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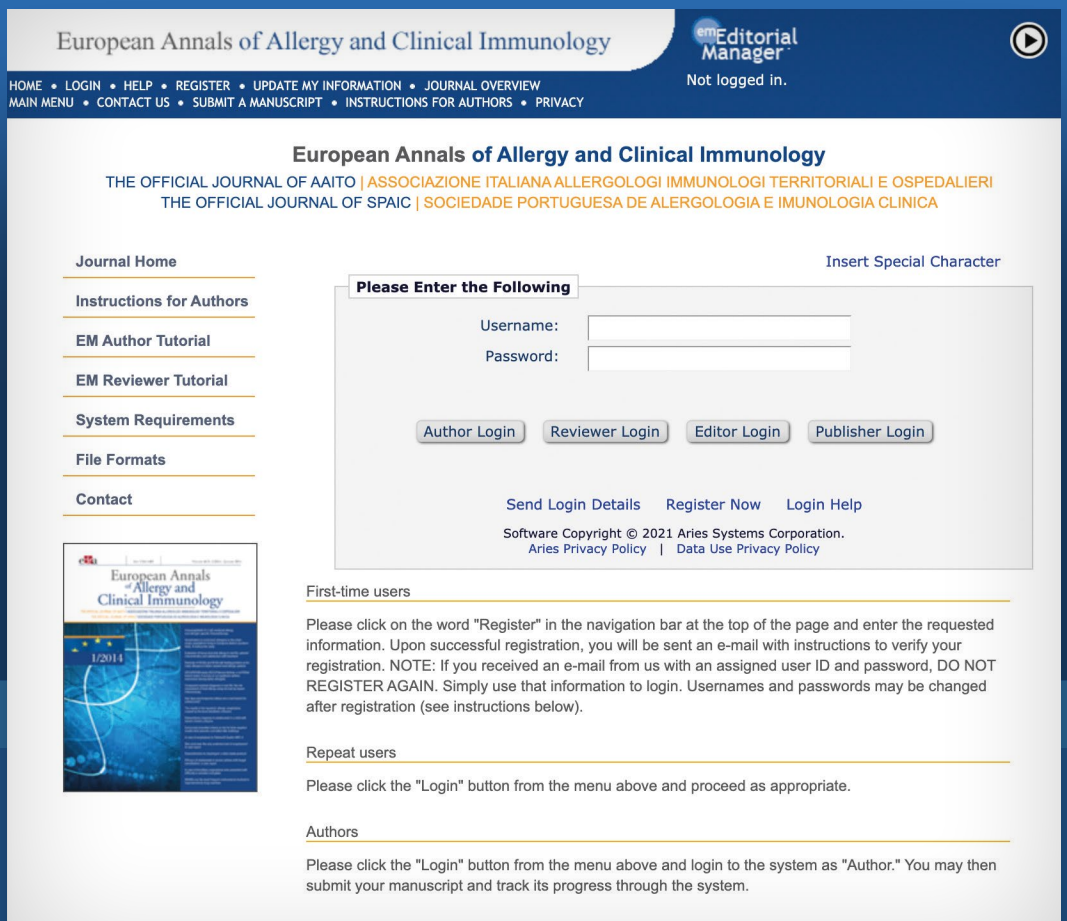
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Jessica Guenzi
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Edra Media S.r.l.

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Anna M. Perino

Long-lived plasma cells: mysterious sentinels and persistent IgE producers?

Department of Clinical and Biological Sciences, University of Turin, Orbassano, Turin, Italy

Key words

Long-lived plasma cells; stromal survival niches; IgE persistence; immune memory trajectories; Treg regulation.

Corresponding author
Anna M. Perino
Department of Clinical and Biological Sciences
University of Turin
Orbassano, Turin, Italy
ORCID: 0009-0003-4360-5421
E-mail: annamaria.perino@unito.it

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Impact statement

LLPCs are long-lived, niche-supported antibody producers whose sustained secretion and resilience might interface with IgE-associated circuits, offering a mechanism that could contribute to the long-term stability and persistence of allergic sensitization.

Summary

Long-lived plasma cells (LLPCs) constitute a specialized and durable arm of humoral memory. While their role in maintaining long-term IgG and IgA immunity is firmly established, their contribution to IgE-mediated allergic disease remains clinically unproven. Nevertheless, recent advances in LLPC biology – accelerated substantially since 2021 – have shown that IgE+ LLPC-like cells do exist in human bone marrow and chronically inflamed tissues, providing an immunological basis for exploring their potential involvement in persistent sensitization.

LLPCs arise through tightly orchestrated developmental programs and rely on survival niches shaped by stromal cells, cytokines and metabolic adaptations. These features allow continuous antibody secretion for years or decades, independently of antigen re-exposure. Their metabolic resilience and resistance to apoptosis make them among the most durable effector cells in adaptive immunity. In parallel, several mechanisms already known to support IgE persistence – early-life programming of type-2 responses, Treg/Tfr disequilibrium, sequential class switching from IgG1 memory, and rapid recall from non-IgE memory B cells – form a robust framework capable of sustaining long-term allergic sensitization irrespective of LLPC involvement. Within this architecture, the confirmed presence of IgE+ LLPCs offers a biologically plausible, though not yet clinically validated, explanation for the remarkable stability of IgE profiles observed in many allergic conditions. Considering LLPCs within the broader context of IgE persistence highlights an area of growing immunological relevance while underscoring that their precise contribution to allergic disease remains to be determined.

Introduction

Plasma cells were identified between the late nineteenth and mid-twentieth centuries through seminal histological and functional studies, which ultimately established their role as antibody-secreting descendants of B lymphocytes (1). For decades, plasma cells were therefore regarded as short-lived terminal effectors, dedicated to transient antibody production during acute immune responses.

Beginning in 1997, this view was challenged by the identification of a distinct subset of long-lived plasma cells (LLPCs), capable of persisting for years within specialized tissue niches and sustaining antibody secretion independently of antigen re-exposure (2). The same persistence mechanisms that ensure durable protective immunity may, in specific contexts, also contribute to the maintenance of unwanted or pathological antibody responses (3). Allergic disease became conceptually defined as a reproducible immunological condition in the twentieth century with the identification of immunoglobulin E (IgE) as the molecular mediator of immediate hypersensitivity (4-6). Despite the short serum half-life of IgE, allergic sensitization frequently persists for years or decades, indicating that IgE-associated immune responses can remain remarkably stable over time (7). This clinical persistence raises the question of whether long-lived antibody-secreting com-

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partments may also sustain IgE responses. Among these, LLPCs may represent a cellular substrate of durable antibody production. The introduction of component-resolved diagnostics (CRD) refined the molecular characterization of IgE sensitization and enabled allergen-specific IgE responses to be followed longitudinally (8, 9). Beyond their diagnostic value, these approaches have consistently revealed the long-term stability of individual IgE repertoires, even in the absence of continuous allergen exposure, reinforcing the concept that IgE persistence reflects durable immunological memory rather than ongoing stimulation alone. Allergen immunotherapy (AIT) further illustrates this persistence. While AIT can modify disease expression through induction of regulatory pathways and competing antibody responses, complete extinction of IgE memory is uncommon, and IgE production often rebounds after treatment discontinuation (10, 11). Together, these observations suggest that mechanisms capable of maintaining long-lived antibody production may also operate within IgE-mediated immunity.

Within this framework, allergic disease provides a clinically accessible model in which long-term humoral immune persistence can be interrogated. The question is therefore not whether IgE-mediated responses persist, but to what extent LLPCs may contribute to the stabilization of IgE sensitization over time.

This review aims to integrate recent advances in long-lived plasma-cell biology with established mechanisms of IgE persistence in allergic disease. In doing so, it addresses the current knowledge gap between the emerging evidence for IgE^+ long-lived plasma cell-like populations in humans and the still unresolved extent of their quantitative and clinical contribution to long-term allergic sensitization.

Inside the life of LLPCs

LLPCs represent one of the most durable outcomes of adaptive immunity, capable of sustaining antibody production long after antigen clearance. Early radiocarbon "bomb-pulse" studies provided the first compelling evidence that a subset of human antibody-secreting cells can persist for decades, long before their cellular identity and regulatory mechanisms were formally defined (2, 8). Despite this early evidence of longevity, LLPCs have long remained experimentally elusive. In humans, they account for only 20-25% of bone-marrow plasma cells and less than 1% of total marrow cellularity, and even after robust immune stimulation only a few antigen-specific LLPCs can typically be detected (9). Several factors have historically limited their investigation, including:

- their extreme numerical rarity within lymphoid tissues;
- their anatomical sequestration within specialized survival niches, particularly in the bone marrow and mucosal sites;
- the lack of unique and definitive surface markers allowing prospective identification;
- their phenotypic overlap with shorter-lived plasma cells, complicating functional discrimination.

