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ORIGINAL ARTICLE

Atopic Dermatitis, Urticaria and Skin Disease

Risk factors for systemic reactions in typical cold urticaria: Results from the COLD-CE study

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Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CIndU, chronic inducible urticaria; ColdA, cold-induced anaphylaxis; COLD-CE, comprehensive evaluation of cold urticaria and other cold-induced reactions, a study of the GA^{2}LEN UCARE network; ColdU, cold urticaria; CR(s), cold-induced reaction(s); CST, cold stimulation testing; CSTT, critical stimulation time threshold; CSU, chronic spontaneous urticaria; CTT, critical temperature threshold; GA^{2}LEN, Global Allergy and Asthma European Network; IQR, interquartile range; OR, odds ratio; UCARE(s), Urticaria Center(s) of Reference and Excellence.

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Abstract

Background: Cold urticaria (ColdU), that is, the occurrence of wheals or angioedema in response to cold exposure, is classified into typical and atypical forms. The diagnosis of typical ColdU relies on whealing in response to local cold stimulation testing (CST). It can also manifest with cold-induced anaphylaxis (ColdA). We aimed to determine risk factors for ColdA in typical ColdU.

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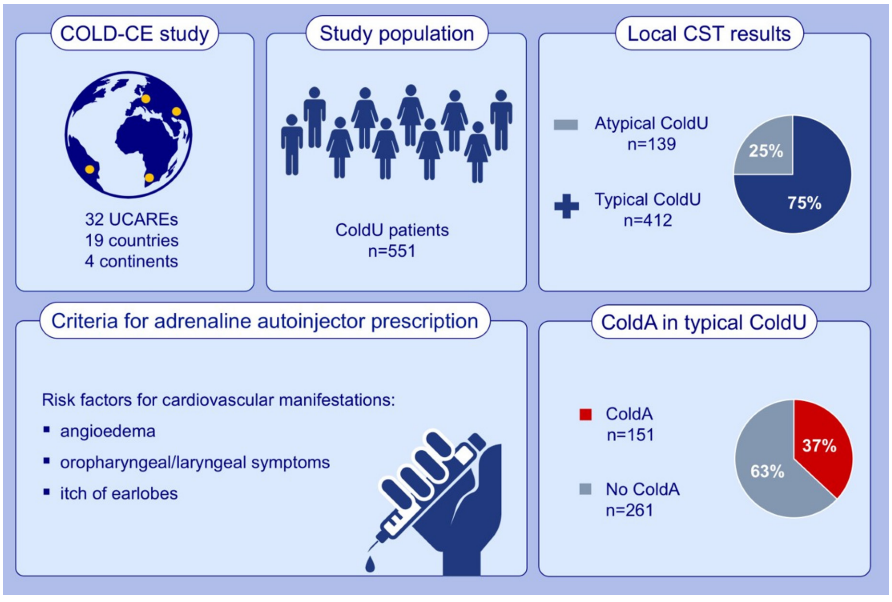
None.

Methods: An international, cross-sectional study COLD-CE was carried out at 32 urticaria centers of reference and excellence (UCAREs). Detailed history was taken and CST with an ice cube and/or TempTest® performed. ColdA was defined as an acute cold-induced involvement of the skin and/or visible mucosal tissue and at least one of: cardiovascular manifestations, difficulty breathing, or gastrointestinal symptoms.
Results: Of 551 ColdU patients, 75% ($n = 412$) had a positive CST and ColdA occurred in 37% ($n = 151$) of the latter. Cold-induced generalized wheals, angioedema, acral swelling, oropharyngeal/laryngeal symptoms, and itch of earlobes were identified as signs/symptoms of severe disease. ColdA was most commonly provoked by complete cold water immersion and ColdA caused by cold air was more common in countries with a warmer climate. Ten percent ($n = 40$) of typical ColdU patients had a concomitant chronic spontaneous urticaria (CSU). They had a lower frequency of ColdA than those without CSU (4% vs. 39%, $p = .003$). We identified the following risk factors for cardiovascular manifestations: previous systemic reaction to a *Hymenoptera* sting, angioedema, oropharyngeal/laryngeal symptoms, and itchy earlobes.
Conclusion: ColdA is common in typical ColdU. High-risk patients require education about their condition and how to use an adrenaline autoinjector.

KEYWORDS
adrenaline autoinjector, cold urticaria, COLD-CE, risk factors, systemic reactions



GRAPHICAL ABSTRACT

The COLD-CE study was carried out at 32 UCAREs from 19 countries and four continents. Among 551 ColdU patients, 75% had positive local CST (i.e., typical ColdU) and ColdA occurred in 37% of the latter. For the first time, we propose the criteria for adrenaline autoinjector prescription for patients with typical ColdU.
Abbreviations: ColdA, cold-induced anaphylaxis; COLD-CE, comprehensive evaluation of cold urticaria and other cold-induced reactions, a study of the GA^{2}LEN UCARE network; ColdU, cold urticaria; CST, cold stimulation testing; UCAREs, Urticaria Centers of Reference and Excellence

1 | INTRODUCTION

Cold urticaria (ColdU) is a subtype of chronic inducible urticaria (CIndU) where wheals, angioedema or both, with or without systemic signs or symptoms occur in response to cooling of the skin and/or mucosal tissue and/or the whole body.[1–3] Patients react to a wide range of triggers including cold air, contact with cold liquids, contact with cold solid surfaces, and the ingestion of cold food or drinks.[2,3] ColdU is classified into typical and atypical forms.[1]

The diagnosis of typical ColdU relies on immediate whealing at the tested skin site on the volar forearm in response to local cold stimulation testing (CST) with an ice cube and/or the thermoelectric device TempTest®.[1,4] Both tests are endorsed by the 2016 EAACI/GA^{2}LEN/EDF/UNEV consensus guidelines for CIndU.[4] In atypical ColdU, local CST induces atypical responses (eg, adjacent or delayed whealing) or specific provocation methods are needed to produce whealing (eg, general body cooling). The pathophysiology underlying negative CST in atypical ColdU represents an enigma. Additionally, clinical features of atypical forms of ColdU are ill-characterized, and a better and clinically useful classification of ColdU needs to be developed.[1]

The CST can also define the critical stimulation time threshold (CSTT) and the critical temperature threshold (CTT), that is, the shortest contact time and the highest temperature that induce a wheal.[1,3–6] TempTest® 4.0 has a single Peltier element (length: 350 mm, width: 2 mm) that provides a continuous gradient of temperatures from 4 to 44°C[4,5] and the previous version 3.0 has 12 cold probes set at 2°C intervals from 4 to 26°C.[7] CTT values obtained by both devices were shown to correlate.[6]

Anaphylaxis is a clinical emergency, and all healthcare professionals should be familiar with its recognition, treatment and prevention.[8–10] Physical triggers such as cold and heat have been described to induce anaphylaxis.[10–12] The term cold-induced anaphylaxis (ColdA) has been used in a few prior studies of ColdU,[3,13,14] but a consensus on its precise definition has not yet been established. ColdA is potentially life-threatening, although the fatality rate remains unknown.[1,15] A delay in adrenaline administration is a risk factor for anaphylaxis-related death.[16–18] Systemic reactions to cold exposure have been reported in 4–47% of ColdU patients (Table 1).[3,13,14,19–30] Some clinical features linked to severe reactions were already described (ie, positive local CST,[21] shorter CSTTs,[23,28] higher CTTs,[23] longer ColdU duration,[23] and oropharyngeal angioedema[27]; Table 1), but predictors for ColdA remain ill defined. High-risk ColdU patients require an adrenaline autoinjector, but exactly which patients should carry it remains to be defined.[31] Yee et al.,[21] Katsarou-Katsari et al.,[25] and Alangari et al.[26] suggested that all patients with ColdU should be provided with an adrenaline autoinjector, but this strategy could lead to high health care costs and trigger unnecessary anxiety in patients who have a low risk of life-threatening reactions.

