Mortality in adult patients with chronic spontaneous urticaria: A real-world cohort study

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Background: Chronic spontaneous urticaria (CSU), a common and debilitating disease, is widely held not to be life limiting, but the mortality of CSU has not been investigated.

Objective: We sought to assess all-cause mortality in patients with CSU, risk for comorbidities that are leading causes of death, and impact of guideline-recommended urticaria treatments on mortality rates.

Methods: This was a retrospective population-based cohort study of electronic health records of 272,190 adult patients with CSU and 12,728,913 controls without urticaria from the US collaborative network TriNetX.

Results: The study included 264,680 propensity score–matched patients with CSU (mean [SD] age = 47.5 [19.8] years; 71.5% female) and a corresponding number of controls without urticaria. Patients with CSU had higher 3-month (hazard ratio [HR] 2.10, 95% CI 1.97-2.22), 1-year (HR 1.77, 95% CI 1.71-1.83), and 5-year (HR 1.69, 95% CI 1.65-1.73) all-cause mortality (all $P < .0001$). Compared with controls, patients with CSU exhibited higher risk and rates of the leading causes of death in the United States, including suicidal ideations/suicide attempts (HR 3.14, 95% CI 3.00-3.28) and malignant neoplasms (HR 2.09, 95% CI 2.02-2.16). The risk of mortality appeared to be more pronounced in White and younger patients with CSU. All-cause mortality rates at 5 years were significantly lower in patients treated with second-generation H_1 antihistamines versus untreated patients (1.0% vs 2.3%; HR 1.84, $P < .0001$) and omalizumab-treated patients versus antihistamine-treated patients (0.7% vs 2.6%; HR 3.99, $P = .0003$).

Conclusions: CSU is associated with increased mortality likely due to comorbidities, especially suicide, and effective CSU treatment may reduce mortality. These findings should be investigated in additional studies and in other populations. (J Allergy Clin Immunol 2025;155:1290-8.)

Key words: *Chronic spontaneous urticaria, mortality, comorbidities, suicide, treatment*

Chronic spontaneous urticaria (CSU) lasts for more than 6 weeks and manifests with wheals, angioedema, or both that develop without specific and definite triggers.[1,2] CSU is a common mast cell–mediated disease with a point prevalence of 1% to 3%.[2] In >50% of patients, CSU is regarded as an autoimmune disease mediated by mast cell–activating IgE and/or IgG autoantibodies.[3,4] CSU has a moderate-to-severe course in most patients, considerably affects patients' everyday life and work/school performance,[5] and is associated with annual economic costs for a patient of up to 2984 purchasing power parity dollars.[6] The international urticaria guideline recommends the stepwise use of a second-generation H_1 antihistamine (sgAH), omalizumab, an anti-IgE mAb, and cyclosporine.[1]

CSU is a long-lasting disease. The urticarial march starts with the progression of acute spontaneous urticaria to CSU, which occurs in about 1 in 10 patients.[2] The average duration of CSU is several years,[2] with 55% of patients affected for more than 5 years and 27% affected for more than 20 years.[7] During the course of their disease, many patients with CSU develop comorbidities including autoimmune diseases such as autoimmune thyroiditis, mental health disorders such as depression and anxiety, and metabolic syndrome, which further contribute to disease burden and impairment of quality of life.[8]

Different mechanisms are responsible for the comorbidities observed in CSU. First, CSU can develop due to an underlying disease, eg, cancer. Second, CSU can share pathogenesis with autoimmune diseases, eg, autoimmune thyroiditis and systemic lupus erythematosus (SLE). Third, low-grade inflammation seen in CSU might be relevant for development of components of metabolic syndrome such as arterial hypertension and diabetes mellitus.[2,8,9] Lastly, mental health diseases can appear due to active CSU and its influence on quality of life, eg, depression and suicidal ideations.[10,11] Although CSU *per se* is not a life-

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Abbreviations used
ATC: Anatomical Therapeutic Chemical
BMI: Body mass index
CSU: Chronic spontaneous urticaria
EHR: Electronic health record
HR: Hazard ratio
ICD-10: *International Classification of Diseases, Tenth Revision*
OR: Odds ratio
PSM: Propensity score matching
S1-S4: Sensitivity analysis 1-4
sgAH: Second generation H_1 antihistamine
SLE: Systemic lupus erythematosus

threatening disease, some of these comorbidities could contribute to the mortality rates in patients with CSU.

Here, we queried TriNetX, a federated electronic health record (EHR) network, to perform a retrospective cohort study assessing mortality rates in patients with CSU compared with controls without urticaria and investigating which leading causes of death are more prevalent in patients with CSU and whether mortality rates differ depending on the treatment.