These constraints have only recently been overcome through advances in single-cell profiling, lineage tracing, and niche-aware experimental approaches. In particular, high-resolution studies such as those by Liu *et al*. have demonstrated that LLPCs do not

Table I *- Comparison between short-lived plasma cells (SLPCs) and long-lived plasma cells (LLPCs).*

Feature	Short-lived plasma cells (SLPCs)	Long-lived plasma cells (LLPCs)
Origin	Mainly extrafollicular B2-derived plasmablasts, early primary responses	Mainly germinal centers; also, extrafollicular (especially IgM and mucosal IgA) and B1-derived
Antibody affinity	Low-moderate; limited SHM	High; extensive SHM
Lifespan	Days to weeks	Months to decades
Survival niche	Minimal or unstable	Specialized, cytokine-rich niches (BM, gut, spleen)
Microenvironmental dependence	Modest	Strong (IL-6, APRIL, BAFF, CXCL12)
Metabolic profile	Predominantly glycolytic	OXPHOS-driven; pyruvate-dependent; robust UPR
Markers	CD138 variable; BCMA low	$CD138^{++}$, $BCMA^+$, $TACI^+$, $CXCR4^+$
Localization	Inflammatory sites, spleen	Bone marrow; intestinal lamina propria (IgA LLPCs); spleen (including IgE LLPCs)
Therapeutic sensitivity	Sensitive to B-cell depletion (CD20 dependence)	Resistant to anti-CD20; niche-protected
Main function	Rapid but transient antibody production	Stable, long-term antibody secretion

SLPCs mediate early, transient antibody responses, whereas LLPCs provide durable humoral immunity supported by specialized survival niches and metabolic adaptations. SLPCs: short-lived plasma cells; LLPCs: long-lived plasma cells; SHM: somatic hypermutation; BM: bone marrow; IL-6: interleukin-6; APRIL: a proliferation-inducing ligand; BAFF: B-cell activating factor; CXCL12: C-X-C motif chemokine ligand 12; OXPHOS: oxidative phosphorylation; UPR: unfolded protein response; BCMA: B-cell maturation antigen; TACI: transmembrane activator and CAML interactor; CXCR4: C-X-C motif chemokine receptor 4; IgE: immunoglobulin E.

represent a homogeneous endpoint, but instead comprise phenotypically and ontogenetically distinct subsets defined by isotype, developmental origin, and tissue context (9).
The authors identified IgG$^+$ or IgM$^+$ LLPCs as EpCAM$^+$CXCR3$^-$, whereas IgA$^+$ LLPCs exhibited a Ly6A$^+$Tigit$^-$ profile (9). High-resolution single-cell work provided the first systematic definition of LLPC heterogeneity across immunization, autoantigen exposure, and microbial stimulation. These analyses established that LLPCs are not a uniform entity but a constellation of phenotypically and ontogenetically distinct subsets. IgG and IgM LLPCs adopt an EpCAM^{hi}CXCR3^{lo} phenotype, whereas IgA LLPCs display a Ly6A^{hi}Tigit^{lo} signature. Germinal center (GC)-derived, somatically hypermutated clones predominantly feed the IgG/IgA LLPC pool, while IgM LLPCs include abundant "public", innate-like, T-independent clones reactive to microbial and self-antigens (9). These phenotypic and developmental features allow a practical distinction between short-lived and LLPCs, summarized in **table I**.

Phenotyping and developmental heterogeneity of LLPCs

Although essential, LLPCs represent a quantitatively small population: in humans they account for only 20-25% of bone marrow plasma cells and < 1% of total marrow cellularity. After immunization, fewer than ten antigen-specific LLPCs per milliliter of bone marrow are typically detected (9), and in mice even robust viral infection generates only ~20,000-30,000 antigen-specific LLPCs in the entire organism. A key limitation – beyond their rarity – has been the inability to prospectively separate LLPCs from their much more abundant shorter-lived counterparts. In humans, LLPCs are thought to reside in a CD19$^-$CD38$^+$CD138$^+$ bone marrow fraction enriched for IgG- and IgA-secreting cells, although the extent of heterogeneity within this population remains unclear (2). A major practical challenge has been the development of prospective flow cytometry-based strategies to isolate LLPCs. Mining transcriptomic datasets, Liu *et al.* identified IgG$^+$ or IgM$^+$ LLPCs as EpCAM$^+$CXCR3$^-$, whereas IgA$^+$ LLPCs exhibited a Ly6A$^+$Tigit$^-$ profile (9). High-resolution single-cell work provided the first systematic definition of LLPC heterogeneity across immunization, autoantigen exposure, and microbial stimulation. These analyses established that LLPCs are not a uniform entity but a constellation of phenotypically and ontogenetically distinct subsets. IgG and IgM LLPCs adopt an EpCAM^{hi}CXCR3^{lo} phenotype, whereas IgA LLPCs display a Ly6A^{hi}Tigit^{lo} signature. Germinal center (GC)–derived, somatically hypermutated clones predominantly feed the IgG/IgA LLPC pool, while IgM LLPCs include abundant "public," innate-like, T-independent clones reactive to microbial and self-antigens (9).

Tissue survival niches and stromal conditioning

LLPCs remain difficult to study because of their rarity, anatomical sequestration, and the lack of unambiguous surface markers. Foundational work on human and murine plasma-cell origins highlighted the profound diversity of the plasma-cell compartment (10), while analyses of human bone marrow plasma cells revealed maturation gradients and transcriptional heterogeneity within LLPC-enriched fractions (11). GC imaging clarified the distinct routes by which early plasmablasts diverge toward short-lived or long-lived fates (12). Refinements in phenotypic classification outlined molecular signatures that differentiate resident from recirculating antibody-secreting cells (13), and recent commentary underscored the implications of these findings for the overlooked population of long-lived IgE-secreting cells (14). A central principle of LLPC biology is the requirement for specialized stromal survival niches. Mapping of bone marrow architecture identified CXCL12$^+$ reticular cells, sinusoidal endothelial networks, and regulatory myeloid populations as key determinants of LLPC anchoring and trophic support (15). Work in chronic inflammatory settings further showed that LLPCs can adopt distinctive phenotypes shaped by local tissue environments (16), demonstrating that LLPC identity is not fixed but niche-conditioned.

Ontogeny, lineage dynamics, and persistence

Maintenance of the memory-plasma cell compartment relies on extrinsic and intrinsic mechanisms that prevent apoptosis and stabilize secretory output (17). Developmental studies clarified how survival dynamics diverge between short-lived plasmablasts and durable LLPCs (18), while trajectory analyses confirmed that LLPC identity is imprinted progressively rather than instantaneously (19). Newly generated antibody-secreting cells undergo metabolic and transcriptional maturation as they transition from blood to bone marrow, acquiring increased mitochondrial dependence, enhanced secretory capacity, and stress-response competence (20). The long-term persistence of discrete plasma-cell clones has been demonstrated through high-fidelity fate-mapping and time-stamping approaches (21), showing that antigen-specific, non-dividing LLPCs remain *in situ* for extended periods. Reconstructions of plasma-cell ontogeny highlight parallel contributions of GC-derived and extrafollicular lineages to the LLPC pool (22). Imaging and computational analyses distinguish genuine LLPCs from transient antibody-secreting cells (23), while extended lineage models reveal unexpected plasticity under chronic immune stimulation (24). Earlier conceptual work framed plasma-cell differentiation as a balance between proliferation arrest, commitment to antibody secretion, and dependence on niche-derived cues (25), while more recent syntheses integrate LLPC longevity within coordinated metabolic, stromal, and epigenetic programs (26). A major advance concerns IgE LLPCs. Miranda-Waldetario *et al.* demonstrated the existence of bona fide long-lived IgE plasma cells with stable transcriptional profiles and protected tissue residence (27). Glaros and Kreslavsky (13) showed that IgE LLPCs persist predominantly in splenic niches, displaying survival signatures distinct from IgG LLPCs. Advanced 2D and

3D epithelial-stromal coculture systems have demonstrated that mucosal tissues possess the intrinsic capacity to sustain LLPC-like plasma cells outside canonical bone-marrow niches. These *ex vivo* models – based on layered epithelial sheets, stromal support cells, and matrix-based 3D architectures – recreate key features of mucosal microenvironments, including cytokine gradients, cell-matrix interactions, and survival factors such as IL-4, IL-6, APRIL, and TSLP. Together, they provide functional evidence that inflamed airway and intestinal tissues can maintain long-lived IgA- or IgE-secreting plasma cells independently of marrow-derived stromal networks (28).