To address these unmet needs, we investigated a large and diverse cohort of patients with typical ColdU for their rates of ColdA and their clinical characteristics. Most importantly, we investigated them for predictors of ColdA. The knowledge of risk factors of ColdA can help to better counsel patients with typical ColdU and help them to prevent ColdA.

2 | PATIENTS AND METHODS

2.1 | Study design

COLD-CE (ie, comprehensive evaluation of ColdU and other cold-induced reactions)[1] is an international, cross-sectional, observational study. The study was led by the University Clinic of Respiratory and Allergic Diseases Golnik, Slovenia and Charité – Universitätsmedizin Berlin, Germany and conducted in additional 30 GA^{2}LEN (Global Allergy and Asthma European Network) UCAREs (Urticaria Centers of Reference and Excellence)[32] from 17 countries between May 2019 and May 2021 (Table S1). The study was approved by the National Medical Ethics Committee of the Republic of Slovenia (KME0120-62/2019/4, 17.04.2019), Ethics Committee at Charité - Universitätsmedizin Berlin (EA1/069/19, 18.06.2019), and the responsible Ethics Committees of other participating institutions as required. Dated and signed written informed consent was obtained for all patients. Analyses of COLD-CE data are ongoing and additional results will be reported in further publications.

2.2 | Study participants

This study included 551 ColdU patients who reported active ColdU during the 12 months prior to evaluation and were enrolled in COLD-CE during their routine clinical visits.

2.3 | The association between cold-induced reactions and cold triggers

Patients were asked whether they had ever experienced the following cold-induced reactions (CRs): itch (CR1), localized wheals only (CR2), generalized wheals (CR3, Figure 1A), angioedema (CR4), swelling on acral body parts (CR5; ie, fingertips, knuckles, or ears; Figure 1B,C), hypotension (ie, RR < 90/60 mmHg) or loss of consciousness (CR6), other signs or symptoms suggestive of hypotension (CR7; ie, dizziness, sensation of fainting, weakness), difficulty breathing (CR8; ie, dyspnea, wheeze, stridor), or gastrointestinal symptoms (CR9). Secondly, they were asked whether the following cold triggers caused at least one CR: complete cold water immersion (T1), cold ambient air exposure (T2), transition from cold outdoors (<17°C) to warm indoors (T3), localized contact with cold liquids or ice (T4), and contact with cold surfaces (T5). Thirdly, we explored the link between CRs and triggers and analyzed additional reactions: oropharyngeal or laryngeal symptoms (ie, indicating swelling of the tongue and pharynx, hoarseness) and itch of earlobes, but we did not collect data on triggers of the latter two reactions.

2.4 | Comorbidity analysis

Patients were asked about the following comorbidities: (i) chronic spontaneous urticaria (CSU), (ii) asthma, (iii) atopic dermatitis and/or

TABLE 1 Previous studies that assessed severe systemic reactions in ColdU

Region	Total cases (n)	Study design	Age group	Systemic reactions			Frequency of typical ColdU	Authors, y
				Description/definition (cited)	Frequency	Indicators[a]		
Slovenia	36	P	Adult	ColdA – sudden cold-induced onset of at least 2 of the following: involvement of the skin and/or mucosal tissue, respiratory involvement, reduced blood pressure or associated symptoms, or gastrointestinal symptoms	33% (12/36)	NP	61% (22/36)	Bizjak et al. 2021[3]
Germany	49	P	Pediatric/adult	ColdA (description NP)	47% (23/49)	NP	69% (34/49)	Ginter et al. 2021[13]
Portugal	52	R	Pediatric/adult	Systemic symptoms (with respiratory and/or cardiovascular compromise)	33% (17/52)	NP	83% (43/52)	Paulino et al. 2021[19]
Thailand	27	R	Adult	Anaphylaxis (one patient had dyspnea and collapsed)	4% (1/27)	NP	100% (27/27)	Kulthanan et al. 2019[20]
United States	415	R	Pediatric	Anaphylaxis (grade 3) – severe systemic reactions consisting of urticaria and/or angioedema associated with airway, respiratory and/or abdominal symptoms and/or cardiovascular or neurologic symptoms suggestive of hypotension including dizziness, lethargy, sensation fainting, disorientation or shock/or symptoms of shock	19% (77/415)	Positive local CST	70% (179/256)	Yee et al. 2019[21]
Canada	59	R	Pediatric/adult	ColdA (description NP)	4% (2/50)	NP	85% (50/59)	Stepaniuk et al. 2018[22]
Australia	99	R, P	Pediatric/adult	Anaphylaxis – respiratory symptoms of noisy or difficulty breathing (dyspnea, bronchospasm/wheeze, cyanosis/hypoxia) and/or cardiovascular compromise (loss of consciousness or reported presyncope)	28% (28/99)	NP	NP	Jain and Mullins, 2016[14]
Spain	74	R	NP	Type III – severe systemic reactions with episodes suggestive of hypotension (ie, dizziness, sensation of fainting, disorientation, or shock) or respiratory distress (eg, shortness of breath or wheezing)	19% (14/74)	Shorter CSTT Higher CTT Longer ColdU duration	72% (53/74)	Deza et al. 2016[23]
Germany	30	P	Adult	A: dizziness/difficulty swallowing/circulation disorders/dyspnea B: unconsciousness/shock	A: 33% (10/30) B: 13% (4/30)	NP	100% (30/30)	Siebenhaar et al. 2009[24]

(Continues)

TABLE 1 (Continued)