METHODS

Study database

A global population-based retrospective cohort study with propensity score matching (PSM) was performed following previously published protocols.[12,13] EHRs of patients with CSU and controls without urticaria for this study were collected from January to April, 2024, from the US Collaborative Network of TriNetX. Time of data retrieval is indicated under Tables I and II. The US Collaborative Network was chosen as it includes the second largest number of EHRs and the most detailed granular information for each EHR among the different networks provided by TriNetX.[14] TriNetX leverages large-scale real-world data and thus constitutes an in-depth tool for retrieval and analysis of real-world evidence. The TriNetX federated network architecture allows real-time, privacy-compliant data access, allowing, among others, retrospective studies to be conducted.[15]

Ethics statement

The data reviewed represent a secondary analysis of existing data, does not involve intervention or interaction with human subjects, and is deidentified per the deidentification standard defined in Section §164.514(a) of the Health Insurance Portability and Accountability Act Privacy Rule. The process by which the data are deidentified is attested to through a formal determination by a qualified expert as defined in Section §164.514(b)(1) of the Health Insurance Portability and Accountability Act Privacy Rule. This formal determination by a qualified expert was refreshed in December 2020. Thus, our study did not require institutional review board approval. The study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[16]

Study population and design

At the start of data retrieval, the network provided access to more than 106 million EHRs from 61 health care organizations. CSU was defined as any instance of *International Classification of Diseases, Tenth Revision* (*ICD-10*) code L50.1, L50.8, or L50.9 documented twice and at least 42 days (6 weeks) apart (Table E1; Fig E1 in this article's Online Repository available at www.jacionline.org). Only patients 18 years old or older were included. The primary analysis compared the rates and risk of all-cause mortality between patients with CSU and controls without urticaria at 3, 12, and 60 months following the index event (first definition of CSU or health care visit registration, ie, *ICD-10* code Z00 or CSU). In all following sensitivity analyses, the risk of death at the same time points was determined.

In sensitivity analysis 1 (S1), the look-back period was confined to 2 years to facilitate a more granular PSM for a total of 16 covariates, as detailed in the covariates section (see this article's Methods section in the Online Repository at www.jacionline.org). Again, to facilitate PSM for all covariates, sensitivity analyses S2 to S4 were performed in EHRs stratified for female or male sex. S2 was conducted similarly to S1; however, it was stratified for either female or male sex. In S3, the first month was excluded from the analysis to mitigate potential bias arising from the development of CSU in seriously ill patients. In S4, the look-back period was limited to 5 years, and cases were stratified by female and male sex separately.

To identify potential differences of the rates and risk of mortality in patients with CSU of different age or race, we analyzed EHRs stratified for age groups (ie, 18-40, 41-60, and 61-80 years) and race (ie, Asian, Black or African American, or White). Age- and race-stratified analyses were performed for the 12-month follow-up only. The look-back period was adjusted for each analysis to accommodate PSM (see this article's Methods section in the Online Repository at www.jacionline.org).

To identify potential causes of death in CSU, the risk of potential causes of death was contrasted between patients with CSU and controls without urticaria. Diagnosis of CSU or health care encounter excluding CSU was set as the index event. The selection of end points was mainly based on the leading causes of death reported by the US Centers for Disease Control and Prevention.[17] We evaluated the risk of developing chronic lower respiratory diseases (*ICD-10*: J40-J4A), other degenerative diseases of the nervous system (*ICD-10*: G30-G32), diabetes mellitus (*ICD-10*: E08-E13), fibrosis and cirrhosis of liver (*ICD-10*: K74), glomerular diseases (*ICD-10*: N00-N08), cerebrovascular diseases (*ICD-10*: I60-I69), external causes of morbidity (*ICD-10*: V00-Y99), hypertensive diseases (*ICD-10*: I10-I1A), malignant neoplasms (*ICD-10*: C00-C26, C30-C58, C60-96, C7A-C7A, or C7B-C7B), suicidal ideations or suicide attempt (*ICD-10*: R45.851, T14.91, T14.91XA, T14.91XD, or T14.91XS), ischemic heart diseases (*ICD-10*: I20-I25), or COVID-19 (*ICD-10*: U07.1) 1 day to 1 year after the index event.

To address if CSU treatment has a potential impact on mortality, the risk of death in patients with CSU treated with urticaria guideline–recommended treatments,[1] ie, sgAHs, omalizumab, or cyclosporine A, was determined. The impact of oral corticosteroid treatment in CSU on mortality was also evaluated. For a descriptive analysis of 3-, 12-, and 60-month mortality rates in CSU, EHRs of patients with CSU exposed to specific treatments were retrieved. In each treatment category, exposure to other CSU treatments

TABLE I. Characteristics of patients with CSU (cases) and controls without CSU in primary analysis before and after propensity score matching

Characteristic	Before matching			After matching		
	CSU	Controls	SMD	CSU	Controls	SMD
No. of participants	272,190	12,728,913	—	264,680	264,680	—
Age at index (y), mean (SD)	47.5 (19.8)	44.6 (20.7)	0.1403	47.5 (19.8)	47.5 (19.7)	0.0004
Female (%)	71.451	52.569	0.3966	71.451	71.451	< 0.0001
White (%)	73.182	61.158	0.2582	73.182	73.186	< 0.0001
Personal history of nicotine dependence (%)	29.239	4.818	0.6869	29.239	29.243	< 0.0001
Nicotine dependence (%)	26.255	5.552	0.5903	26.255	26.25	0.0001
BMI, mean (SD)	29.6 (7.41)	28.4 (6.93)	0.1600	29.6 (7.41)	28.8 (7.12)	0.1019

Data were retrieved from the US Collaborative Network of TriNetX on March 25, 2024.
SMD, Standardized mean difference.

