	NA	NA	NA	NA	- Surgery: neoplasm removal for rectal carcinoma	NA	Complete control	NA	NA

Anderson et al (1991)[95]	N = 1 of 1	Previous use of - Hydroxyzine (dose: NA) with no improvement	- Terfenadine (dose: NA)	NA	Previous use of - Systemic corticosteroid (unmentioned name, dose: NA) for short course with no improvement	Previous use of - Hydrocortisone cream (dose: NA) with no improvement	NA	NA	NA	- Surgery: neoplasm removal for colon carcinoma	NA	Complete control	60 months	NA
Amoroso et al (1997)[69]	N = 1 of 1	NA	NA	NA	Previous use of - Betamethasone (dose: 4 mg IV) - Betamethasone (dose: 0.5 mg/d orally) with no improvement	NA	NA	NA	NA	- Surgery: total thyroidectomy for Hashimoto's thyroiditis	NA	Complete control	18 months	NA
Zhang et al (2004)[79]	N = 1 of 1	Previous use of - Chlorpheniramine (dose: 12 mg/d) with no improvement	NA	NA	- Prednisolone (dose: 10 mg/d) for 3 months and 1 week	NA	NA	NA	- Melphalan (dose: 2 mg) for 1 week followed by - Cyclophosphamide (dose: 50 mg/d) for 3 months for IgA Myeloma	NA	3.25 months	Complete control then discontinued prednisolone, melphalan, and cyclophosphamide	NA, symptom relapsed when myeloma relapsed	NA
Wong et al (2010)[56]	N = 1 of 1	Previous use of - Diphenhydramine (dose: 50 mg once) with complete control	- Cetirizine (dose: 10 mg/d) for prophylaxis	NA	NA	NA	NA	NA	NA	- Epinephrine auto-injector (dose: NA)	24 months	Marked improvement but 2 months later she acquired another hymenoptera sting, and within 2 weeks developed systemic urticaria when exposing to cold temperature	NA	NA
Baroni et al (2012)[85]	N = 1 of 1	NA	NA	Previous use of 0 (dose: NA) with no improvement	Previous use of - Systemic corticosteroid (unmentioned name, dose: NA) with no improvement	Previous use of - Topical corticosteroid (unmentioned name, dose: NA) with no improvement	NA	NA	NA	- Surgery: radical prostatectomy for prostate adenocarcinoma	NA	Complete control	24 months	NA

(*Continued*)

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Table 4 (Continued).

Study (year)	N = Elderly CU/ Total	Treatment									Duration of treatment	Treatment response	Follow-up after treatment and outcome	Side-effects after treatment
		AH_1			Corticosteroids		LTRA	Omalizumab	Immunosuppressant	Others				
		$fgAH_1$	$sgAH_1$	Unspecified AH_1	Systemic	Topical								
Hui-Hui et al (2012)[84]	N = 1 of 1	NA	Previous use of - Loratadine (dose: NA, taken once every other day) for 4 months with partial improvement	NA	NA	NA	NA	NA	NA	- Surgery: right middle lobectomy for lung cancer removal	NA	Complete control	6 months	NA
Zimmer et al (2016)[82]	N = 1 of 1	NA	NA	Previous use of -AH_1 (unmentioned name, dose: up to 4 times of licensed dose) with no improvement	NA	NA	NA	- Omalizumab 300 mg sc every 4 weeks	NA	NA	4 months	Marked improvement then discontinued omalizumab	5 months, then relapse occurred	No
Sussman et al (2016)[60]	N = 1 of 1	Previous use of - Hydroxyzine (dose: 25–200 mg/d) - Diphenhydramine (dose: 25–200 mg/d) - Doxepin (dose: 25–125 mg/d) with no improvement in all treatment but caused sedation	Previous use of - Cetirizine (dose: 10–40 mg/d) - Loratadine (dose: 10 mg/d) with no improvement in all treatment - Cetirizine (dose: 20 mg/d)	Previous use of 0 (dose: NA dosage as needed) with no improvement	Previous use of - Prednisolone (dose: 5–40 mg/d) with no improvement - Prednisolone (dose: tapering doses from before study until discontinued)	NA	Previous use of - Montelukast (dose: 10 mg/d) with no improvement	- Omalizumab 150 mg sc every 4 weeks	Previous use of - HCQ (dose: 400 mg/d) for 2 months - CsA (dose: 300 mg/d) for 2 months with no improvement in all treatment	Previous use of - Ranitidine (dose: 300 mg/d) with no improvement - IVIG (dose: NA, discontinued due to hemolytic reaction) Both with partial improvement	36 months	Marked improvement after 1 week then continued same dose of omalizumab but stopped taking prednisolone, resulting in low daily UAS7 scores. After 36 months, symptoms became severe, required longer courses and doses of prednisolone. Moreover, omalizumab was increased to 300 mg sc every 4 weeks to maintain low UAS7.	NA	NA
Kasperska-Zajac et al (2016)[91]	N = 1 of 1	NA	NA	Previous use of 0 (high dose) with no improvement	Previous use of - Prednisolone (dose: up to 15 mg) for the past 3–10 years with no improvement	NA	NA	- Omalizumab 300 mg sc	NA	NA	NA	Complete control after 1 dose of omalizumab then continued with omalizumab 150–300 mg every 5–6 weeks	NA	No