Region	Total cases (n)	Study design	Age group	Systemic reactions			Frequency of typical ColdU	Authors, y
				Description/definition (cited)	Frequency	Indicators[a]		
Greece	62	P	Adult	Type III – severe systemic reactions with one or more episodes of generalized urticaria or angioedema associated with hypotension (dizziness, fainting, disorientation, shock)	29% (18/62)	NP	84% (46/55)	Katsarou-Katsari et al. 2008[25]
United States	30	R	Pediatric	Type III – severe systemic reactions with ≥1 episodes suggestive of respiratory distress (such as wheezing or shortness of breath) or hypotension (ie, dizziness, sensation of fainting, disorientation, or shock) A: respiratory distress B: decrease in the level of consciousness (dizziness, faintness, or hypotension)	Type III: 37% (11/30) A: 17% (5/30) B: 27% (8/30)	NP	59% (17/29)	Alangari et al. 2004[26]
France	35	P	NP	Shocklike reactions concurrently with hypotension, dizziness, and fainting.	34% (12/35)	Oropharyngeal angioedema	100% (35/35)	Mathelier-Fusade et al. 1998[27]
United States	50	P	NP	Type III – severe systemic reactions with one or more episodes of generalized urticaria and/or angioedema associated with episodes suggestive of hypotension, that is, dizziness, sensation of fainting, disorientation, or shock	38% (19/50)	CSTT ≤3 min	80% (40/50)	Wanderer et al. 1986[28]
Netherlands	39	R, P	Pediatric/adult	A: collapse B: dyspnea	A: 36% (14/39) B: 8% (3/39)	NP	92% (36/39)	Doeglas et al. 1986[29]
Finland	220	R, P	NP	A: fainting or shock B: dyspnea	A: 7% (16/220) B: 14% (31/220)	NP	94% (207/220)	Neittaanmäki, 1985[30]

Abbreviations: ColdA, cold-induced anaphylaxis; ColdU, cold urticaria; CST, cold stimulation testing; CSTT, critical stimulation time threshold; CTT, critical temperature threshold; NP, not provided; P, prospective study; R, retrospective study; y, year.

[a]Patient-related features linked to systemic reactions.

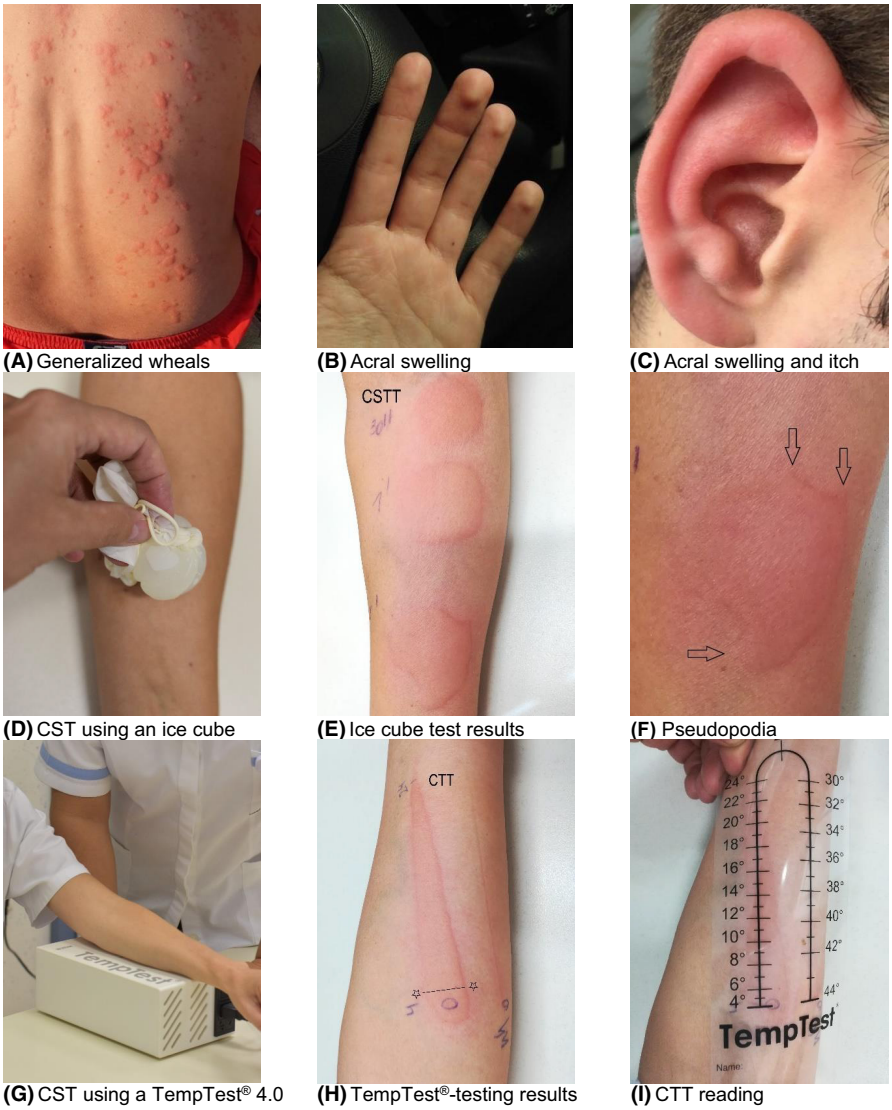


FIGURE 1 Characteristics linked to systemic reactions in typical ColdU. Patients were asked whether they had ever experienced cold-induced generalized wheals (A), swelling on acral body parts (B and C), and itchy earlobes (C). CST with an ice cube melting in a small amount of water (D) was done and CSTT determined (E). The tested sites were also observed for the presence of pseudopodia (F). TempTest®-testing (G) was used to determine a maximal wheal diameter and CTT (H and I). The photos are a courtesy of Dr Mojca Bizjak. ColdU, cold urticaria; CST, cold stimulation testing; CSTT, critical stimulation time threshold; CTT, critical temperature threshold

allergic rhinoconjunctivitis (we did not obtain data on frequency of atopic dermatitis and frequency of allergic rhinoconjunctivitis), (iv) previous systemic reaction to a *Hymenoptera* sting, and (v) thyroid disease.

2.5 | Cold stimulation testing (CST)

Study participants discontinued H_1-antihistamines and systemic glucocorticoids at least 3 and 7 days before CST, respectively.[4] A 5 min stimulation was performed with an ice cube melting in a small amount of water in a non-latex medical glove (Figure 1D) or a plastic bag and/or with TempTest® 3.0 or 4.0 device (Figure 1G). TempTest® version 3.0 was used in five UCAREs and version 4.0 in 17 UCAREs. Skin responses were assessed 10 min after the end of stimulation. Tests were considered positive if whealing appeared at the tested skin site. In patients with a positive ice cube test, shorter stimulation (30 s, 1 min, 2 min, 3 min, 4 min) was done to determine the CSTT (Figure 1E). Tested sites were observed for the presence of pseudopodial whealing indicating spreading of the wheal beyond the stimulated area (Figure 1F). In patients who tested positive with TempTest®, the CTT and the maximal wheal diameter were measured (Figure 1H,I). Participants receiving omalizumab therapy (n = 43) were excluded from analyses of these CST-parameters.

2.6 | Categorization of patients

The diagnosis of typical ColdU was based on a positive CST at enrollment and/or in the past. We defined ColdA as an acute cold-induced involvement of the skin and/or visible mucosal tissue (CR1–5) and at least one of the following: cardiovascular manifestations (CR6 and/or CR7), difficulty breathing (CR8), or gastrointestinal symptoms (CR9).[1,3,8,10,33] Cardiovascular manifestations, considered the most severe and reliable criterion for ColdA, were analyzed separately. We explored ColdA induced by: (i) at least one of triggers (T1–5), (ii) complete cold water immersion, (iii) cold air, (iv) transition from cold outdoors to warm indoors, and (v) localized contact with cold liquids, ice or surfaces. Patients were also categorized into residents of countries with a temperate, cold or tropical climate as shown in Table S1.