TABLE II. Description of mortality risk in patients with CSU exposed to different treatments or no treatment

Characteristic	Untreated	Second-generation H_1 antihistamines	Omalizumab	Cyclosporine A	Oral corticosteroids
No. of participants	19,839	113,334	1,514	356	117,372
Age at index (y), mean (SD)	38.9 (21.2)	37.5 (19.4)	40.3 (17.7)	53.1 (19.4)	46.7 (19.2)
Female (%)	63	69	71	82	72
Male (%)	33	30	24	18	26
African American or Black (%)	7	11	8	4	11
White (%)	69	64	69	84	75
Glomerular diseases (%)	0	0	1	3	1
Personal history of nicotine dependence (%)	0	6	3	13	14
Nicotine dependence (%)	0	6	2	6	16
Fibrosis and cirrhosis of liver (%)	0	1	1	3	2
Other degenerative diseases of nervous system (%)	0	1	1	3	1
Chronic lower respiratory diseases (%)	0	15	16	16	30
COVID-19 (%)	0	1	1	3	3
Neoplasms (%)	1	17	11	31	35
Diabetes mellitus (%)	0	9	6	15	17
Hypertensive diseases (%)	0	16	9	26	34
Cerebrovascular disease (%)	0	4	1	8	9
External causes of morbidity (%)	0	14	7	13	25
Ischemic heart diseases (%)	0	5	2	8	11
Suicidal ideations (%)	0	3	1	3	1
Suicide attempts (%)	0	1	1	3	6
BMI, mean (SD)	25.6 (6.32)	27.5 (7.26)	28.4 (6.59)	28 (6.64)	29.7 (7.38)
Montelukast (%)	0*	4	26	7	8
Famotidine (%)	0*	4	16	8	12
Doxepin (%)	0*	1	4	4	1
Cimetidine (%)	0*	0*	1	3	1
Nizatidine (%)	0*	0*	0*	0*	0*
3 mo, all-cause mortality rates (%)†	0.313	0.484	0.658	3.012	0.903
1-y, all-cause mortality rates (%)†	0.716	1.125	0.661	3.012	2.434
5-y, all-cause mortality rates (%)†	2.798	3.244	0.658	4.518	7.732

Data were retrieved from the US Collaborative Network of TriNetX on April 25, 2024. EHRs of patients with CSU receiving different treatments were retrieved from the US Collaborative Network with natural language processing. Mortality was determined following 1 year after prescription of each indicated drug. Codes were as follows: ATC R06A: antihistamines for systemic use; ATC H02: corticosteroids for systemic use; RxNorm 3008: cyclosporine; RxNorm 302379: omalizumab.
*Absolute number ranges from 0 to 115.
†EHRs were censored after the outcome or after the last documented health care encounter.

recommended by the international and US urticaria guidelines[1,18] was excluded, with the exception of sgAH, as follows:

1. Second-generation antihistamines, defined by use of any of the following—RxNorm 28889 (loratadine), 23796 (ebastine), 87636 (fexofenadine), 18603 (azelastine), 275635 (desloratadine), 20610 (cetirizine), or 356887 (levocetirizine)—in patients with CSU and excluding exposure to corticosteroids for systemic use (Anatomical Therapeutic Chemical [ATC] code H02), cyclosporine (RxNorm 3008), or omalizumab (RxNorm 302379)
2. Oral corticosteroids, defined by use of corticosteroids for systemic use (ATC code H02, filtered for "oral product") and excluding exposure to cyclosporine (RxNorm 3008) or omalizumab (RxNorm 302379)

3. Omalizumab, defined by use of omalizumab (RxNorm 302379) and excluding exposure to corticosteroids for systemic use (ATC code H02) or cyclosporine (RxNorm 3008)
4. Cyclosporine, defined by use of cyclosporine (RxNorm 3008) and excluding exposure to corticosteroids for systemic use (ATC code H02) or omalizumab (RxNorm 302379)
5. No treatment, defined by presence of CSU and excluding exposure to any of the following—corticosteroids for systemic use (ATC code H02), cyclosporine (RxNorm 3008), omalizumab (RxNorm 302379), doxepin (RxNorm 3638), nizatidine (RxNorm 42319), famotidine (RxNorm 4278), cimetidine (RxNorm 2541), montelukast (RxNorm 88249), or antihistamines for systemic use (ATC code R06A).

In addition to the mortality risks, demographic information, comorbidities, and body mass index (BMI) were retrieved (Tables I, II). To mitigate the bias imposed by potential differences in comorbidity prevalence and age distribution among treatment groups, the risk of 60-month all-cause mortality in patients with CSU was compared between the different urticaria guideline–recommended treatments (no treatment vs sgAHs only and sgAHs only vs sgAH+omalizumab) following PSM. The results of these analyses were challenged in a sensitivity analysis, in which the first 3 months following the index event (registration of treatment) were excluded.

Statistical analysis

The statistical analysis was performed using the survival package (https://cran.r-project.org/web/packages/survival/index.html) in R (R Foundation for Statistical Computing, Vienna, Austria) and validated by comparison with the outputs of SAS version 9.4 (SAS, Cary, NC); graphs were created using GraphPad Prism (GraphPad Software, Boston, Mass). PSM and covariates are explained in the Online Repository (at www.jacionline.org). The index event was set as the diagnosis of CSU or the reported health care encounter in the control group. Outcomes before the index events were excluded. Relative risks and risk differences were calculated. Survival analyses were performed using the Kaplan-Meier method. Kaplan-Meier curves were compared using the log-rank test. If more than 1 outcome was investigated, Bonferroni correction was applied. Specifically, Bonferroni correction was used when investigating potential causes of death in patients with CSU. A univariate Cox proportional hazards regression was used to express hazard ratios (HRs) with 95% CIs.