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Aldasouqi et al (2018)[96]	N = 1 of 1	NA	NA	NA	NA	NA	NA	NA	NA	- Surgery: parathyroidectomy for primary hyperparathyroidism caused by large parathyroid adenoma	NA	Complete control	NA	NA
Pannofino (2018)[58]	N = 1 of 1	NA	- Rupatadine (dose: 10 mg twice daily) for 20 days then continue with 10 mg/d for 6 months then discontinued	Previous use of - unspecified AH_1 (dose: NA) with no improvement	Previous use of - Oral corticosteroid (unmentioned name, dose: NA) with no improvement	NA	NA	- Omalizumab 300 mg sc every 4 weeks	NA	NA	6 months	Complete control then discontinued omalizumab	12 months	NA

Notes: [a]It should be noted that the study of Kaplan et al included 12 CU patients (with 2 elderly patients) to be received placebo for 4 weeks and then omalizumab for 16 weeks. Omalizumab was injected every 2 weeks or every 4 weeks, dosed according to the patient's body weight, and serum IgE at the screening visit.

Abbreviations: AH1, H1-antihistamine; AH2, H2-antihistamine; AZA, azathioprine; CsA, cyclosporine; d, day; fgAH1, first generation antihistamine; HCQ, hydroxychloroquine; IM, intramuscular; IV, intravenous; IVIG, intravenous immunoglobulin; LTRA, Leukotriene-receptor antagonist; mg, milligram; MMF, mycophenolate mofetil; MTX, methotrexate; NA, not available/not applicable; sc, subcutaneous; SD, symptomatic dermographism; sgAH1, second generation antihistamine; TNF-α inhibitor, tumor necrosis factor-α inhibitors; UAS7, Weekly Urticarial Activity Score.

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Table 5 Comparison of the Reported Demographic and Clinical Characteristics of Elderly Patients with Chronic Urticaria (CU) with Those of Non-Elderly