2.7 | Statistical analyses

The data were analyzed using IBM SPSS software V25. Descriptive measures included frequencies, proportions, ranges, and medians with the first and third quartile range. Numerical variables were first assessed for normality distribution by visualization and tests of normality. Non-parametric statistic test (Mann-Whitney *U* test) was used given a non-normal distribution of all numerical variables. Categorical variables were assessed by the Fisher's Exact test. Univariate logistic regression analysis was done to assess the effect of these variables to three possible binary outcomes in typical ColdU. To control for possible confounder effects, we further assessed statistically significant variables by multivariate logistic regression analysis. A set of seven independent variables was chosen in the final equation (ie, multiple regression model with the highest Nagelkerge's R square coefficient of multiple determination) based on clinical reasoning, their odds ratio (OR) and forward and backward selection. The OR and adjusted OR (aOR) were reported with a 95% confidence interval (CI) and $p < .05$ was considered statistically significant (Figure 2A–C, Table S3).

3 | RESULTS

3.1 | Three of four patients with ColdU have typical ColdU

Of 551 patients with ColdU, 75% ($n = 412$) were diagnosed with typical ColdU. Among the latter, 70% ($n = 289$) were females, 91% ($n = 374$) adults, and 24% ($n = 99$) had a pediatric onset of typical ColdU. Their median age was 36 years (IQR 26–48), age at onset of ColdU 29 years (IQR 18–42), and disease duration (ie, time since first signs/symptoms) 42 months (IQR 17–108) (Table S2).

3.2 | More than a third of patients with typical ColdU experience ColdA

ColdA occurred in 37% ($n = 151$) of patients with typical ColdU (Table 2). The most common triggers were complete cold water immersion, in 27% ($n = 112$) of patients, and cold ambient air exposure, in 13% ($n = 54$) of typical ColdU patients ($n = 412$). Additional reported triggers of ColdA were transition from cold outdoors to warm indoors ($n = 11$), localized contact with cold liquids or ice ($n = 8$), and contact with cold surfaces ($n = 2$).

3.3 | Comorbid CSU is linked to a decreased frequency of ColdA reactions

Ten percent ($n = 40$) of typical ColdU patients had a concomitant CSU (Table 2). Comorbid CSU was linked to a lower frequency of ColdA and cardiovascular manifestations caused by at least one of triggers (T1–5; Table 2) and by complete cold water immersion (Table S4). Further analyses were done in typical ColdU patients without CSU ($n = 372$; Tables 2 and 3).

3.4 | Cold-induced generalized wheals, angioedema and acral swelling are signs of severe ColdU

Patients with generalized wheals ($n = 231$) and angioedema ($n = 184$) had a higher frequency of ColdA provoked by complete cold water immersion or cold air than those without (Table 3, Tables S4 and S5A). Acral swelling ($n = 126$) was linked to a higher frequency of ColdA provoked by cold air (Table 3, Table S5A), and it was more common in patients with angioedema caused by at least one of triggers (T1–5) than those without (69% vs. 31%, $p < .001$).

3.5 | Oropharyngeal/laryngeal symptoms and itch of earlobes are symptoms of severe typical ColdU

A history of oropharyngeal/laryngeal symptoms ($n = 117$) and itchy earlobes ($n = 146$) were associated with a higher frequency of ColdA induced by complete cold water immersion or cold air (Table 3, Tables S4 and S5A). Oropharyngeal/laryngeal symptoms were more common in patients with angioedema caused by at least one of triggers (T1–5) than those without (40% vs. 23%, $p < .001$).

3.6 | ColdA induced by exposure to cold air is more common in countries with a tropical climate

Residents of tropical countries had: (i) a higher frequency of ColdA (including cardiovascular manifestations, difficulty breathing, and gastrointestinal symptoms) induced by cold air and (ii) a lower frequency of ColdA (including cardiovascular manifestations) induced by complete cold water immersion than residents of temperate or cold climate countries (Table 3, Table S1).

3.7 | ColdA induced by complete cold water immersion is linked to clinical characteristics of patients living in temperate climates

Residents of temperate regions had a higher frequency of ColdA (including cardiovascular manifestations and difficulty breathing) induced by complete cold water immersion than residents of cold climate countries (Table 3). Patients living in temperate regions, who experienced ColdA induced by complete cold water immersion ($n = 94$), had significantly: (i) longer disease duration, (ii) higher frequency of generalized wheals, angioedema, oropharyngeal/laryngeal symptoms, and itchy earlobes, (iii) shorter CSTTs, and (iv) larger