Metabolic programming and survival fitness

The longevity of LLPCs relies on a profoundly remodeled metabolic program centered on mitochondrial fitness, oxidative phosphorylation (OXPHOS), and sustained endoplasmic reticulum (ER) homeostasis. During the transition from blood to bone marrow, nascent antibody-secreting cells acquire increased mitochondrial mass, elevated spare respiratory capacity, controlled glycolytic flux, and a lipid-handling program compatible with continuous membrane biosynthesis (19). A defining feature is the preferential use of pyruvate as a mitochondrial substrate. LLPCs depend on an efficient mitochondrial pyruvate carrier (MPC1/2) to transport pyruvate into the mitochondrial matrix, fueling the Tricarboxylic Acid (TCA) Cycle and sustaining high-level OXPHOS. Adequate pyruvate availability is essential to maintain ATP generation, mitochondrial membrane potential, and long-term survival. These metabolic adaptations support the continuous secretory load while preventing apoptosis through enhanced UPR activity within the ER (25). LLPCs counterbalance chronic ER stress through stabilized secretory architecture, coordinated lipid remodeling, and robust proteostasis mechanisms (22). Their metabolic resilience is niche-dependent: IL-6, APRIL/BAFF, and stromal-derived metabolites from $CXCL12^{+}$ perivascular cells supply essential substrates that reinforce both mitochondrial and ER homeostasis (14). Key metabolic adaptations are summarized in **table II**.

Microbiota-driven imprinting

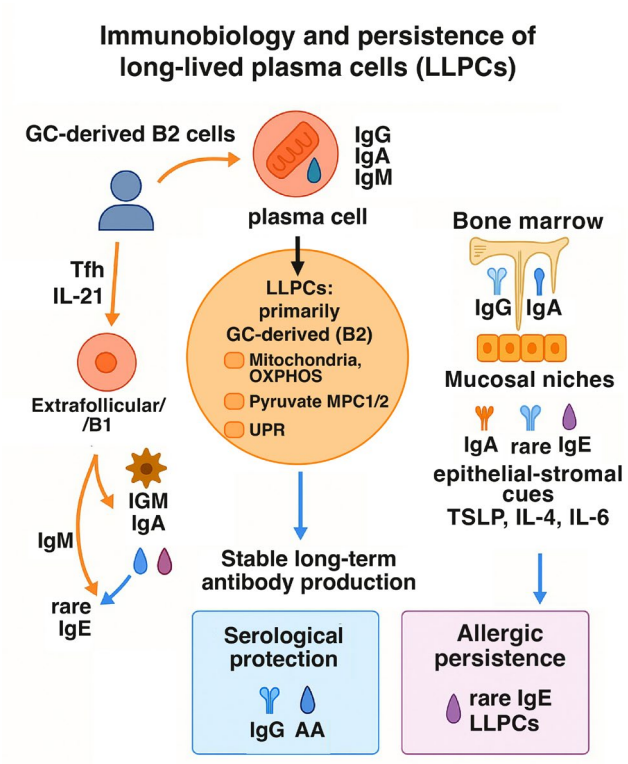
The microbiota integrates naturally into this metabolic architecture. As shown by Liu *et al.* (9), a substantial fraction of IgM LLPCs derives from T-independent, microbiota-reactive public clones, indicating that commensal signals can seed durable LLPC reservoirs. Human data from Ding *et al.* (10) show that mucosal antigenic tone shapes early plasma-cell trajectories, influencing the metabolic imprinting associated with LLPC persistence. These observations collectively position the microbiota not merely as a generator of short-lived plasmablasts but as a driver of long-term LLPC programming. Taken together, these elements outline the internal logic of LLPC persistence – an interplay between niche signals, metabolic fitness, and microbial imprinting – providing the conceptual framework illustrated in **figure 1**.

Table II *- Differentiation, maturation, and maintenance of long-lived plasma cells (LLPCs).*

Phase / Component	Principal processes	Key molecules / cells
Commitment to plasmacytic fate	B-cell activation → CSR → IRF4/Blimp-1 induction	CD40–CD40L, IL-4, IL-21, Tfh cells
Plasmablast stage	Migration, early secretion, partial metabolic rewiring	CXCR4↑, IRF4↑, XBP1↑
Niche entry	Competitive access to limited survival spaces	CXCL12, VLA-4/VCAM1, CD44
Maturation into LLPCs	Full metabolic specialization (OXPHOS, pyruvate use, UPR)	Mitochondrial fitness, GLUT1/ASCT2, ATF4/XBP1
Long-term maintenance	Anti-apoptotic signaling + nutrient support	APRIL, BAFF, IL-6; BCMA, TACI; stromal cells, eosinophils, Treg
Tissue localization	BM (primary), gut mucosa, spleen	$CXCL12^{+}$ stromal niches, mesenchymal support
Isotype-specific features	Predominantly IgG/IgA; presence of IgM LLPCs	IgE LLPCs recently identified in spleen
Fine regulation	Continuous competition; nutrient/oxygen modulation	Survival cytokines, metabolic circuits

Major cellular and molecular processes governing LLPC differentiation, maturation, and long-term survival. LLPCs: long-lived plasma cells; CSR: class-switch recombination; IRF4: interferon regulatory factor 4; Blimp-1: B lymphocyte–induced maturation protein 1; IL-4: interleukin-4; IL-21: interleukin-21; Tfh: T follicular helper cells; CXCR4: C-X-C motif chemokine receptor 4; XBP1: X-box binding protein 1; CXCL12: C-X-C motif chemokine ligand 12; VLA-4: very late antigen-4; VCAM1: vascular cell adhesion molecule 1; OXPHOS: oxidative phosphorylation; UPR: unfolded protein response; GLUT1: glucose transporter 1; ASCT2: alanine–serine–cysteine transporter 2; ATF4: activating transcription factor 4; APRIL: a proliferation-inducing ligand; BAFF: B-cell activating factor; BCMA: B-cell maturation antigen; TACI: transmembrane activator and CAML interactor; Treg: regulatory T cells; BM: bone marrow; IgG: immunoglobulin G; IgA: immunoglobulin A; IgE: immunoglobulin E.

***Figure 1** - Immunobiology and persistence of long-lived plasma cells (LLPCs).*



Long-lived plasma cells (LLPCs) arise predominantly from germinal center (GC)-derived B2 cells, with additional contributions from extrafollicular and B1 pathways. T follicular helper (Tfh) cells and interleukin-21 (IL-21) support plasma-cell differentiation. LLPC persistence depends on metabolic adaptations including mitochondrial fitness, oxidative phosphorylation (OXPHOS), pyruvate import via the mitochondrial pyruvate carriers (MPC1/2), and activation of the unfolded protein response (UPR). Bone marrow niches primarily support IgG- and IgA-secreting LLPCs, whereas mucosal niches sustain IgA and rare IgE plasma cells under epithelial-stromal cues such as thymic stromal lymphopoietin (TSLP), interleukin-4 (IL-4), and interleukin-6 (IL-6). Stable long-term antibody production underlies durable serological protection and, in specific contexts, may contribute to allergic persistence through rare IgE$^+$ LLPCs.

The immunological footprint of LLPCs

LLPCs are not static repositories of immunological memory but active regulators of long-term humoral immunity. By residing in specialized stromal niches of the bone marrow and mucosal tissues, LLPCs sustain durable IgG and IgA production long after antigen clearance, preserving serological protection for years or decades and reflecting plasma-cell differentiation pathways shaped by germinal center responses, particularly in viral infections.

During the COVID-19 pandemic, it became clear that only a fraction of SARS-CoV-2-specific plasmablasts successfully entered the long-lived marrow niche, and this selective engraftment critically determined the durability of antiviral antibody titers (29). Complementary evidence showed that vaccine-induced plasma cells inefficiently establish residency in bone-marrow LLPC compartments, explaining the limited longevity of antibody responses after some mRNA vaccinations (30). The surge of research on LLPCs during this period reflected an increased interest in understanding why some antibody responses consolidate into long-term humoral memory while others do not.

The persistence of LLPCs profoundly shapes secondary immune responses. The concept of original antigenic sin (OAS) – coined by Thomas Francis Jr. in 1960 – captures the immune system's tendency to preferentially recall memory responses generated during the first antigenic encounter. Beyond antibodies, OAS also operates through CD4$^+$ T-cell imprinting, whereby rapid activation of cross-reactive memory T cells limits naïve-cell recruitment upon exposure to antigenically drifted variants. Mechanistic work in SARS-CoV-2 infection shows that early T-cell imprinting narrows epitope targeting during variant exposure, reinforcing dominance of pre-existing responses (31). Broader immunological reviews confirm that both influenza and coronavirus immunity are strongly shaped by early exposures, influencing vaccine responsiveness and serological breadth (32, 33).

In this landscape, LLPC-derived antibodies actively contribute to immunological imprinting. Persistent titers directed against conserved epitopes modulate antigen availability, influence B-cell competition, and shape the distribution of T-cell help-mechanisms that can reinforce immune trajectories established during the initial encounter. Importantly, imprinting is not inherently restrictive: LLPC-mediated cross-reactive antibodies can mitigate disease severity upon re-exposure to related pathogens providing an early stabilizing layer of protection. Some theoretical frameworks propose that stable antibody landscapes may even limit diversification of autoreactive clones, suggesting a possible protective dimension of imprinting.