Clinical features: N/Total (%)	Elderly (our systematic review)	Non-elderly
Demographic Data		
Prevalence of CU in population	22,900/9,757,210 (0.2) – 13,476/488,145 (2.8)[29,33,35,46]	6019/7,555,991 (0.1) – 90/2613 (3.4)[9,19,29,30,33,98,134–140]
CSU proportion in CU	127/153 (83.0) – 63/65 (96.9)[10,20,45]	145/220 (66.0) – 215/231 (93.1)[26,34,74,108–111,141–146]
CIndU proportion in CU	2/65 (3.1) – 26/153 (17.0)[10,20,32,45]	17/329 (5.2) – 75/220 (34.0)[26,74,108–111,141–146]
Sex ratio (Male: Female)	1: 0.9–3.3[10–12,20–25,30–33,37,39,40,45,90]	1: 1.0–5.7[10,12,19,28–30,33,34,36–38,40,41,74,100,109,114,130,131,134,136,139,142–144,147–163]
Clinical presentation		
Wheal alone	10/30 (33.3) – 86/99 (86.9)[10,12,20,37,40,90]	96/330 (29.1) – 77/102 (75.5)[12,20,40,107,109,136,141,143,147,149,163–168]
Wheal with angioedema	13/99 (13.1) – 20/30 (66.7)[10,12,20,37,40,90]	17/248 (6.9) – 152/199 (76.4)[12,28,36–40,74,109,111,120,136,141,143,147,149,158,159,163,165–173]
Wheal with anaphylaxis [a]	1/1 (100.0)[56]	0/2,175 (0.0)[28,174,175]
Personal history of atopy	2/92 (2.2) – 9/26 (34.6)[10,11,20,37,45,64,90]	171/13,479 (1.3) –101/147(68.7)[11,12,28,34–38,74,100,106,114,147,159,160,163,176–179]
Comorbidities		
Gastrointestinal diseases	5/104 (4.8) – 708,415/985,278 (71.9)[20,64]	127/12,185 (1.0) – 145/330 (44.0)[12,28,100,111,131,178,180–182]
Metabolic syndrome	21/63 (33.3) – 44/92 (47.8)[20,90]	276/12/185 (2.3) – 1,741/11,261 (15.5)[100,114,116]
Thyroid diseases	1/67 (1.5) – 19/99 (19.2)[10,20,37,45]	34/13,479 (0.3) – 20/47 (42.5)[12,28,30,35–37,67,70,100,153,159,165,170–172,178,183,184]
Autoimmune diseases	8/63 (12.7)[90]	40/12,185 (0.3) –25/209 (12.0)[30,100,153,159,170,172]
Psychiatric problems		
Anxiety disorders	NA	266/13,479 (2.0) – 24/30 (80.0)[35,139,185–189]
Depression & other psychiatric problems	2/99 (2.0) – 2/26 (7.7)[37,45,65]	121/12,185 (1.0) – 21/30 (70.0)[12,30,36,37,100,139,148,154,159,185–187,189–192]
Malignancies		
Hematologic malignancy [b]	33/3,615 (0.9)[19]	80/36,910 (0.2) – 25/9,105 (0.3)[18,19]
Other	415/3,615 (11.5) – 11/92 (12.0)[19,20]	231/9,105 (0.3) – 330/13,479 (2.5)[18,19,35,148]
Most common subtype of CIndU	Symptomatic dermographism[10,20,45]	Symptomatic dermographism[10,36,37,74,108,111,193–195]
Laboratory investigations		
Positive antinuclear antibodies	13/63 (20.6) of CSU[10]	248/12,778 (1.9) – 131/195 (67.2) of CSU[10,120,155,158,160,196,197]
Elevated erythrocyte sedimentation rate	18/63 (28.6)[10]	3/184 (1.6) – 65/133 (48.9)[10,74,155,160,165,172,178,198]
Elevated total serum IgE [c]	NA	14/330 (4.2) – 34/62 (54.8)[12,28,36,74,165,199–201]
Positive ASST	11/61 (18.0) – 3/5 (60.0) of CSU[20,37,40,42]	12/45 (26.7) – 49/67 (73.1) of CSU[10,28,36,37,40,74,108,111,130,142,150,155,156,160,168,196,202–211]
Abnormal thyroid function test [c]	NA	20/330 (6.1) – 20/66 (30.3)[12,38,67,70,78,198,212,213]
Abnormal free T3 [c]	NA	1/56 (1.8) – 99/165 (60.0)[74,214]
Abnormal free T4 [c]	NA	97/165 (58.8)[74]
Abnormal TSH [c]	NA	2/56 (3.6) – 99/167 (59.3)[74,165,171,183,214,215]
Positive thyroid autoantibodies	3/24 (12.5) – 21/63 (33.3)[10,11,40]	3/79 (3.8) – 27/47 (57.5)[10,11,36,40,67,70,71,73,74,106,109,120,130,153,155–157,160,161,163,165,168,170–173,183,184,196,198,199,201–203,207,209–237]
Positive HBsAg	8/63 (12.7)[10]	0/121 (0.0) – 2/56 (3.6)[10,28,111,128,129,192,238]

(*Continued*)

Table 5 (Continued).

Clinical features: N/Total (%)	Elderly (our systematic review)	Non-elderly
Duration of disease prior to diagnosis (years)	0.2–2.0[39,60,67,69,79,85,87]	3.2–6.3[87,172]
Treatment		
Response to 1st line (standard dose AH_1)	17.045/99 (45.5) – 23/26 (88.5)[37,38,45]	164/516 (31.8) – 163/248 (65.9)[36–39,160,170]
Needed 2nd line	3/26 (11.5) – 24/96 (25.0)[37,45]	36/335 (10.8) – 199/569 (34.9)[36,37,170,172]
Needed 3rd line	5/32 (15.6) – 28/95 (29.5)[37,40]	36/361 (10.0) – 93/329 (28.3)[36,37,40,74,108,159,172,178]

Notes: [a]Wheal with anaphylaxis in elderly was found in only one case report of cold urticaria. [b]It should be noted that the only retrospective study which reported malignancy in population was from Chen et al [c]Proportion of elevated IgE, abnormal thyroid function test, free T3, free T4, and TSH in elderly patients were reported in only case reports and case series. No prospective or retrospective cohort study was found.