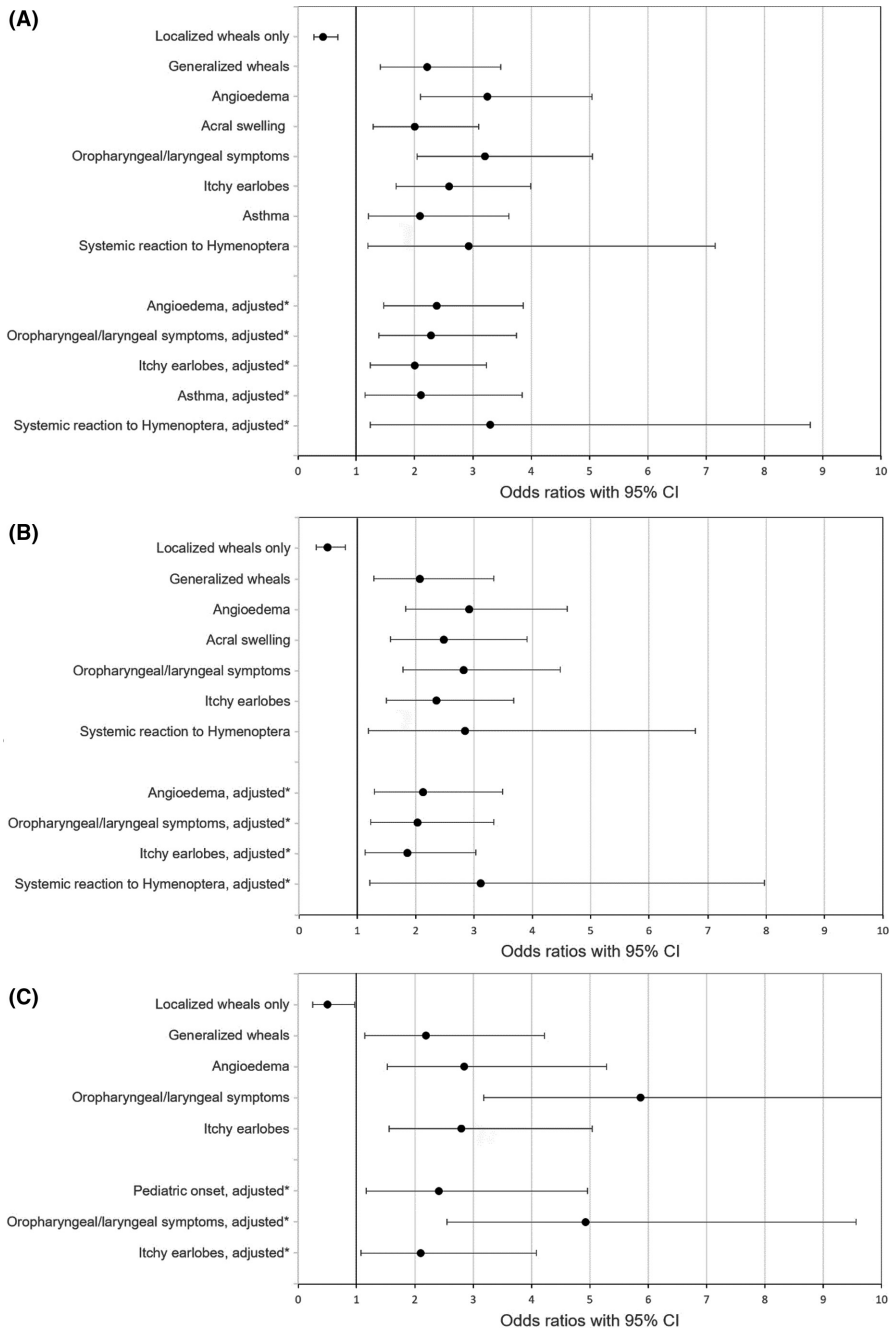


FIGURE 2 Risk factors for ColdA, cardiovascular manifestations, and difficulty breathing caused by at least one of triggers (T1–5). Statistically significant ($p < .05$) results of the univariate (OR) and multivariate (aOR) logistic regression analysis for 3 binary outcomes in typical ColdU are shown. Panel A shows risk factors for ColdA in 372 patients with a typical ColdU ($R^2 = .238$), Panel B risk factors for cardiovascular manifestations in 372 patients with a typical ColdU ($R^2 = .184$), and Panel C risk factors for difficulty breathing in 309 patients with a typical ColdU and no asthma ($R^2 = .246$). Results are also shown in Table S3. ColdA was defined as an acute cold-induced involvement of the skin and/or visible mucosal tissue and at least one of the following: cardiovascular manifestations (CR6 and/or CR7), difficulty breathing (CR8), or gastrointestinal symptoms (CR9). Cardiovascular manifestations were defined as hypotension or loss of consciousness (CR6) and/or other signs or symptoms suggestive of hypotension (ie, dizziness, sensation of fainting, weakness; CR7). Difficulty breathing (CR8) was defined as dyspnea, wheeze or stridor. aOR, adjusted odds ratio; ColdU, cold urticaria; ColdA, cold-induced anaphylaxis; R^2, Nagelkerge's R Square

TempTest®-induced wheal diameters than those without this ColdA phenotype (Table 3). Two of them also had aquagenic urticaria. Additionally, patients living in temperate regions, who experienced cardiovascular manifestations induced by complete cold water immersion ($n = 80$), had a higher frequency of pseudopodial whealing than those without (Table 3).

3.8 | Pediatric onset of typical ColdU was linked to severe systemic reactions

Hypotension and/or loss of consciousness induced by complete cold water immersion was linked to a pediatric onset of typical ColdU. Patients with these reactions also had a higher frequency of angioedema and previous systemic reactions to *Hymenoptera* stings (Table 3, Table S4).

3.9 | The features of ColdA induced by transition from cold outdoors to warm indoors are similar to those of ColdA induced by cold air

ColdA induced by transition from cold outdoors to warm indoors was rare ($n = 11$). It was more common in patients who had also experienced ColdA triggered by cold air exposure than those without (13% vs. 1%, $p < .001$), and both phenotypes had similar clinical features (Table S6).

TABLE 2 Characteristics of typical ColdU patients stratified by the presence of ColdA, cardiovascular manifestations, and difficulty breathing caused by at least one of triggers (T1–5)

			ColdA – broad definition[a,b]				Cardiovascular manifestations (CR6 and/or CR7)[b]			Difficulty breathing (CR8)[b], no asthma			
(A) All typical ColdU patients			Total, *n* = 412	Yes, *n* = 151	No, *n* = 261	*p*-value	Yes, *n* = 120	No, *n* = 292	*p*-value	Total, *n* = 343	Yes, *n* = 59	No, *n* = 284	*p*-value
Comorbid CSU			40 (10%)	6 (4%)	34 (13%)	**.003**	4 (3%)	36 (12%)	**.005**	34 (10%)	2 (3%)	32 (11%)	.091
(B) Typical ColdU patients without CSU			Total, *n* = 372	Yes, *n* = 145	No, *n* = 227	*p*-value	Yes, *n* = 116	No, *n* = 256	*p*-value	Total, *n* = 309	Yes, *n* = 57	No, *n* = 252	*p*-value
Demographics and baseline characteristics	Female gender		258 (69%)	102 (70%)	156 (69%)	.818	81 (70%)	177 (69%)	1.000	210 (68%)	40 (70%)	170 (68%)	.755
	Age at study enrollment (y)		36 (26–48)	36 (26–49)	36 (26–48)	.897	36 (25–48)	36 (26–48)	.730	36 (26–50)	35 (24–48)	37 (26–50)	.465
	Age ≥18 y at study enrollment		338 (91%)	135 (93%)	203 (89%)	.271	106 (91%)	232 (91%)	1.000	283 (92%)	54 (95%)	229 (91%)	.437
	Age at onset of ColdU (y)		30 (18–42)	30 (16–40)	29 (19–44)	.287	30 (16–39)	29 (19–44)	.284	30 (18–44)	24 (15–39)	30 (20–44)	.072
	Pediatric onset of ColdU (<18 y)		90 (24%)	40 (28%)	50 (22%)	.264	32 (28%)	58 (23%)	.360	70 (23%)	18 (32%)	52 (21%)	.082
	ColdU duration (months)		41 (17–99)	60 (24–129)	36 (13–80)	**.001**	56 (24–120)	36 (14–84)	**.041**	48 (17–108)	60 (26–132)	41 (14–108)	**.046**
	BMI		24 (22–28)	25 (22–28)	24 (22–28)	.773	24 (22–27)	24 (22–28)	.789	24 (22–28)	24 (22–28)	24 (22–28)	.852
Cold-induced reactions	Itch[b]		356 (96%)	139 (96%)	217 (96%)	1.000	111 (96%)	245 (96%)	1.000	294 (95%)	54 (95%)	240 (95%)	.745
	Wheals[b]		360 (97%)	140 (97%)	220 (97%)	1.000	113 (97%)	247 (97%)	.761	300 (97%)	56 (98%)	244 (97%)	1.000
	Localized wheals only[b]		126 (34%)	33 (23%)	93 (41%)	**<.001**	27 (23%)	99 (39%)	**.004**	107 (35%)	13 (23%)	94 (37%)	**.045**
	Generalized wheals[b]		231 (62%)	106 (73%)	125 (55%)	**<.001**	85 (73%)	146 (57%)	**.003**	190 (62%)	43 (75%)	147 (58%)	**.016**
	Angioedema, unknown/any location[b]		184 (50%)	97 (67%)	87 (38%)	**<.001**	78 (67%)	106 (41%)	**<.001**	154 (50%)	40 (70%)	114 (45%)	**.001**
	Acral swelling[b]		126 (34%)	63 (43%)	63 (28%)	**.002**	56 (48%)	70 (27%)	**<.001**	101 (33%)	25 (44%)	76 (30%)	.060
	Oropharyngeal/laryngeal symptoms		117 (32%)	68 (47%)	49 (22%)	**<.001**	55 (47%)	62 (24%)	**<.001**	93 (30%)	36 (63%)	57 (23%)	**<.001**
	Itchy earlobes		146 (39%)	77 (53%)	69 (30%)	**<.001**	62 (53%)	84 (33%)	**<.001**	116 (38%)	33 (58%)	83 (33%)	**.001**
Comorbidities	At least one of asthma, AD or AR		144 (39%)	60 (41%)	84 (37%)	.445	47 (41%)	97 (38%)	.647	81 (26%)	17 (30%)	64 (25%)	.507
	Asthma		63 (17%)	34 (23%)	29 (13%)	**.010**	26 (22%)	37 (15%)	.073	NA	NA	NA	NA
	Systemic reaction to *Hymenoptera*		22 (6%)	14 (10%)	8 (4%)	**.022**	12 (10%)	10 (4%)	**.030**	20 (7%)	6 (11%)	14 (6%)	.227
	Thyroid disease		58 (16%)	22 (15%)	36 (16%)	0.885	16 (14%)	42 (16%)	.644	49 (16%)	11 (19%)	38 (15%)	.426
CST results	Ice cube	CSTT (s)	300 (120–300), *n* = 206	180 (60–300), *n* = 66	300 (120–300), *n* = 140	.098	180 (60–300), *n* = 47	300 (120–300), *n* = 159	**.011**	300 (60–300), *n* = 170	240 (60–300), *n* = 28	300 (120–300), *n* = 142	.507
		Pseudopodial whealing	31 (9%), *n* = 337	15 (12%), *n* = 125	16 (8%), *n* = 212	.178	15 (15%), *n* = 98	16 (7%), *n* = 239	**.021**	27 (10%), *n* = 279	4 (9%), *n* = 45	23 (10%), *n* = 234	1.000
	TempTest®	CTT (°C)	18 (14–24), *n* = 200	18 (14–24), *n* = 81	18 (14–24), *n* = 119	.689	20 (14–24), *n* = 66	18 (14–24), *n* = 134	.420	19 (14–24), *n* = 170	20 (14–24), *n* = 27	18 (14–24), *n* = 143	.514
		Maximal TempTest® 4.0-wheal diameter (mm)	9 (5–13), *n* = 146	10 (6–14), *n* = 65	8 (5–12), *n* = 81	.114	10 (6–15), *n* = 53	8 (5–12), *n* = 93	**.012**	10 (6–13), *n* = 121	10 (5–13), *n* = 24	10 (6–13), *n* = 97	.700