Interferons add another regulatory dimension. Type I IFNs – elevated in viral infection and chronically activated in autoimmune diseases – enhance early plasmablast differentiation and can potentiate emerging LLPC programs by amplifying IRF4- and BLIMP-1-dependent transcriptional networks (34). Chronic IFN-I exposure also remodels stromal environments in bone marrow and inflamed tissues, altering the production of APRIL, BAFF, and CXCL12 and favoring survival of autoreactive LLPCs. IFN-γ similarly supports extrafollicular antibody responses and contributes to LLPC retention in chronically inflamed tissues, linking inflammatory tone to persistent autoantibody production (34). In autoimmune conditions such as systemic lupus erythematosus and rheumatoid arthritis, autoreactive LLPCs reside in bone marrow and inflamed tissues and receive survival signals analogous to those sustaining protective LLPCs (35). Their lack of CD20 expression renders them resistant to B-cell-depleting therapies,

and their deep integration into metabolic and stromal networks makes them particularly difficult to eliminate. Although autoimmunity is not the focus of this review, it is immunologically relevant that emerging therapeutic approaches, such as anti-CD38, anti-BCMA, and modulators of APRIL/BAFF signaling, aim to selectively reduce autoreactive LLPCs while attempting to preserve protective humoral memory (34). These strategies highlight the delicate balance between maintaining durable immunity and mitigating pathogenic chronic antibody production.

LLPCs thus exert a lasting immunological footprint. They safeguard antiviral and antibacterial memory essential for survival, yet their stability can constrain adaptive flexibility or perpetuate chronic autoantibody responses. Evolution appears to have favored long-lived humoral memory because its protective advantages outweigh the trade-off in adaptability. In an era shaped by emerging pathogens, mucosal infections, and therapeutic pressures, recalibrating LLPC survival with precision represents a central immunological challenge-one that seeks to retain the evolutionary strengths of durable immunity while limiting its potentially harmful echoes (36).

IgE LLPCs and long-term allergic memory

Immunoglobulin E (IgE) occupies a uniquely specialized evolutionary niche, having emerged in mammals following divergence from the ancestral IgY approximately 220-300 million years ago (37). Retaining the four constant domains of its precursor, IgE evolved as a rigid, high-affinity effector molecule optimized for mammalian type-2 immunity, an architecture that explains both its potency and its biological constraints.

Classically, IgE has been considered incompatible with long-lived humoral memory because of its low serum concentration, rapid turnover, and the risks associated with maintaining a potent antibody effector systemically. Yet several IgE-mediated disorders – including venom allergy, persistent food allergy, and perennial aeroallergen sensitization – can persist for decades, implying the existence of a durable IgE-imprinted state that outlives the antibody itself. Early evidence supporting this possibility emerged from chronic rhinosinusitis with nasal polyps, where local IgE class switching and IgE-secreting plasma cells were demonstrated within structured inflammatory niches, consistent with long-lived plasma-cell behavior (38).

Subsequent studies strengthened this concept. Immunopathological analyses showed that CRSwNP tissues contain broad IgE repertoires and organized IgE-driven inflammatory networks, suggesting an integrated and persistent IgE–plasma cell axis (39). Together, these observations provided early mechanistic clues that chronic type-2 mucosal inflammation can sustain IgE-producing cells long term.

More recent mechanistic studies directly demonstrate that IgE-secreting plasma cells can acquire long-lived characteristics under specific microenvironmental conditions (40, 41). In chronically inflamed mucosae, tertiary lymphoid–like structures, epithelial-derived cytokines, and sustained type-2 signals (IL-4, IL-13, TSLP) enable differentiation and persistence of IgE plasma cells outside the bone marrow, establishing a noncanonical, tissue-resident LLPC niche (42). These cells display minimal proliferation, resistance to apoptosis, and stable antibody secretion, features aligned with LLPC biology even when expressed in peripheral tissues (43). These tissue-resident IgE LLPCs help explain the stability of allergic IgE imprinting, accounting for long-term allergen specificity and the difficulty in extinguishing chronic IgE responses. This inflammation-driven LLPC architecture also clarifies why anti-IgE therapy –such as omalizumab, which neutralizes circulating IgE but does not eliminate IgE-secreting plasma cells –rarely induces durable immunological reprogramming, allowing rapid IgE rebound after treatment discontinuation (37). Conversely, therapies targeting plasma-cell survival pathways may influence IgE LLPCs, although selectivity and safety remain open challenges (44). Allergen immunotherapy (AIT) appears instead to reshape the microenvironment sustaining IgE LLPCs by modifying T-cell help, attenuating epithelial alarm signaling, and promoting IgG4 competition (37, 42).

Altogether, current evidence indicates that IgE can support long-term memory through noncanonical, inflammation-driven, tissue-resident LLPC niches rather than classical bone-marrow sanctuaries. This framework resolves the long-standing paradox of a potent effector antibody capable of imprinting decades-long allergic susceptibility and identifies IgE LLPCs as a central determinant of persistent and treatment-resistant allergic disease.

Translational entry points into IgE persistence

Persistent IgE-mediated diseases often show long-term stability even when allergen exposure is minimized. This observation suggests that IgE production reflects an underlying and durable immunological organization rather than being maintained solely by recurrent allergen contact, consistent with long-standing patterns of sensitization observed across different allergic conditions. Component-resolved diagnostics (CRD) offer increasingly refined tools to characterize IgE sensitization. The Italian nsLTP consensus highlights the clinical utility of CRD in stratifying risk and guiding management (45), while recent work on *Parthenium hysterophorus* maps immunodominant epitopes and supports the development of more precise molecular approaches (46).

Severe asthma, characterized by recurrent or relapsing disease activity, provides a complementary illustration. Longitudinal biomarker trajectories from the Italian Registry on Severe Asthma (IRSA) show reproducible patterns of IgE, eosinophils and FeNO over time, even across heterogeneous treatments (47). Mechanistic studies emphasize the role of epithelial–immune crosstalk – via IL-33, IL-25 and TSLP – in maintaining type-2 readiness at mucosal barriers (48).

Some patients remain allergic even under strict avoidance, indicating that IgE persistence reflects a pre-established immunological trajectory rather than continuous allergen exposure, pointing toward deeper immunological mechanisms.

Early-life interactions between the immune system and the microbiota provide an explanatory framework for how such trajectories become fixed. Prenatal, perinatal and early postnatal life represent windows in which immune maturation is highly sensitive to environmental signals. Microbial colonization, microbial metabolites such as short-chain fatty acids, and early cytokine cues influence whether immune pathways acquire stable regulatory properties or diverge toward type-2-prone profiles (49).

A large population-based study further confirms these long-term trajectories: although most children outgrow cow's-milk allergy by school age, a substantial minority remain allergic in adulthood (50), illustrating how a subset of patients follows a lifelong IgE-stabilizing pathway.

In parallel, the biology of oral tolerance provides an additional explanatory layer. Oral tolerance is now understood as an active mucosal program involving antigen sampling, induction of FoxP3$^+$ regulatory T cells, generation of IgA responses, and continuous low-dose antigen exposure supported by microbiota-derived cues. Failure to consolidate this program during early life leaves mucosal tissues insufficiently regulated and predisposed to type-2 reactivity, helping to explain why allergic sensitization may persist even in the absence of significant allergen contact (51).

Beyond early-life imprinting and tolerance, IgE itself functions as a potent amplifier of adaptive immunity, enhancing secondary immune activation through FcεRI- and CD23-mediated pathways, modulating antigen presentation, and shaping helper T-cell polarization, processes that reinforce IgE-centric circuits (52, 53).

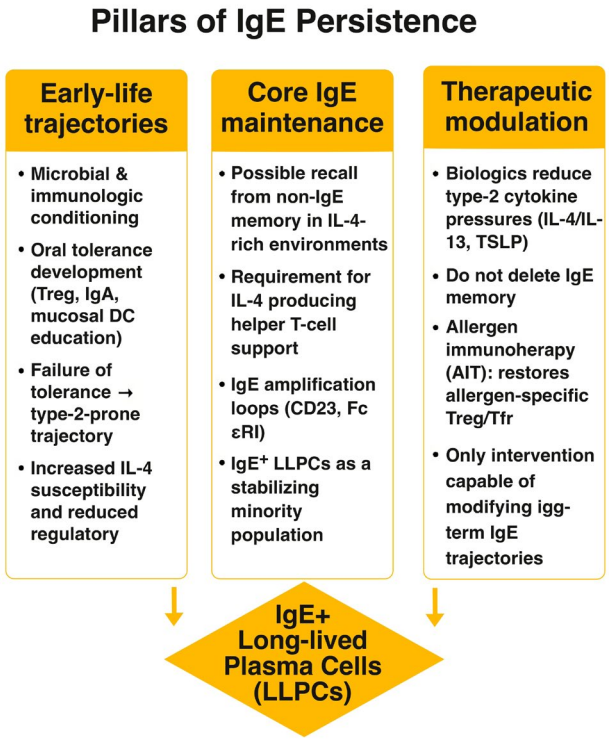
Koenig proposes that the persistence of allergen-specific IgE arises from the convergence of several complementary processes. These include the absence of a true IgE memory compartment; recall responses generated from non-IgE memory B cells capable of IL-4-dependent secondary switching; the indispensable role of IL-4-producing helper T cells; and the possibility of minimal or cross-reactive exposures sustaining recall machinery.