RESULTS

CSU is associated with increased mortality

Preceding PSM, 272,190 EHRs of patients with CSU and 12,728,913 EHRs of controls without urticaria from the US collaborative network TriNetX showed that patients with CSU were older, were more often female, exhibited a higher proportion of past or current nicotine dependence, and had a higher BMI. Following PSM, 264,680 EHRs per CSU group and control group were retrieved, and the aforementioned differences were mitigated (mean [SD] age: 47.5 [19.8] years; 71.5% female) (Table I). In patients with CSU, the all-cause mortality at 3 months, 1 year, and 5 years (Fig 1; Table E2 in the Online Repository available at www.jacionline.org) was significantly higher compared with controls, ie, 1.35% versus 0.63% (HR 2.10, 95% CI 1.97-2.22), 3.33% versus 1.82% (HR 1.77, 95% CI 1.71-1.83), and 9.0% versus 5.14% (HR 1.69, 95% CI 1.65-1.73), respectively (all $P < .0001$).

Four sensitivity analyses, S1 to S4, corroborated the robustness and reliability of these findings. S1, incorporating comorbid diagnoses recognized as primary contributors to mortality in the United States,[17] with a total of 16 covariates, confirmed that mortality rates are markedly higher in patients with CSU versus controls at 3 months (1.23% vs 0.41%, HR 3.04, 95% CI 2.57-3.61), 1 year (2.35% vs 1.27%, HR 1.97, 95% CI 1.78-2.19), and 5 years (2.61% vs 1.69%, HR 1.71, 95% CI 1.56-1.88) (all $P < .0001$) follow-up. S2, stratifying by sex, demonstrated that mortality rates are elevated in female and male patients. Female patients with CSU compared with female controls showed higher mortality rates at 3 months (1.21% vs 0.71%, HR 1.70, 95% CI 1.59-1.82), 1 year (2.97% vs 2.14%, HR 1.38, 95% CI 1.32-1.43), and 5 years (7.88% vs 5.92%, HR 1.31, 95% CI 1.28-1.34) (all $P < .0001$) of follow-up, and this was similar in male patients (1.86% vs 1.30%, HR 1.42, 95% CI 1.30-1.55; 4.54% vs 3.52%, HR 1.27, 95% CI 1.20-1.34; and 11.68% vs 9.22%, HR 1.22, 95% CI 1.18-1.26, respectively) (all $P < .0001$). S3, stratifying by sex and not considering outcomes during the first month following the index event, confirmed that the risk of mortality is elevated in both female and male patients with CSU, by 32% to 77% and 21% to 40%, respectively, across the observation period (all $P < .0001$). S4, stratifying by sex and recruiting only EHRs from 5 years before the analysis, also identified higher mortality rates in patients compared with controls (Fig 1; Tables E3-E6 in the Online Repository available at www.jacionline.org).

Mortality rates are increased across patients of all ages and races and are highest in younger and White patients

Compared with controls, patients with CSU had higher 12-month all-cause mortality rates across all age groups, ie, 18 to 40 years (1.36% vs 0.62%, HR 2.14, 95% CI 1.92-2.38, $P < .0001$), 41 to 60 years (2.19% vs 1.41%, HR 1.52, 95% CI 1.41-1.64, $P < .0001$), and 61 to 80 years (4.56% vs 3.43%, HR 1.32, 95% CI 1.25 to 1.39, $P < .0001$) (Fig 1; Tables E2, E7-E9 in the Online Repository available at www.jacionline.org). The risk of mortality was most increased, by 114%, in young adults, ie, patients 18 to 40 years of age. In the race-stratified analysis, increased mortality rates were observed across all investigated racial groups. Specifically, the 12-month, all-cause mortality risk was as follows (in ascending order): African American or Black: HR 1.19 (95% CI 1.06-1.33, $P = .0027$), Asian: HR 1.37 (95% CI 1.01-1.87, $P = .0439$), White: HR 2.14 (95% CI 2.04-2.25, $P < .0001$) (Tables E2 and E10-E12 in the Online Repository available at www.jacionline.org). Increased mortality rates were observed in White patients compared with Black or African American patients (2.97% vs 2.50%, HR 1.25, 95% CI 1.12-1.38, $P < .0001$) (Tables E13-E15 in the Online Repository available at www.jacionline.org).

CSU is associated with increased risk for comorbidities that are leading causes of death

To identify potential causes of death in patients with CSU, 227,477 EHRs were retrieved after PSM for CSU cases and