Note: Data are given as no. (%) and median (IQR). If not obtained in all patients, patient numbers are displayed as "*n*". Statistical significance of differences between patient groups was calculated by Fisher's Exact test and Mann-Whitney *U* test. Statistically significant values ($p < .05$) are in bold.

Abbreviations: AD, atopic dermatitis; AR, allergic rhinoconjunctivitis; BMI, body mass index; ColdA, cold-induced anaphylaxis; ColdU, cold urticaria; CR, cold-induced reaction; CST, cold stimulation testing; CSTT, critical stimulation time threshold; CSU, chronic spontaneous urticaria; CTT, critical temperature threshold; CWI, complete cold water immersion; IQR, interquartile range; n, number of patients; y, year(s).

[a]ColdA was defined as an acute cold-induced involvement of the skin and/or visible mucosal tissue and at least one of the following: cardiovascular manifestations (CR6 and/or CR7), difficulty breathing (CR8), or gastrointestinal symptoms (CR9). Cardiovascular manifestations were defined as hypotension or loss of consciousness (CR6) and/or other signs or symptoms suggestive of hypotension (ie, dizziness, sensation of fainting, weakness; CR7). Difficulty breathing (CR8) was defined as dyspnea, wheeze or stridor.

[b]Induced by at least one of triggers (T1–5): complete cold water immersion (T1; CWI), cold ambient air exposure (T2), transition from cold outdoors to warm indoors (T3), local contact with cold liquids or ice (T4), and contact with cold surfaces (T5).

3.10 | ColdA induced by localized contact with cold liquids/ice/surfaces occurred only in colder countries

ColdA induced by localized contact with ice, cold liquids or surfaces was reported only in countries with a temperate climate ($n = 9$) and a country with a cold climate ($n = 1$). Of these 10 patients, 50% ($n = 5$) had cardiovascular manifestations and 70% ($n = 7$) difficulty breathing. Patients with locally triggered ColdA also had shorter CSTTs than those without this ColdA phenotype (median [IQR]: 60 [45–60] vs. 300 [120–300] sec, $p = .015$).

3.11 | Five independent risk factors are associated with ColdA in typical ColdU

Of 16 analyzed categorical variables (Table 2), seven were risk factors for ColdA based on univariate logistic regression analysis (Table S3). Further multivariate logistic regression analysis identified the following five independent risk factors for ColdA: a previous systemic reaction to a *Hymenoptera* sting (aOR = 3.30, CI: 1.24–8.79, $p = .017$), angioedema (aOR = 2.38, CI: 1.47–3.86, $p < .001$), oropharyngeal/laryngeal symptoms (aOR = 2.28, CI: 1.39–3.75, $p = .001$), concomitant asthma (aOR = 2.11, CI: 1.15–3.85, $p = .015$), and itchy earlobes (aOR = 2.00, CI: 1.24–3.23, $p = .005$) (Figure 2A, Table S3).

3.12 | Four factors increase the risk for cardiovascular manifestations

We identified four independent risk factors for cardiovascular manifestations: a previous systemic reaction to a *Hymenoptera* sting (aOR = 3.11, CI: 1.21–7.97, $p = .018$), angioedema (aOR = 2.12, CI: 1.29–3.49, $p = .003$), oropharyngeal/laryngeal symptoms (aOR = 2.03, CI: 1.23–3.34, $p = .006$), and itchy earlobes (aOR = 1.85, CI: 1.13–3.03, $p = .014$) (Figure 2B, Table S3).

3.13 | Comorbid asthma is linked to a higher frequency of ColdA induced by cold air

Analysis of patients with typical ColdU ($n = 372$) showed that ColdA induced by cold air was more prevalent in patients with comorbid asthma than those without (25% vs. 12%, $p = .009$; Table S7). Asthma patients did not express unique features of their ColdU when compared to non-asthma patients (Tables S7 and S8).