Abbreviations: ASST, autologous serum skin test; CIndU, chronic inducible urticaria; CSU, chronic spontaneous urticaria; CU, chronic urticaria; HBsAg, hepatitis B surface antigen; NA, not available/not applicable; TSH, thyroid stimulating hormone.

depression to be common in adult CU, while elderly CU was reported mainly in dementia and other non-specific psychological problems.[100]

The high rate of malignancies, both hematologic and non-hematologic, in the present study may be explained by the advanced age. Most studies reported CU patients to be at high risk of developing cancers, and the incidence of cancer also increased with age.[19,89,125,126] A possible mechanism is alteration of the immune system by the tumor.[126] Age-appropriate malignancy screening is, therefore, strongly encouraged for early detection and treatment, which will improve the outcomes of both cancer and urticaria.[89,93,97,126]

The high prevalence of thyroid autoantibodies in both geriatric and adult CU suggests the relationship between CU and thyroid autoimmunity,[10,11,40,67,70,120,123,127] even though this study and the previous report showed no difference of thyroid autoantibodies between the two groups.[11] Focusing on infections, hepatitis B virus was the only infection in this study that was reported at higher prevalence (12.7%) than in previously reported general CU patients (0–3.6%).[128,129] There was no difference in other laboratory findings, such as ESR, ANA, and total serum IgE levels. However, elderly CSU was reported to have a relatively lower proportion of positive ASST than adult CSU, as in the study by Magen et al.[20]

Treatment of CU in elderly patients usually follows the same guidelines as the general population. $SgAH_1$ is recommended as the first-line treatment for elderly CU. The regular dose of $SgAH_1$ is generally sufficient to achieve complete control in most patients, with a higher proportion of response in elderly CU than adults. This was in line with the finding of a lower rate of ASST in the elderly. As ASST positivity correlates with higher severity and longer duration of disease of CSU,[127,130–132] geriatric patients may have less severe CU symptoms than adult CU, resulting in fewer associated angioedema and good response to standard treatment. Updosing to a higher dose or 4-times was also reported the good efficacy in $SgAH_1$. For patients who fail on antihistamines, successful symptom control has been achieved by the use of omalizumab 150–300 mg every 2–4 weeks.

Some patients with autoimmune thyroiditis and hypothyroid were treated by levothyroxine, which also helps in improving urticaria.[51,67,73] The risks and benefits of these third-line drugs have not been sufficiently explored and additional studies are needed.[7,83] Another treatment strategy that significantly improved CU symptoms was treatment of secondary causes concurrent with standard treatments, especially in aging patients in whom autoimmune disorders, malignancies and infections are more common. A systematic review by Kolkhir et al[133] found CSU to be quite common in patients with strongyloidiasis. Its pathogenesis may be due to eosinophil and complement activation leading to skin mast cell activation. Magen et al[63] and Zubrinich et al[92] reported an association between *H. Pylori* infection, *Strongyloides* infection, and CU. Treatment with standard antiparasitic drugs yielded complete control.[63,92,133] Therefore, treatment of these associated comorbidities, including infection, might result in a better CU control.

Table 6 Quality and Risk of Bias Assessment of Included Articles in Systematic Review

A. Randomized controlled trials

Study, year [Ref]	Random sequence generation (selection bias)	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Staubach et al, 2016[239]	+	+	+	+	+	+
Kaplan et al, 2005[240]	?	?	+	+	+	+
Goldsobel et al, 1986[68]	+	+	+	+	+	+