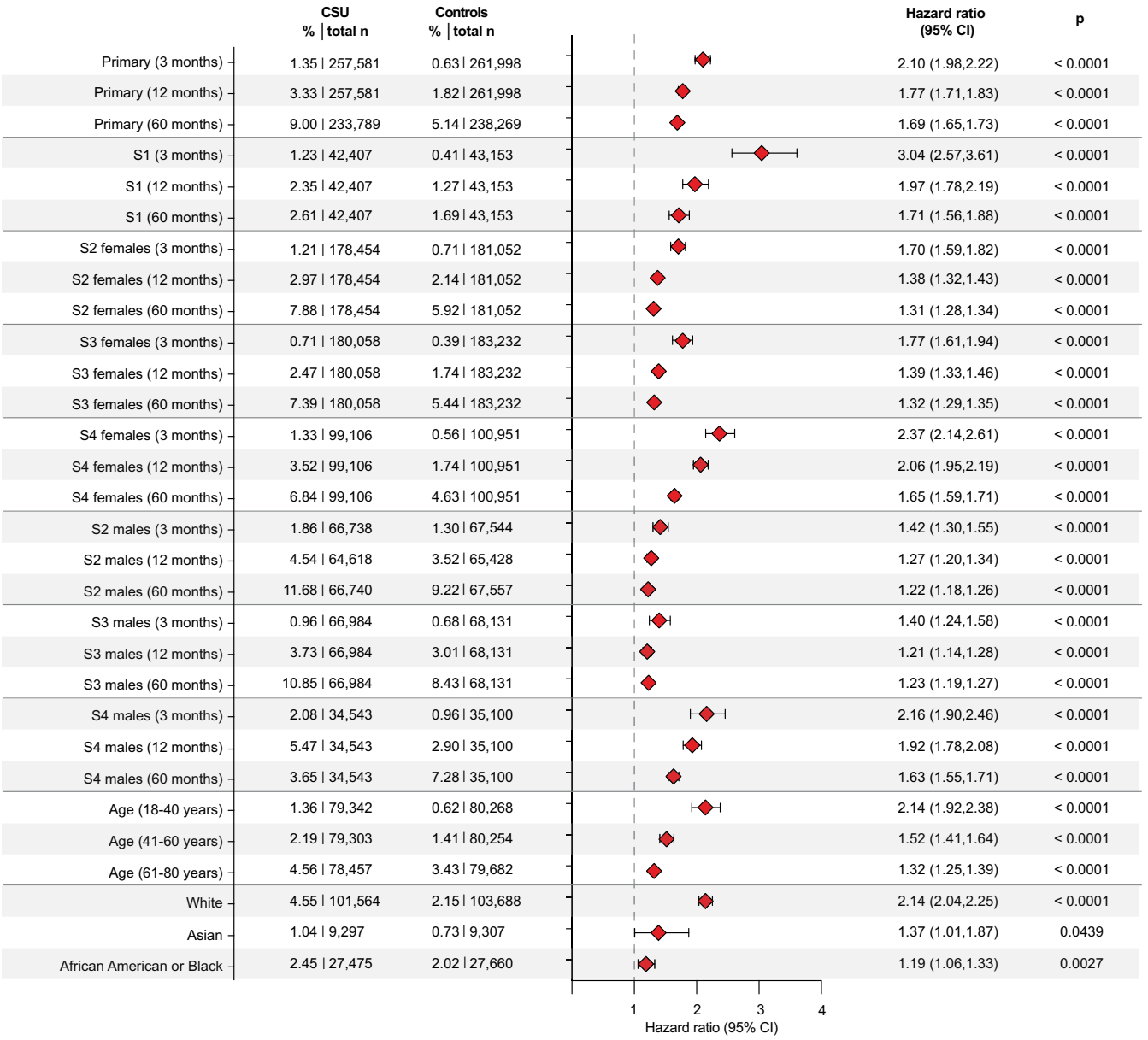

FIG 1. Mortality rates in patients with CSU. Comparison of rates and risk of all-cause mortality between the propensity score–matched patients with CSU (cases) versus controls without urticaria within 3, 12, and 60 months following the index event (documentation of *ICD-10* code Z00 or CSU). Age- and race-stratified analyses were done for the 12-month follow-up only. For each group, the risk (%) is shown defined as the number of cases or controls with outcomes during the time windows 3, 12, and 60 months divided by the number of cases or controls in the group at the beginning of the time window. HRs were calculated using Kaplan-Meier analysis to estimate the probability of outcome. A univariate Cox proportional hazards regression was used to express HRs with 95% CI. *Primary*, Primary analysis.

controls. Apart from a higher BMI observed in CSU cases, there were no discernible differences in the characteristics of the 2 cohorts following PSM (Table E16 in the Online Repository available at www.jacionline.org). The highest risk increment in CSU cases was observed for suicidal ideations or suicide attempts; CSU cases exhibited a greater than 3-fold increased risk compared with controls (3.89% vs 1.25%, HR 3.14, 95% CI 3.00-3.28, $P < .0001$). Patients with CSU were also at increased risk for ischemic heart diseases (HR 1.86, 95% CI 1.79-1.92, $P < .0001$), cerebrovascular diseases (HR 2.27, 95% CI 2.19-2.35, $P < .0001$), malignant neoplasms (5.80% vs 2.79%, HR 2.09, 95% CI 2.02-2.16, $P < .0001$), and diabetes mellitus (6.03% vs 2.98%, HR 2.05, 95% CI 1.98-2.12, $P < .0001$). After correction for multiple testing, the risk of hypertensive diseases showed no differences between the groups (Fig 2; Table E17 in the Online Repository available at www.jacionline.org).