3.14 | Three factors increase the risk for difficulty breathing in patients without asthma

Regression analysis of risk factors for difficulty breathing was done on a subgroup of patients without asthma ($n = 309$, Table 2). Pediatric onset of typical ColdU was associated with a 2.4 fold increased risk of cold-induced difficulty breathing (CI: 1.17–4.96, $p = .018$). Oropharyngeal/laryngeal symptoms and itchy earlobes were also predictors and increased the risk of difficulty breathing by 4.9 and 2.1 fold (CI: 2.55–9.56, $p < .001$; CI: 1.08–4.08, $p = .030$, respectively; Figure 2C, Table S3).

4 | DISCUSSION

This study demonstrates, in a large and multicenter patient cohort, that more than a third of patients with typical ColdU develop ColdA, which is within a range of previous reports.[3,14,20–30] We identified clinical features linked to ColdA, characterized the triggers that prompt it, and present predictors for its occurrence. ColdA was mostly caused by complete cold water immersion, and this is also consistent with previous studies.[14,21,23,26,27,30] Our report is the first to characterize trigger-based ColdA phenotypes.

Differences in clinical features between typical ColdU patients who do or do not have comorbid CSU have not been described before. Interestingly, concomitant CSU was linked to a lower frequency of ColdA. It is important to assess typical ColdU patients for comorbid CSU.

Our ColdA patients had a significantly longer duration of ColdU than the ones without ColdA. This is consistent with the study by Deza et al.[23] who also reported the association between longer ColdU duration and its higher severity. By contrast, duration was not correlated with patient-related disease severity in a study by Jain et al.[14]

Cold-induced generalized wheals have previously been recognized as a feature of severe typical ColdU.[20,21,23,25,26,28] In a French study of 35 patients, angioedema after eating cold food was predictive of the risk of ColdA provoked by complete cold water immersion, but statistical significance of this finding was not reported.[27] Our study showed that both angioedema and oropharyngeal/laryngeal symptoms present independent risk factors for ColdA, including cardiovascular manifestations. Acral swelling and itchy earlobes, which were also linked to severe reactions, present a novel described sign/symptom in ColdU.

We found that shorter CSTTs as determined by CST are associated with a higher frequency of ColdA induced by complete cold water immersion. In a study of 50 ColdU patients, Wanderer et al. made a more general (ie, not trigger-specific) conclusion that CSTT of ≤180 s was associated with a higher incidence of severe systemic reactions.[28] In a study of 74 ColdU patients by Deza et al. shorter CSTTs were likewise significantly related to systemic reactions.[23] Neittaanmäki reported that 14% of patients with a 30 s CSTT had a severe type of ColdU.[30] TempTest® has been used in many studies to confirm typical ColdU and to measure the CTT. Deza et al.[23] and Mlynek et al.[34] reported the association between higher CTT and higher ColdU severity, but CTTs in our study were not associated with increased likelihood of ColdA. On the other hand, larger TempTest®-induced wheal diameters were associated with an increased frequency of ColdA and cardiovascular manifestations induced by complete cold water immersion. In a study

TABLE 3 Characteristics of systemic reactions caused by at least one of triggers (T1–5), complete cold water immersion or cold ambient air exposure in all patients with typical ColdU and residents of countries with temperate, cold, and tropical climate

Trigger		ColdA - broad definition[a,b]			Cardiovascular manifestations (CR6 and/or CR7)[b]			Hypotension and/or loss of consciousness (CR6)[b]			Difficulty breathing (CR8), no asthma[c]			Gastrointestinal symptoms (CR9)[b]		
		Any[d]	CWI	Air	Any[d]	CWI	Air	Any[d]	CWI	Air	Any[d]	CWI	Air	Any[d]	CWI	Air
		T1–5	T1	T2	T1–5	T1	T2	T1–5	T1	T2	T1–5	T1	T2	T1–5	T1	T2
All patients Δ○	Yes (n=372[b], n=309[c])	145	107	53	116	88	31	48	41	10	57	40	26	39	23	20
	% within yes	39%	29%	14%	31%	24%	8%	13%	11%	3%	18%	13%	8%	11%	6%	5%
Temperate ▲●	Yes (n=264[b], n=220[c])	115	94	32	95	80	18	38	35	3	43	35	14	24	19	8
	% within yes	44%	36%	12%	36%	30%	7%	14%	13%	1%	20%	16%	6%	9%	7%	3%
Cold ▲●	Yes (n=75[b], n=64[c])	16	10	9	9	7	2	3	3	1	5	3	3	4	3	2
	% within yes	21%	13%	12%	12%	9%	3%	4%	4%	1%	8%	5%	5%	5%	4%	3%
Tropical ▲●	Yes (n=33[b], n=25[c])	14	3	12	12	1	11	7	3	6	9	2	9	11	1	10
	% within yes	42%	9%	36%	36%	3%	33%	21%	9%	18%	36%	8%	36%	33%	3%	30%
Tropical vs temperate or cold (p-value)		.710	**.008**	**.001**	.556	**.002**	**<.001**	.168	1.000	**<.001**	**.029**	.754	**<.001**	**<.001**	.708	**<.001**
Tropical vs temperate (p-value)		1.000	**.001**	**.001**	1.000	**<.001**	**<.001**	.306	.781	**<.001**	.070	.388	**<.001**	**<.001**	.710	**<.001**
Tropical vs cold (p-value)		**.035**	.750	**.007**	**.007**	.430	**<.001**	**.009**	.367	**.003**	**.002**	.617	**<.001**	**<.001**	1.000	**<.001**
Temperate vs cold (p-value)		**<.001**	**<.001**	1.000	**<.001**	**<.001**	.267	**.015**	**.023**	1.000	**.036**	**.021**	.771	.352	.431	1.000
Pediatric onset of ColdU (<18 y)								○●	○							
↑ ColdU duration		Δ●	○●	○●	○●		○			○	○					
↑ BMI		●					○									
Generalized wheals[d]		Δ▲	○●	Δ●	○●●	●	Δ●	○●		○	○		○	●		
Angioedema, uknown/any location[d]		Δ▲●●	Δ●	Δ●●●	Δ▲●	○●	Δ●	○●	○●	Δ	Δ●	○●	○	○		○
Acral swelling[d]		○●●●	●	Δ●●	Δ▲●●	●	Δ▲●	○●		Δ●	●		○●●	○●●		Δ●
Oropharyngeal/laryngeal symptoms		Δ▲▲	Δ●	Δ●▲	Δ●▲	○●	Δ▲	●		○●	Δ▲▲	Δ▲	Δ▲	○▲		Δ▲
Itchy earlobes		Δ▲▲	○▲	Δ▲	Δ●▲	○●	○▲	○●		●	Δ●●		Δ●	○▲		○▲
Asthma		○●		○●												
Systemic reaction to *Hymenoptera*		○●		●	○●			○●	○●							
↓ CSTT		●	○●		○●	Δ▲										
Pseudopodial whealing					○	○●										
↑ TempTest® 4.0-wheal diameter			○●		○	○●								○	○●	

Note: Statistical significance of differences between patient groups was calculated by Fisher's Exact test and Mann–Whitney *U* test. Statistically significant results are shown as Δ▲ ▲ ▲ for $p \le 0.001$ and ○●●● for $p < 0.05$. Analogous symbols of different colors are used for 4 patient groups: Δ○ for all patients with typical ColdU (detailed results are provided in Tables S5A–E), ▲● for residents of countries with a temperate climate, ▲● for residents of countries with a cold climate, and ▲● for residents of countries with a tropical climate (Table S1).