Within this conceptual framework, IgE persistence could reflect the contribution of recall-supporting circuits, alongside additional mechanisms that may include the long-term survival of IgE-secreting cells (54).

Within this broader landscape, LLPCs provide an additional explanatory dimension. IgE-expressing LLPCs have been identified in human bone marrow (55), suggesting that in some contexts a fraction of IgE production may become partially independent of ongoing exposure. Additional support comes from LLPC-like behavior in extramedullary tissues such as the spleen (27). Although their quantitative impact remains uncertain, LLPCs could provide one stabilizing component of IgE persistence.

Tissue environments help stabilize these circuits. At mucosal sites, epithelial-derived cytokines such as TSLP, IL-33 and IL-25 can license dendritic cells and lower the threshold for re-engaging type-2 immunity (48). In contrast, bone-marrow niches enriched in CXCL12, APRIL and BAFF support plasma-cell survival, offering a permissive environment for persistent antibody production. These complementary niches – mucosal for reactivation, marrow for persistence – illustrate how long-term IgE stability can emerge from distributed but interacting immunological sites.

Figure 2 *- Long-term IgE persistence.*



Long-term IgE persistence emerges from the convergence of early-life immune trajectories, core IgE maintenance mechanisms, and therapeutic modulation. Early-life conditioning includes microbial and immunological imprinting and the development of oral tolerance mediated by regulatory T cells (Treg), immunoglobulin A (IgA), and mucosal dendritic cells (DCs). Core IgE maintenance involves recall from non-IgE memory B cells in interleukin-4 (IL-4)-rich environments, dependence on IL-4-producing helper T cells, and amplification loops mediated by the low-affinity IgE receptor CD23 and the high-affinity receptor FcεRI. Therapeutic interventions such as biologics reduce type-2 cytokine pressure but do not delete IgE memory, whereas allergen immunotherapy (AIT) promotes allergen-specific regulatory T cells (Treg) and T follicular regulatory cells (Tfr). Within this framework, IgE$^+$ long-lived plasma cells (LLPCs) represent a rare, niche-supported population that may contribute to stabilization of IgE responses.

This framework also clarifies why certain interventions can modify long-term IgE trajectories. Allergen immunotherapy (AIT) promotes allergen-specific Treg responses, enhances IL-10 and TGF-β, and redirects class switching toward IgG4. Long-term studies indicate that these changes can persist after treatment discontinuation. Biologic therapies targeting IL-4Rα or TSLP attenuate key cytokine nodes in type-2 inflammation and may synergize with AIT. Combined strategies have shown encouraging results in severe asthma (56-58).

Within this framework, **figure 2** provides a visual synthesis of how LLPC persistence emerges from the interplay between niche-derived cues, immune signaling, and antigenic imprinting, highlighting key convergence points for therapeutic intervention.

Concluding remarks

LLPCs have moved from being viewed as terminal survivors to active, adaptive participants in immune memory. Rather than static remnants, they integrate transcriptional programs, metabolic demands, and niche-derived cues to maintain antibody production across years or decades. Their persistence is not a fixed attribute but a continuous exchange with their environment.

This duality lies at the center of their paradox.

The same biology that preserves life-long protection against pathogens may also sustain persistent IgE responses in allergic diseases. In this sense, persistence is neither inherently beneficial nor harmful; it reflects the accumulated history of signals that shape LLPC fate over time: some adaptive, others maladaptive in contemporary settings.

Emerging methods, from single-cell transcriptomics to spatial imaging and metabolic tracing, reveal that LLPCs form not a uniform category but a spectrum of states, each defined by its niche and its past. Long-term immunity therefore appears less as a static endpoint and more as a dynamic equilibrium between survival cues, regulatory forces, and antigenic experience.

Future therapies could succeed not by erasing persistence, but by redirecting it, preserving the durable memory that protects us while attenuating the circuits that sustain IgE-mediated disease. Guiding this equilibrium, rather than dismantling it, may represent the next step toward restoring tolerance.

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Contributions

AMP contributed entirely to this work.

Conflict of interests

The author declares that she has no conflict of interests.

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ORIGINAL ARTICLE

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Guilherme Azizi, Sérgio Dortas Jr, Alfeu França, José Elabras, Omar Lupi, Solange Valle

Provocation test on stairs: a new accessible method to cholinergic urticaria diagnosis – Azizi-Valle Test

Immunology Service, Hospital Universitário Clementino Fraga Filho (HUCFF-UFRJ), Rio de Janeiro, Brazil

Key words

Cholinergic urticaria; chronic inducible urticaria; provocation test.

Corresponding author
Guilherme Azizi
Immunology Service
Hospital Universitário Clementino Fraga Filho (HUCFF-UFRJ)
Rua Rodolpho Paulo Rocco 255, Ilha do Fundão
Rio de Janeiro (RJ), Brazil 21941-590
ORCID: 0000-0002-4772-1599
E-mail: gazizi247@gmail.com

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Impact statement

This study aims to publicize the presentation of a new diagnostic technique with low technological and safe input, seeking to assist diagnosis outside reference centers and in developing countries.

Summary

Background. *Cholinergic urticaria (CholU) is characterized by itching and/or stinging, painful micro wheals due to systemic heating. There are two standardized protocols to diagnose CholU using an exercise bike with heart rate or warming passive. The objective of the study is to provide an affordable, new, low-tech test to assist the diagnostic.* ***Methods.*** *Cross-sectional study with a convenience sample: 10 with a diagnostic or high suspicion of CholU and 20 participants without suspicion of CholU, recruited in a UCARE from a developing country. After the pre-participation assessment, the provocation test through movements of going up and down a flight of stairs and with a heart rate monitor, an increasing 15 bpm every 5 min until an increase of 90 bpm above the initial level, for 30 min and/or stopped immediately, upon visualization of wheals and with body temperature measured in 3 different locations every 5 min.* ***Results.*** *The group CholU comprised eight females and two males (29.6 y), and the other group had eleven females and nine males (27.2 y). Data analysis demonstrated that in a positive test in a body temperature measured above 37.05 °C and with a variation of 0.35 °C above the initial value, sensitivity of 80% and specificity of 100% in the forehead region and sensitivity of 80% and specificity of 90% in tympanic region.* ***Conclusions.*** *Thus, with the feasibility of reproducing the method, it is expected that this simple and accessible method for diagnosing CholU can be a tool for application, mainly in developing countries.*

Introduction

Urticaria is characterized by the appearance of wheals, angioedema, or both. Chronic urticaria (≥ 6 weeks) can occur spontaneously (chronic spontaneous urticaria) or be motivated by specific stimulation (chronic inducible urticaria - CIndU), which is reported through provocation tests (1).

Cholinergic urticaria (CholU) is a subtype of CIndU with sweat in its genesis and occurs due to systemic heating (2, 3). CholU is characterized by itching and/or stinging, painful papular wheals (1-3 mm) that develop simultaneously with sweating, related to increased body temperature from physical exercise, hot baths, stress, spicy foods or hot drinks; symptoms generally disappear within 1 hour, and these sensations are highly impacted to disturb the quality of life (4). CholU has its incidence and prevalence predominantly between the second and third decades of life (5, 6). There is consensus that an increase in body temperature above 1 °C from baseline, as indicated by a passive warming test while sitting for ≤ 15 min in a 42 °C water bath, confirms the diagnosis of CholU (10). A standardized protocol was proposed to diagnose CholU using an exercise bike with heart rate and temperature control. The patient positions himself on the exercise bike and begins pedaling, being instructed so that the pulse increases by 15 bpm every 5 min, reaching 90 bpm above the basal level after 30 min (14). The time for urticaria to appear is inversely proportional to the intensity of the disease; therefore, the shorter the time for the lesions to occur, the more severe CholU is considered (7-14).