To approximate the cause of death, the mortality risk of patients with the comorbidity exhibiting the highest (suicidal ideations or suicide attempts) or lowest (hypertensive diseases) risk increment was compared with patients not exposed to that specific

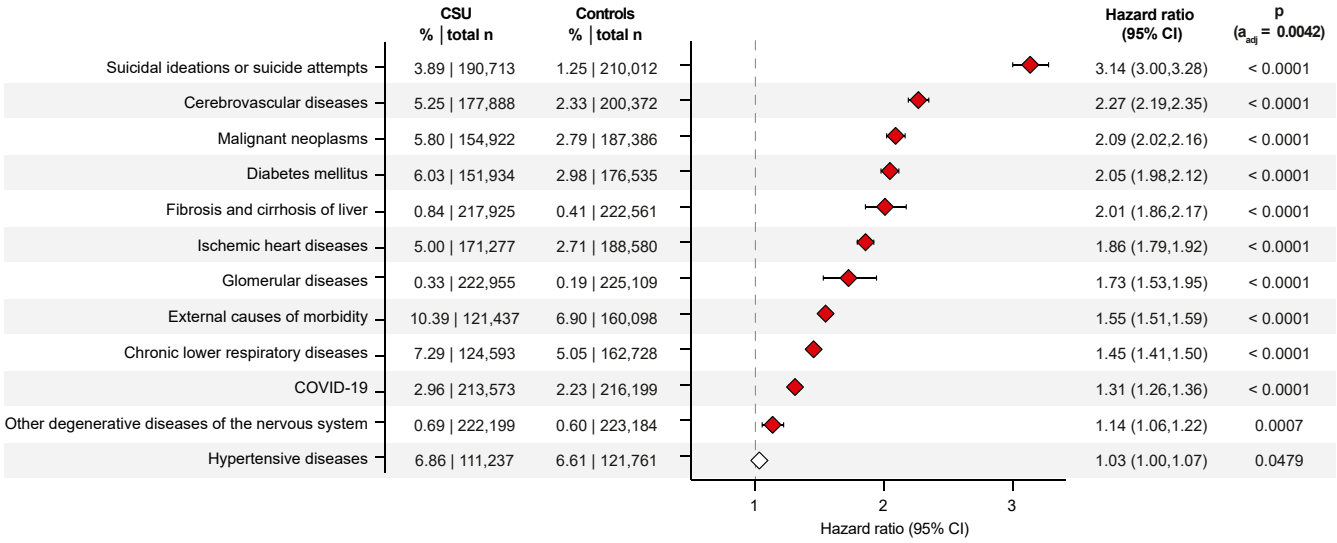

FIG 2. Mortality from the leading causes of death in the United States in patients with CSU. Comparison of mortality rates/risk for leading causes of death in the United States between the propensity score–matched patients with CSU (cases) versus controls without urticaria. For each group, the risk (%) is shown defined as the number of cases or controls with outcomes divided by the number of cases or controls in the group at the beginning of the time window. HRs were calculated using Kaplan-Meier analysis to estimate the probability of outcome. A univariate Cox proportional hazards regression was used to express HRs with 95% CIs. *Red diamonds* indicate statistically significant values; *white diamond* indicates a statistically nonsignificant value. a_{adj} = adjusted alpha value.

comorbidity (Tables E18-E19 in the Online Repository available at www.jacionline.org). In these analyses, the mortality risk in patients was significantly increased if, in addition, suicidal ideations or attempts were recorded (HR 1.77, 95% CI 1.66-1.89, $P <$ .0001). By contrast, when comparing the mortality risk of patients with hypertensive disease with patients without hypertensive disease, no risk difference was observed (HR 1.02, 95% CI 0.95-1.11, $P = .5518$).

Urticaria guideline–recommended treatment correlates with reduced mortality in patients with CSU

Oral corticosteroids were the most commonly prescribed treatment (n = 117,372 patients), followed by sgAHs (n = 113,334 patients), omalizumab (n = 1,514 patients patients), or cyclosporine A (n = 356 patients). One in 14 patients (n = 19,839) was not prescribed treatment (Table II). In a descriptive analysis, CSU treatment with oral corticosteroids and cyclosporine A was linked to the highest mortality rates across all time points, ie, 3 months, 12 months, and 60 months (0.90%, 2.43%, and 7.73% and 3.01%, 3.01%, and 4.52%, respectively), followed by sgAHs (0.48%, 1.13%, and 3.24%) and omalizumab (0.66% at all time points).

Compared with patients treated with sgAHs, untreated patients showed higher mortality (1.01% vs 2.28%, HR 1.84, 95% CI 1.37-2.46, $P <$ .0001) (Fig 3, *A*). Compared with patients treated with omalizumab, patients treated with sgAHs alone exhibited markedly higher mortality rates (0.69% vs 2.62%, HR 3.99, 95% CI 1.78-8.97, $P = .0003$) (Fig 3, *B*). These results persisted in the sensitivity analysis that excludes the first 3 months following the index event (Tables E20-E23 in the Online Repository available at www.jacionline.org).

DISCUSSION

This retrospective study, which included a large number of EHRs stemming from US-based health care, revealed higher mortality rates in patients with CSU compared with controls without urticaria, more pronounced in White and younger patients 18 to 40 years of age. Few previous studies have assessed the mortality risk in CSU. In contrast to our study, the Danish National Patient Registry study did not show higher mortality rates in patients with chronic urticaria likely due to relatively low sample size, limited matching, and investigation of urticaria as opposed to CSU.[19]

Whereas the retrospective design of the study precludes inferring causality, we speculate that the reported increased mortality risk in CSU stems from CSU-associated comorbidities. These diseases can be potentially fatal and/or increase the risk of other potentially fatal conditions. For example, depression, metabolic syndrome, and SLE can lead to suicide, cardiovascular events (ischemic heart disease, myocardial infarction, and stroke), and nephritis, respectively. In line with this, we found CSU to be associated with an increased risk for comorbidities that are leading causes of death as reported by the US National Center for Health Statistics in 2021,[17,20] including suicide, cerebrovascular diseases, diabetes mellitus, glomerular diseases, and cancer.