B. Non-randomized controlled trials

Study, year [Ref]	Criteria								Additional criteria in the case of comparative study					
	A stated aim of the study	Inclusion of consecutive patients	Prospective collection of data	End point appropriate to the study aim	Unbiased evaluation of end points	Follow-up period appropriate	Loss to follow-up not exceeding 5%	Prospective calculation of the study size	A control group having the criterion standard intervention	Contemporary groups	Baseline equivalence of groups	Prospective calculation of the sample size	Statistical analyses adapted to the study design	Total
Martina et al, 2021[90]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Napolitano et al, 2021[45]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Gaber et al, 2020[46]	2	2	2	2	0	2	2	0	-	-	-	-	-	12
Chung et al, 2020[74]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Seo et al, 2019[32]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Zubrinich et al, 2019[92]	1	1	1	2	0	2	0	0	-	-	-	-	-	7
Wertenteil et al, 2019[33]	2	2	2	2	0	0	0	0	-	-	-	-	-	8
Jankowska-Konsur et al, 2019[34]	2	2	2	2	0	0	0	0	-	-	-	-	-	8
Jo et al, 2019[39]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Curto-Barredo et al, 2019[37]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Eun et al, 2018[31]	2	2	2	2	0	2	2	0	-	-	-	-	-	12
Nettis et al, 2018[40]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Napolitano et al, 2018[93]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Chanprapaph et al, 2018[160]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Curto-Barredo et al, 2018[36]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Pannofino, 2018[58]	2	0	2	1	0	2	0	0	-	-	-	-	-	7
Aldasouqi, 2018[96]	2	0	2	1	0	1	0	0	-	-	-	-	-	6
Kulthanan et al, 2017[57]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Lee et al, 2017[64]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Chu et al, 2017[30]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Ali, 2016[152]	2	2	2	2	0	2	2	0	0	2	2	0	2	20
Chuamanochan et al, 2016[10]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Kasperska-Zajac et al, 2016[91]	2	2	2	2	0	2	0	0	-	-	-	-	-	10

Lapi et al, 2016[35]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Zimmer et al, 2016[82]	1	0	0	2	0	2	0	0	-	-	-	-	-	5
Sussman et al, 2016[60]	1	0	0	2	0	2	0	0	-	-	-	-	-	5
Romano et al, 2015[62]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Sugiyama et al, 2015[73]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Uysal et al, 2014[61]	2	2	2	2	0	2	2	0	-	-	-	-	-	12
Ban et al, 2014[11]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Vikramkumar et al, 2014[42]	2	2	2	2	0	0	0	0	-	-	-	-	-	8
Magen et al, 2013[20]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Song et al, 2013[55]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Magen et al, 2013[20]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Lefevre et al, 2013[75]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Hiragun et al, 2012[38]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Armengot-Carbo et al, 2013[81]	1	1	1	2	0	2	0	0	-	-	-	-	-	7
Kirkpatrick et al, 2012[51]	2	1	2	2	0	2	0	0	-	-	-	-	-	9
Chen et al, 2012[19]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Krupashankar et al, 2012[28]	2	2	2	2	0	2	2	0	-	-	-	-	-	12
Ivyanskiy et al, 2012[76]	1	1	1	2	0	1	0	0	-	-	-	-	-	6
Hui-hui et al, 2012[84]	2	0	0	2	0	2	0	0	-	-	-	-	-	6
Baroni et al, 2012[85]	1	1	1	2	0	2	0	0	-	-	-	-	-	7
Groffik et al, 2011[49]	1	1	1	2	0	2	0	0	-	-	-	-	-	7
Godse, 2011[48]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Asero et al, 2011[86]	2	2	2	2	0	0	0	0	-	-	-	-	-	8
Sagi et al, 2011[83]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Metz et al, 2011[52]	1	1	1	2	0	2	0	0	-	-	-	-	-	7
Mitzel-Kaoukhov et al, 2010[53]	2	2	2	2	0	2	2	0	-	-	-	-	-	12
Mozena et al, 2010[72]	2	2	2	2	0	0	0	0	-	-	-	-	-	8
Perez et al, 2010[241]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Wong et al, 2010[56]	1	0	0	2	0	2	0	0	-	-	-	-	-	5
Staubach et al, 2009[80]	2	2	2	2	0	0	0	0	-	-	-	-	-	8
Kaplan et al, 2008[50]	2	2	2	2	1	2	2	0	0	2	2	0	2	19
Katsarou-Katsari et al, 2008[44]	2	2	2	2	2	0	0	0	-	-	-	-	-	10
Feibelmann, 2007[71]	2	2	2	2	0	0	0	0	-	-	-	-	-	8
Manganoni et al, 2007[89]	1	1	1	2	0	2	0	0	-	-	-	-	-	7
Cebeci et al, 2006[70]	2	2	2	2	0	0	0	0	-	-	-	-	-	8
McGirt et al, 2006[94]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Sanada et al, 2005[242]	2	2	2	2	0	2	2	0	-	-	-	-	-	12
Yang et al, 2005[41]	2	2	2	2	0	0	0	0	-	-	-	-	-	8

(*Continued*)

Table 6 (Continued).