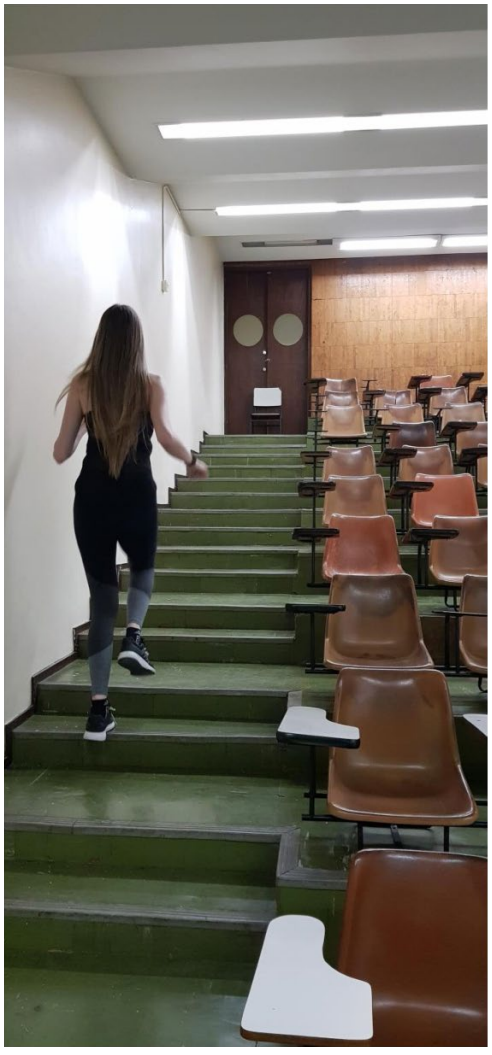
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In this way, the site team of this study asked if it would be possible to provide a simple, affordable, low-tech test with statistically reliable indices to assist specialists and primary care diagnoses, especially in environments outside reference centers and in developing countries.

Materials and methods

Cross-sectional intervention study with a convenience sample, in which 30 participants were divided into two groups: 10 with a diagnostic and/or high clinical suspicion of CholU and twenty participants without clinical suspicion of CholU and with other CIndU, who were recruited from the Urticaria Centers of Reference and Excellence (UCARE) Immunology Service outpatient clinic in a developing (Human Development Index - HDI = 0.76) and tropical country. All were between 12-65 years old, both sexes and with body mass index (BMI) in the range 18.5-30 kg/m^2.

Figure 1 *- Provocation test to CholU on stairs.*



The exclusion criteria were to avoid corticosteroids for 15 days, antihistamines for 7 days, or anti-IgE therapies for 6 months before the test. They should not regularly use immunosuppressive therapy, have a comorbidity that makes it impossible to practice physical activity, have been suspected of exercise-induced anaphylaxis, or have skin comorbidities that could make it impossible to assess the body surface. The patient should not have performed physical exercise in the last 24 hours before the test or ingested stimulant medications.

On the previous visit, the participant underwent a complete clinical examination, electrocardiogram, and Physical Activity Readiness Questionnaire (PAR-Q) to avoid unfavorable outcomes and increase safety in the test. On the second day (7 to 15 days after the first visit), the participants underwent the CholU provocation test on stairs. The acclimatization time was 20 min, during which the participant underwent temperature measurement in 3 sites (forehead, oral and tympanic) using a digital infrared thermometer. The provocation test was carried out in a room or auditorium with a controlled ambient temperature of 20-23 °C by moving up and down a flight of stairs (13 steps) with a slow. It gradually increased initial speed through the evaluator's commands, aiming to obtain an increase of 15 bpm every 5 min until a rise of 90 bpm above the initial level, for 30 min. A heart rate monitor (Polar F11®) was adapted to the patient's chest using a chest strap suitable for the instrument and to the wrist using a watch-type marker (**figure 1**).

The provocation test was stopped immediately, regardless of the period elapsed, upon visualization of pruritic wheals associated with erythema characteristic of CholU. Body temperature was measured in 3 different locations every 5 min with interruptions that did not exceed 10 seconds. In addition, a small amount of starch and iodine was placed on the individual's dorsal region to analyze the positivity regarding the appearance of sweat during the diagnostic test. The ambient temperature (°C) and relative humidity (%) were measured.

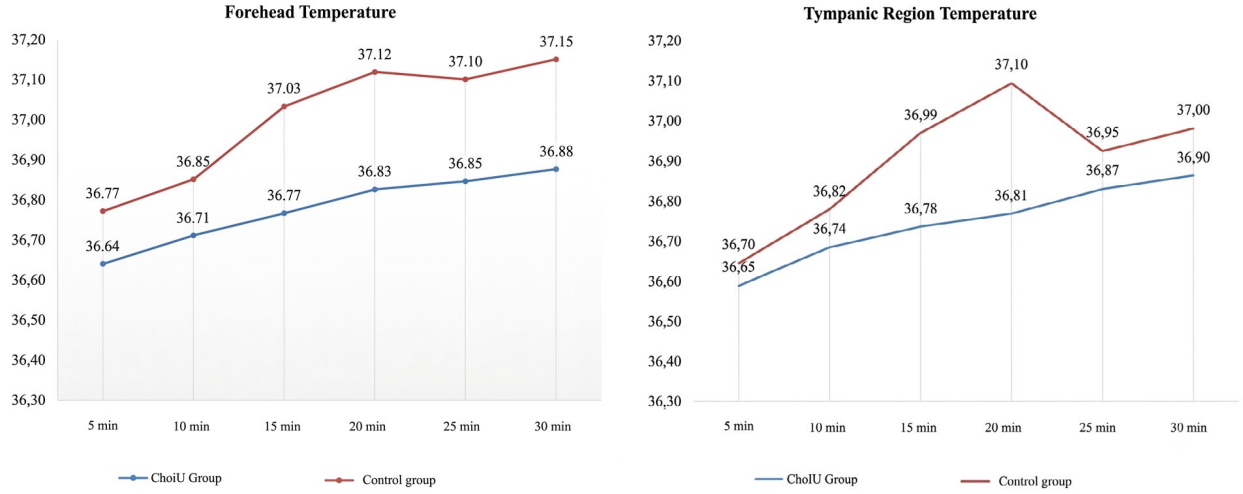
The research (CAAE 57071122.6.0000.5257) was approved by the local ethics committee on August 4, 2022, after being submitted for consideration by CEP/HUCFF-UFRJ (C.E.P. number: 5.562.556.). The participants signed the informed consents.

Results

The sample from the group CholU was composed of eight female and two male participants, with an average age of 29.6 years (18-55 y) and an average BMI of 23.5 kg/m² (20.2-28.8 kg/m²). Proportionally, the control group had eleven female and nine male participants, with an average age of 27.25 years (19-52 y) and an average BMI of 24.2 kg/m² (21.4-29.2y).

All patients presented a reactive starch-iodine test during physical activity, demonstrating sweat associated with the test. Among

Figure 2 *- Average temperature variations between both groups.*



the control group, 14 individuals were observed with dermographism, four with cold urticaria, one with vibratory urticaria and another with solar urticaria. All tests were conducted at a controlled temperature between 20 °C and 23 °C, with an average relative humidity of 66% (58%-72%).

The final temperatures among the subjects and sites were: final oral temperature of the group with CholU (average 37.1 °C, standard deviation = 0.277) *vs* participants without CholU (average 36.85 °C, standard deviation 0.161); P-value = 0.013. The forehead temperature in the study group with CholU (average 37.17 °C, standard deviation = 0.295) *vs* control group (average 36.88 °C, standard deviation = 0.159); P-value = 0.001. The tympanic temperature in the study group with CholU (average 37.14 °C, standard deviation 0.26) *vs* control group (average 36.9 °C, standard deviation = 0.13); P-value = 0.002. All patients with positive provocation tests showed an increase of 0.5 °C compared to basal temperature (**figure 2**).

Data analysis demonstrated that in a positive CholU provocation test, presenting clinical characteristics compatible with the disease, in a temperature measured in the forehead region above 37.05 °C and with a variation of 0.35 °C above the initial temperature value, sensitivity is 80% and specificity is 100%. The probability of obtaining a positive result for CholU, considering the variation in the forehead temperature and variation in this temperature at the end of the exam if the person has the disease, is 80%. In contrast, the probability of obtaining a negative result for CholU, considering the variation in forehead temperature and this temperature at the end of the exam if the person does not have the disease, is 100%. The positive predictive value (100%) and negative predictive value (90%) depend on the specificity and sensitivity and the prevalence of the disease in the population investigated.

A positive provocation test for CholU, presenting compatible clinical characteristics, at a temperature measured close to the tympanic region above 37.05 °C and with a variation of 0.35 °C above the initial temperature value, sensitivity is 80% and specificity of 90%. The positive predictive value (80%) and negative predictive value (90%) depend on the specificity and sensitivity and the prevalence of the disease in the population investigated. The oral temperature did not present statistically relevant values. However, it showed an increase in temperature like the other sites and above the control group (**figures 3, 4**).

Discussion and conclusions

This study looked for a simple, affordable, low-tech test that could help diagnose CholU, especially in environments outside reference centers and in developing countries. This technique is a new method controlled by a frequency meter and performed on stairs, which proved to be objective and reproducible for the diagnosis of CholU. As in other tests proposed in the literature, all CholU patients showed characteristic signs and symptoms but not in healthy controls (4, 14).