With every year of CSU duration, the risk of developing mental health disorders increases (relative risk 1.64),[11] but little is known about suicidal ideation/suicide attempts in patients with CSU. Suicidal ideations have been documented to be highly prevalent in patients with chronic pruritus (18.5%).[21] In a cross-sectional study of the Korean National Health Insurance Research Database, patients with undefined urticaria showed an increased prevalence of anxiety (odds ratio [OR] 1.10), suicidal ideation (OR 1.33), and sleep disorder (OR 1.18) compared with patients with nonatopic eczema.[22] In a systematic review and meta-

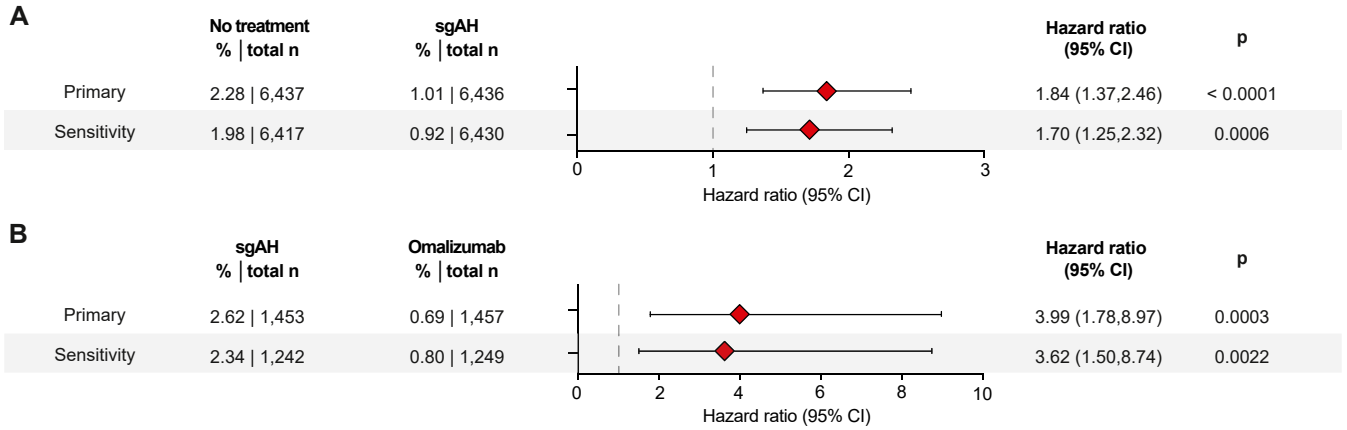

FIG 3. Risk of 60-month, all-cause mortality in patients with CSU associated with different urticaria guideline–recommended treatments. Comparison of mortality rates/risk between propensity score–matched patients with CSU treated with sgAHs and untreated patients **(A)** and patients treated with omalizumab (as add-on to sgAHs) and patients treated with sgAHs alone **(B)**. For each group, the risk (%) is shown defined as the number of cases or controls with outcomes divided by the number of cases or controls in the group at the beginning of the time window. HRs were calculated using Kaplan-Meier analysis to estimate the probability of outcome. A univariate Cox proportional hazards regression was used to express HRs with 95% CIs.

analysis, the prevalence of suicidal ideations/attempts in patients with undefined chronic urticaria was 12% to 19%.[23]

Furthermore, our data support the previous reports that patients with CSU are at increased risk of cancer (standardized incidence ratio 2.2, 95% CI 2.0-2.3), especially hematologic malignant tumors.[24] However, this association is considered to be very rare, although cure of cancer can lead to CSU remission.[25] Previous studies have also reported increased risk of metabolic syndrome and its components in patients with CSU (OR 1.1-1.2).[26] Up to 30% of patients with CSU have autoimmune disease.[27] In about 80% of patients with autoimmune diseases, especially female patients, autoimmune diseases including SLE and diabetes mellitus type I, develop within 10 years after CSU diagnosis.[28]

Finally, our study provides novel insights into the link of treatment and mortality in patients with CSU. Treatment with sgAHs and omalizumab was associated with reduced mortality risk in matched patients with CSU compared with patients with untreated CSU and patients treated with sgAHs alone. Treatment with sgAHs is the first-line CSU treatment and is recommended to be used as isolated treatment, ie, without other treatments including second-line treatments or glucocorticoids. Our findings suggest that patients with untreated CSU would benefit from sgAH treatment, ie, conferring a decreased mortality risk. Because we can expect that sgAH treatment reduces disease activity and increases control but does not benefit most comorbidities identified to be linked to mortality in patients with CSU, this strengthens the point that suicide is a main driver of mortality in CSU. However, we could not directly prove this assumption as there are no data on how many patients with and without sgAH treatment died by suicide.