Abbreviations: BMI, body mass index; ColdA, cold-induced anaphylaxis; ColdU, cold urticaria; CR, cold-induced reaction; CSTT, critical stimulation time threshold; CWI, complete cold water immersion; y, year(s).

[a]ColdA was defined as an acute cold-induced involvement of the skin and/or visible mucosal tissue and at least one of the following: cardiovascular manifestations (CR6 and/or CR7), difficulty breathing (CR8), or gastrointestinal symptoms (CR9). Cardiovascular manifestations were defined as hypotension or loss of consciousness (CR6) and/or other signs or symptoms suggestive of hypotension (ie, dizziness, sensation of fainting, weakness; CR7). Difficulty breathing (CR8) was defined as dyspnea, wheeze, or stridor.

[b]Analysis of typical ColdU patients without CSU (n = 372).

[c]Analysis of typical ColdU patients without CSU and without asthma (n = 309).

[d]Induced by at least one of triggers (T1–5): complete cold water immersion (T1; CWI), cold ambient air exposure (T2), transition from cold outdoors to warm indoors (T3), local contact with cold liquids or ice (T4), and contact with cold surfaces (T5).

by Yee and coworkers, the median diameter of wheals induced by an ice cube (a non standardized method) was higher in patients with ColdA than in those without, but the difference did not reach significance.[21] Since TempTest® testing has been validated for identifying CTTs, further studies are needed to evaluate its usefulness in wheal diameter assessment.

We identified a higher frequency of ColdA induced by cold air in countries with a tropical climate. Cold tolerance induction by repeated exposures to cold temperatures (eg, cold baths or showers) has been used to achieve temporary cold desensitization in ColdU.[35–40] It remains unknown whether typical ColdU patients residing in colder countries develop tolerance to cold ambient air exposure or whether ColdA in residents of tropical countries is triggered by different mechanisms.

Ten patients had severe cold sensitivity with ColdA provoked by localized contact with ice, cold liquids or surfaces in real life, which is an important reminder that caution is needed during CST. The mechanism for the occurrence of a systemic reaction after a local cold stimulation remains unknown. Interestingly, it has been described that systemic symptoms in ColdU have been prevented when venous return from the exposed site was obstructed with a tourniquet.[41]

COLD-CE has several strengths. The study was conducted in several certified UCAREs by physicians specialized in urticaria, with a robust protocol, with well-defined data collection tools and provocation testing, and in a sizable cohort of more than 500 patients. The limitations of our study are inherent in the cross-sectional study design, lacking prospective evaluations of risk

factors for ColdA. Further studies are needed to confirm their relevance and to establish their predictive values including their specificity and sensitivity. Additionally, the frequency of cold-induced cardiovascular reactions and systemic reactions to venoms were determined based on patient history data collected by physicians. It remains unknown how many of these patients had proper tests required for the diagnosis of IgE-mediated allergy to venoms or systemic mastocytosis. Patient- or physician-reported "venom allergy" without a proper allergological work-up might overestimate the real prevalence of venom allergy and the relevance of this feature as a risk factor for ColdA. We assume that ColdA patients need to be tested for underlying mastocytosis similarly to patients with *Hymenoptera* venom-triggered anaphylaxis.[42–44] Bizjak et al. recently reported a patient in whom a clonal mast cell disorder was suspected (and confirmed) only based on clinical features of severe ColdU.[3] Potential limitation of our study may also arise from the fact that patients with mild ColdU or with ColdA that resolved without treatment, may not seek medical advice, and our data may over-represent severe ColdU compared to that occurring in the community. Our study provides novel insights into ColdU characteristics in tropical, temperate and cold climates, significantly extending previous observations.[20,30,45] However, the climate-based comparison of ColdU has limitations which need to be assessed in future studies taking into account the latitude of the patient's residence and behavior patterns regarding swimming in open waters and other risk taking behaviors.

The results of our study imply changes in clinical practice. For the first time, we propose the criteria for adrenaline autoinjector prescription for patients with typical ColdU, as shown in Figure 3. ColdU patients with risk factors for ColdA need to be educated on the avoidance of relevant cold triggers and recognition of the onset of severe reactions. High-risk ColdU patients need to carry an adrenaline autoinjector and know how and when to self-inject and follow-up with a specialist if ColdA occurs.

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CONFLICT OF INTEREST

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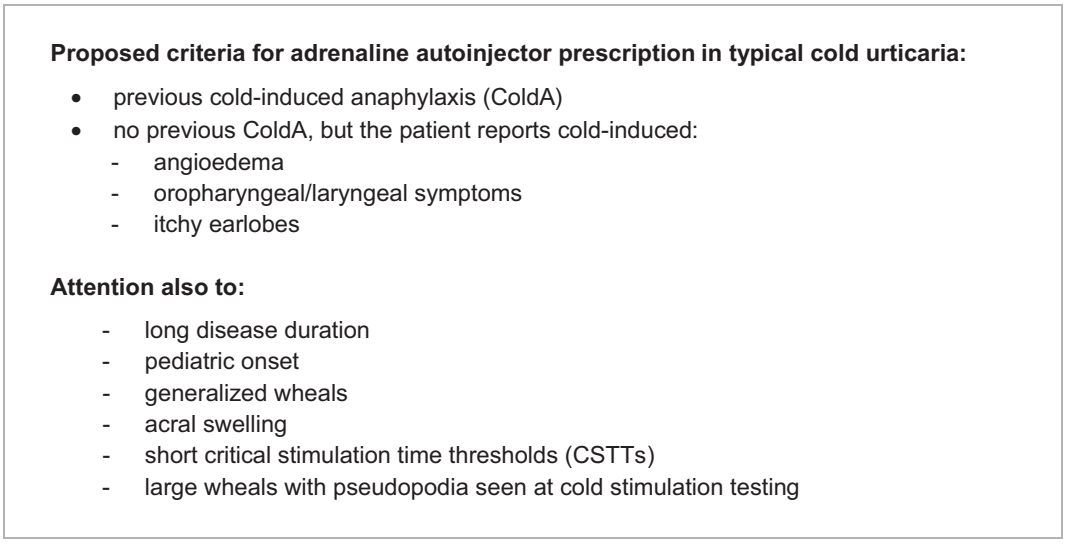

FIGURE 3 Proposed criteria for adrenaline autoinjector prescription in ColdU patients. ColdA, cold-induced anaphylaxis; ColdU, cold urticaria; CST, cold stimulation testing; CSTT, critical stimulation time threshold

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AUTHOR CONTRIBUTIONS

M. Bizjak initiated, entitled and designed the COLD-CE study, collected data, performed data quality controls, and developed the manuscript. D. Terhorst-Molawi and M. Maurer contributed to study design and provided critical input to the manuscript. M. Bizjak and D. Terhorst-Molawi were principal investigators. M. Bizjak and D. Dinevski performed statistical analyses. All authors contributed to acquisition of data, interpretation of data and manuscript development and approved it for publication.

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