The method's sensitivity and specificity assessment presented robust values, mainly using two temperature measurement sites (forehead region and tympanic region). The values exceeded 80% sensitivity and 90% specificity, validating the method and providing reliability for its implementation in daily practice. However, measuring temperature in the oral region did not present statistically robust values, but the increase in temperature above the values of the control group was noticeable.

The method proved reproducible and bearable for the sample, as there were no interruptions during the test due to fatigue. However, going up and down stairs also presents itself as a limitation

Figure 3 *- Flowchart to diagnostic cholinergic urticaria through provocation testo on stairs.*

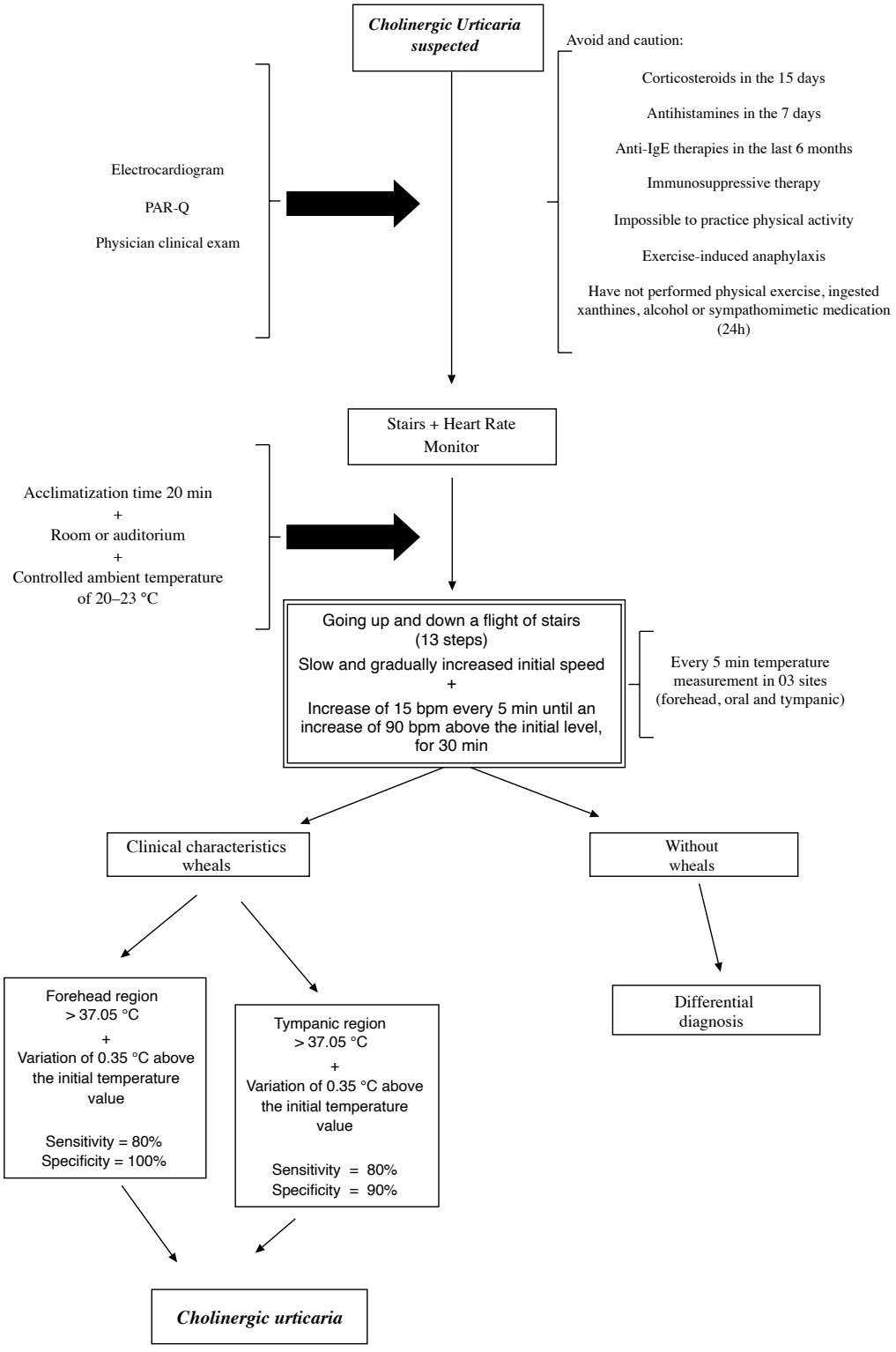
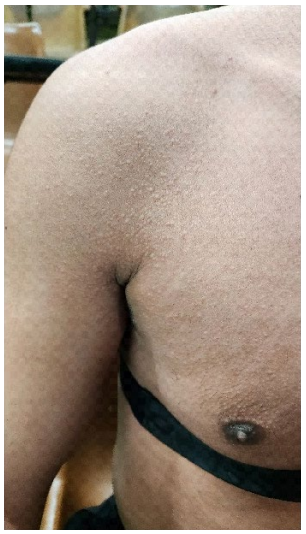


Figure 4 *- Cholinergic urticaria during provocation testo on stairs.*



of the method, as patients suspected of CholU with risks inherent to the practice of physical activity or musculoskeletal limitations cannot perform the provocation test.

The average onset of signs and symptoms characteristic of CholU occurred at 19.5 minutes (10-30 min). In this study, the correlation within the studied sample – between the moment of onset of the characteristic manifestations of CholU and severity – was not evaluated. These parameters were assessed in another study (14) and demonstrated an inversely proportional correlation between the speed at which lesions appear and the severity of the disease.

The temperature of the provocation test environment was artificially controlled and varied between 20 °C and 23 °C. However, it is not possible to control only the relative air humidity; therefore, the partial results showed an average relative air humidity of 66% (58%-72%), characteristic of a tropical region with high rainfall levels such as Rio de Janeiro.

Many studies present a progressive increase in body temperature reaching 1°C as a direct correlation with the appearance of pruritic micropapular lesions associated with intense erythema in patients with CholU (4, 14). However, the sample evaluated and presented in partial results demonstrated lower values as an average variation above 0.5 °C between the initial and final temperatures.

Thus, the results demonstrate the feasibility of reproducing the method and its consistency with the clinical findings characteristic of the disease. Therefore, it is expected that this simple and accessible method for diagnosing CholU can be a tool for application, mainly in developing countries, regions with difficulty obtaining high technological support, and the Public Health System. Therefore, it will assist in diagnosing a condition that is extremely harmful to the quality of life of the affected individual.

Fundings

None.

Contributions

GA: formal analysis, investigation, methodology, project administration, writing – original draft, resources, software, supervision, validation. SDJ, JE: formal analysis, investigation, methodology. AF, OL, SV: writing – original draft, investigation, methodology. GA, SV: data curation, writing - review & editing.

Conflict of interests

SDJ declares lecture fees from AstraZeneca Brazil and G.S.K. Brazil. SDJ and SV declare lecture fees from Novartis Brazil. SV declared lecture fees from Takeda, Brazil. GA and AF have no conflicts of interest to declare. OL declares fees from Sanofi Brazil. JE declares lecture fees from Sanofi Brazil, G.S.K. Brazil and AstraZeneca Brazil.

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ORIGINAL ARTICLE

Eur Ann Allergy Clin Immunol Vol 58, N.5, 210-217, 2026

Laura Franceschini[1], Donatella Bignardi[2], Maria Beatrice Bilò[3,4], Francesca Buzzulini[5], Gabriele Cortellini[6], Domenico Gargano[7], Elena Pinter[8], Roberto Battista Polillo[9], Danilo Villalta[5], Alessandro Farsi[1] and AAIITO study group on Eosinophilic Esophagitis

Multicenter survey on eosinophilic esophagitis in Italy: trends in diagnosis, diagnostic delay, and type 2 comorbidity burden

[1]SOSD Allergy and Immunology, Prato-Pistoia, Italy
[2]Allergology Unit, IRCCS San Martino Polyclinic Hospital, Genoa, Italy
[3]Allergy Unit, Department of Internal Medicine, University Hospital delle Marche, Ancona, Italy
[4]Department of Clinical and Molecular Sciences, Marche Polytechnic University, Ancona, Italy
[5]Immunology and Allergy Unit, S. Maria degli Angeli Hospital, Pordenone, Italy
[6]SSI Allergology Romagna Health Authority, Rimini Hospital, Rimini, Italy
[7]Allergy Unit, Azienda Ospedaliera S. Giuseppe Moscati, Avellino, Italy
[8]Clinic Immunology Unit, Policlinico Umberto I, Rome, Italy
[9]Allergologist, BIOS Spa, Rome, Italy

Key words

Eosinophilic esophagitis; type 2 comorbidity; allergic comorbidities; type 2 inflammation; diagnostic delay.