Several reasons may explain reduced mortality rates in patients with CSU treated with omalizumab. First, similar to sgAH, better control of CSU with omalizumab improves patients' quality of life, thereby potentially decreasing psychological distress, anxiety, and depression including suicidal risk.[29,30] Second, omalizumab is more effective in non-autoimmune CSU.[3] Autoimmune CSU is likely associated with higher fatality risk as it is linked to comorbid autoimmune diseases including potentially fatal diseases such as SLE.[27] IgE autoantibodies were detected in both CSU and lupus,[31] and patients with CSU had an increased risk of SLE compared with individuals without CSU.[28,32] In CSU, functional mast cell–activating IgE-anti-IL-24 have been associated with higher disease activity.[33] Similarly, in SLE, IgE autoantibodies were linked to increased disease activity and active nephritis.[34] Omalizumab can bind IgE autoantibodies in both CSU and SLE, and its use in patients with CSU and SLE was associated with improvement in disease activity.[35,36] Third, omalizumab can decrease inflammatory response in patients with CSU,[37,38] which may decrease the risk of development of other chronic inflammatory diseases including metabolic syndrome. Lastly, omalizumab can reduce the risk of fatal anaphylaxis in patients with CSU with concomitant allergies, eg, food allergy, or chronic inducible urticaria, eg, cold urticaria and cold anaphylaxis.[39] However, anaphylaxis is a rare event in patients with both CSU and cold urticaria compared with cold urticaria alone (4% vs 39%)[40] and was not assessed in the present study.

The international urticaria guideline recommends systemic glucocorticosteroids for short-term use during periods of high CSU activity lasting up to 10 days.[1] Data on the duration of corticosteroid treatment are not available in our dataset. We believe the majority of patients with CSU received corticosteroids continuously; however, we cannot exclude that some patients received several short-term courses for <10 days within these 3 months. Nevertheless, our data suggest that even short-term corticosteroid treatment contributes directly to death in patients with CSU, eg by adverse effects, or that patients who receive corticosteroid treatment have higher rates of comorbidities that are linked to death (including suicide due to high disease activity, a known driver of the use of corticosteroids). On the other hand, corticosteroids are also known to increase the risk of suicidal behavior and neuropsychiatric disorders.[41]

Limitations of our study, inherent to the retrospective observational design and studies based on patient EHRs, include underdiagnosis, overdiagnosis, misdiagnosis, unmeasured or uncontrolled confounders, self-selection, and reverse causality. For example, the *ICD-10* code L50.8 is rarely used for chronic inducible urticaria or urticarial vasculitis, but it cannot be excluded

that a few such patients were also included in the analysis. Also, no causal inferences can be drawn as TriNetX does not provide the capability to identify the specific cause of death recorded in the EHRs. There is a lack of biologic plausibility for a few potential causes of death with elevated HR for the CSU group (Fig 2) such as "external causes of morbidity" when considering the natural history and immunopathogenesis of CSU. No analyses were performed for American Indian or Alaska natives and Native Hawaiian or other Pacific Islander race due to the low number of cases. Ethnicities such as Hispanic were not compared. Although we assume that the majority of patients with CSU received their medications due to CSU, we cannot exclude that some patients received some treatments, eg, corticosteroids, due to other causes. Data on some antihistamines, including rupatadine and bilastine, were not available in TriNetX and therefore were not included in the analysis. Furthermore, the selected US Collaborative Network of TriNetX database contains data only from US-based health care providers, and the results of our study need to be confirmed in other populations. In addition, the use of alternative statistical tests may be more accurate. Specifically, paired *t* tests instead of 2-sample *t* tests for continuous variables and McNemar test instead of the χ^2 test for binary variables would account better for dependency of the data.[42] The goal of these comparisons is to assess the balance achieved by the matching process, which was achieved as indicated by the relatively small standardized mean differences. Likewise, the TriNetX analytics interface uses the Kaplan-Meier method (for survival analysis), and Kaplan-Meier curves are compared using the log-rank test. Other tests, eg, frailty models, may be better suited for analysis[43] because they are more appropriate to account for unobserved heterogenicity that is not captured by measured covariates. To address this limitation, we performed several sensitivity and subgroup analyses. Lastly, it is important to exercise caution when interpreting the data concerning patients with CSU exposed to cyclosporine due to the relatively low number of patients in this group.

In conclusion, our analyses support concerns of increased mortality in patients with CSU, which can be explained, at least in part, by increased risk for comorbidities, with suicidal ideations/suicide attempts likely a consequence of having CSU and a main driver of mortality in patients. Screening for these comorbidities in patients as well as effective CSU treatment and treatment of concomitant conditions may reduce the risk of mortality. Systemic corticosteroids as a possible confounding factor to mortality rates should be limited to only short-term (<10 days) use in severe CSU exacerbation. Further studies should investigate validity and real-world significance of our findings, especially in other populations, and address unmet needs and knowledge gaps, eg, the association between duration of CSU and rates/risk of mortality including stratification for the type of treatment.

Data sharing statement

These data used population-level aggregate and deidentified data collected by the TriNetX Platform and are available from TriNetX, LCC (https://trinetx.com/), but third-party restrictions apply to the availability of the data. The data were used under license of this study with restrictions that do not allow for the data to be redistributed or made publicly available. To gain access to the data, a request can be made to TriNetX (join@trinetx.com), but costs might be incurred, and a data-sharing agreement would be necessary. Data specific to this study including diagnosis codes and group characteristics in aggregated format are included in the article as tables, figures and supplement files.

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Key messages

- **CSU is associated with increased mortality, especially in White and younger patients.**
- **Patients with CSU exhibit an increased risk of diseases that are leading causes of death including suicide.**
- **Effective urticaria guideline–recommended treatment of CSU may reduce the mortality rates.**

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