A. Randomized controlled trials															
Study, year [Ref]	**Random sequence generation (selection bias)**			**Allocation concealment**		**Blinding of participants and personnel**		**Blinding of outcome assessment**		**Incomplete outcome data**		**Selective reporting**		
O'Donnell, 2005[77]	2	2	2	2	0	0	0	0	-	-	-	-	-	8
Gaig et al, 2004[29]	2	2	2	2	0	0	0	0	-	-	-	-	-	8
Zhang et al, 2004[79]	1	0	0	2	0	1	0	0	-	-	-	-	-	4
Asero et al, 2003[78]	2	2	2	2	0	0	0	0	-	-	-	-	-	8
O'Donnell, 1998[54]	2	2	2	2	0	2	2	0	-	-	-	-	-	12
Amoroso, 1997[69]	1	0	0	2	0	2	0	0	-	-	-	-	-	5
Rumbyrt et al, 1995[88]	2	2	2	2	0	2	2	0	-	-	-	-	-	12
Hashiro et al, 1994[27]	2	2	2	2	0	0	0	0	-	-	-	-	-	8
Barlow et al, 1993[26]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Anderson, 1991[95]	1	0	0	1	0	2	0	0	-	-	-	-	-	4
Lindelof et al, 1990[148]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Reisman et al, 1989[243]	2	2	2	2	0	2	2	0	-	-	-	-	-	12
Dover, 1988[43]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Lanigan et al, 1987[66]	2	0	0	1	0	0	0	0	-	-	-	-	-	3
Mekkes et al, 1986[25]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Greene et al, 1985[244]	2	2	2	2	2	2	2	0	0	2	2	0	2	20
Lanigan et al, 1984[65]	1	1	2	2	0	0	0	0	-	-	-	-	-	6
Leznoff et al, 1983[67]	1	2	2	2	0	2	2	0	-	-	-	-	-	11
Vaida et al, 1983[87]	2	2	2	2	0	2	0	0	-	-	-	-	-	10
Juhlin, 1981[12]	1	0	2	2	0	0	0	0	-	-	-	-	-	5
Urbach, 1942[97]	1	0	0	1	0	0	0	0	-	-	-	-	-	2

Notes: +, low risk of bias; -, high risk of bias; ?, unclear risk of bias; 0, not reported; 1, reported but inadequate; 2, reported and adequate.

Limitations

Most of the included articles were retrospective studies, case reports, and case series, which are inherently classified as having a lower level of evidence (Table 6). Only three randomized controlled trials were eligible to be included in the analysis, hence, the number of control groups was low. Furthermore, only a few studies had a study population consisting only of elderly patients. These limitations further underscore the potential value of this study and make clinicians more aware that more prospective studies are needed on cases of CU in the elderly.

Conclusions

This systematic review found that the prevalence CU ranges between 0.2–2.8% in the elderly population. CSU was still the most common type, and exhibited a female predominance. Compared with adult CU, a lower rate of atopy, more age-related comorbidities including metabolic syndrome, autoimmune disorders, and malignancies, a lower rate of associated angioedema, and lower ASST positivity, were reported in elderly CU. The use of antihistamines often yielded good results as first-line treatment. Omalizumab was effective in AH_1-resistant cases, and other differential diagnosis should be considered in patients refractory to standard treatment. More prospective studies are necessary to further elucidate the characteristics of the disease in this age group.

Abbreviations

AH_1, H_1-antihistamine; CIndU, Chronic inducible urticaria; CSU, Chronic spontaneous urticaria; CsA, Cyclosporine; CU, Chronic urticaria; ESR, Erythrocyte sedimentation rate; $fgAH_1$, First generation H_1-antihistamine; GI, Gastrointestinal; *H. pylori*, *Helicobacter pylori*; IVIG, Intravenous immunoglobulin; MTX, Methotrexate; RCT, Randomized controlled trial; SD, Symptomatic dermographism; $sgAH_1$, Second generation H_1-antihistamine.

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