Corresponding author
Alessandro Farsi
Allergy and Clinical Immunology, Prato-Pistoia
USL Toscana Centro
Santo Stefano Hospital
via Suor Niccolina Infermiera 20/22
59100 Prato, Italy
ORCID: 0000-0001-6036-9094
E-mail: alessandro.farsi@uslcentro.toscana.it

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Impact statement

This multicenter Italian study highlights frequent and often multiple type 2 comorbidities in eosinophilic esophagitis, with relevant comorbidity burden, persistent diagnostic delays, and rising diagnoses, emphasizing early, coordinated, multidisciplinary care.

Summary

Background. *Eosinophilic esophagitis (EoE) is a chronic, immune-mediated esophageal disorder that has been increasingly recognized over recent decades. It is characterized by a type 2 inflammatory response, shared with other type 2 inflammatory conditions such as allergic rhinitis (AR), food allergy (FA), atopic dermatitis (AD), bronchial asthma (BA), and chronic rhinosinusitis with nasal polyps (CRSwNP). This study aimed to assess the diagnostic trends in EoE over time and evaluate the burden of type 2 comorbidities in a multicenter cohort of Italian patients.* ***Methods.*** *A total of 295 patients with EoE, followed at seven Italian allergy centers with expertise in managing EoE, were included. We analyzed annual EoE diagnoses, diagnostic delay, and the presence of type 2 comorbidities – including AR, FA, BA, AD and CRSwNP – assessed via allergological evaluations at the participating centers. Statistical analyses included non-parametric trend tests, linear and logistic regressions, chi-square tests, and descriptive analyses.* ***Results.*** *Annual EoE diagnoses showed a significant upward trend from 2014 to 2024 ($p = 0.002$). However, the diagnostic delay remained consistently high, showing no corresponding reduction despite the rise in diagnoses. The burden of type 2 comorbidities was substantial, with 83.4% of patients presenting at least one comorbidity, and most patients exhibited multiple comorbidities.* ***Conclusions.*** *Our findings are consistent with previously reported increases in EoE diagnoses in Italy, alongside persistent diagnostic delays, and highlight the substantial burden of type 2 comorbidities in these patients, emphasizing the importance of systematic allergological evaluation and multidisciplinary managementin patients with EoE.*

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Introduction

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated disorder of the esophagus, characterized by eosinophilic infiltration and tissue remodeling (1). Over the past few decades, EoE recognition has increased markedly worldwide, with incidence and prevalence rising steadily, positioning it as one of the leading causes of esophageal dysfunction, particularly among young adults (2-3).

Despite this growing recognition, diagnostic delay remains significant, underscoring the persistent challenges in achieving timely diagnosis and early intervention (4).

In the pathogenesis of EoE, the interplay of genetic predispositions, environmental factors, including food antigens, and pathogenic microorganisms critically influence maintenance of epithelial barrier integrity. Genetic studies have revealed that epithelial-derived genes such as calpain 14 and TSLP are dysregulated in EoE. This dysregulation leads to epithelial barrier impairment, partly due to the loss of desmoglein 1 expression (5).

Barrier disorders induce type 2 immunity, and the imbalanced immune response further exacerbates epithelial damage, leading to a chronic vicious cycle. The manifestation of type 2 inflammatory disease varies according to the specific organs and tissues affected. In response to epithelial barrier damage, epithelial-derived cytokines (for example, thymic stromal lymphopoietin (TSLP), interleukin (IL)-25, IL-33) initiate the type 2 inflammatory cascade by activating tissue-resident immune cells (such as mast cells, dendritic cells and group 2 innate lymphoid cells (ILC2)), and recruiting eosinophils and basophils. These cells induce the production of type 2 cytokines (IL-4, IL-13, and IL-5), histamine, and other mediators such as TGF-β and eotaxin (6-8). Mast cells (MCs) are also increased in EoE, although their contribution to disease pathogenesis remains to be fully elucidated (9).

Type 2 inflammation is characterized by overexpression and increased activity of type 2-associated cytokines including IL-4, IL-5, IL-13, and IL-31 and alarmins including IL-25, IL-33, and thymic stromal lymphopoietin (TSLP). The overactivation of the type 2 inflammatory pathway in the skin, airway, and gastrointestinal tract leads to a spectrum of diseases, including allergic rhinitis (AR), bronchial asthma (BA), atopic dermatitis (AD), food allergy (FA) and chronic rhinosinusitis with nasal polyps (CRSwNP) (10).

Patients frequently present with one or more of these comorbidities, reflecting the systemic nature of type 2 immune responses; their presence may influence both clinical management and therapeutic strategies. Accordingly, dupilumab – a monoclonal antibody blocking IL-4/IL-13 signaling via IL-4Rα inhibition – was approved for EoE (11) after it had already been widely used for other type 2-mediated disorders, including AD, BA and CRSwNP. Its efficacy across multiple type 2-mediated diseases underscores the clinical relevance of identifying type 2 comorbidities in EoE, as these may inform therapeutic decisions and support an integrated, personalized approach to management (12).

Given the complexity of EoE and its frequent overlap with other type 2 inflammatory conditions, effective management of EoE requires a multidisciplinary, coordinated approach involving allergists, gastroenterologists, pathologists, dietitians, and psychologists. Such an approach is needed not only for accurate diagnosis but also for long-term follow-up. Allergists, in particular, play a central role in identifying type 2 comorbidities and guiding patients through the appropriate management strategies (13).

Although the increase in EoE diagnoses and the persistence of diagnostic delays described in previous studies, comprehensive country-specific data in Italy remain limited. Understanding the local diagnostic trends and the burden of type 2 comorbidities is essential to optimize patient care and support a precision-medicine approach.

Building on these premises, the aim of this study was to examine temporal trends in EoE diagnoses and diagnostic delays, and to characterize the burden of type 2 comorbidities in affected patients, within the broader context of type 2 inflammatory conditions and their management. Specifically, we aimed to 1) evaluate changes in annual diagnosis rates and diagnostic delays over the past decade, and 2) delineate the prevalence and patterns of coexisting type 2 inflammatory conditions, including AR, BA, AD, FA, and CRSwNP.

Materials and methods

Study design and setting

We conducted a retrospective, multicenter, observational survey using clinician-completed structured questionnaires to characterize demographic and diagnostic characteristics, as well as type 2 comorbidity profiles, in patients with EoE. All data were systematically collected at seven Italian allergy centers with established experience in managing EoE, distributed across northern, central, and southern Italy, providing a comprehensive national overview (SOD Allergy and Clinical Immunology, Prato-Pistoia, Tuscany; Allergology Unit, IRCCS San Martino Polyclinic Hospital, Genoa; Allergy Unit, Department of Internal Medicine, University Hospital of Marche, Ancona; Department of Clinical and Molecular Sciences, Marche Polytechnic University, Ancona; Immunology and Allergy Unit, S. Maria degli Angeli Hospital, Pordenone; SSI Allergology Romagna Health Authority, Rimini Hospital, Rimini; Allergy Unit, Azienda Ospedaliera S. Giuseppe Moscati, Avellino; Clinic Immunology Unit, Policlinico Umberto I, Rome; BIOS Spa, Rome).

The survey instrument was specifically developed for this investigation, based on clinical expertise, and underwent internal review to ensure clarity, relevance, and consistency of all items.

Data for each patient were retrospectively extracted from medical records by participating clinicians and entered into the stan-

dardized questionnaire. No interventions were performed, and clinical management was not modified; only anonymized patient information was collected and used for analysis. Each center had access only to its own submissions, while the research team analyzed anonymized, aggregated data, ensuring data confidentiality and centralized evaluation.

Participants

Patients were eligible if they had a confirmed diagnosis of EoE according to established diagnostic guidelines (1). EoE diagnosis was performed at the corrispomding gastroeneterology centers and the istopathology was evaluated locally. Clinicians retrospectively entered data for consecutive eligible patients, ensuring a non-selective sample. Data were anonymized at the study entry.

Survey instrument

A structured questionnaire was developed to collect standardized clinical information on patients with EoE referred to participating Allergy Centers. Item generation was based on clinical expertise and focused on demographic, diagnostic, and type 2 comorbidity characteristics. The study team performed a secondary quality review before analysis.

The survey captured the following analyzable items:

1. Demographic and diagnostic variables: patient sex, age at diagnosis, year of diagnosis, and diagnostic delay. Data on diagnostic delays were obtained during medical history taking at allergological centers.
2. Type 2 comorbidity burden: allergological evaluation at the participating centers for the presence of type 2 comorbidities, including AD, AR, BA, FA, and CRSwNP.

Type 2 comorbidity status was systematically evaluated at these centers using standardized immunoallergological assessments, with all comorbidities defined according to current reference criteria (14-17). Following EAACI guidelines (18), food sensitization and FA (with clinically relevant reactions) were distinguished. FA was classified according to clinical manifestations, including oral allergy syndrome, cutaneous reactions such as urticaria or angioedema, and anaphylaxis of other degrees (19). For practical purposes, we grouped all these conditions together under the umbrella term "food allergy (FA)" in our analyses.

Statistical analysis

Items with incomplete or non-interpretable responses were excluded from the analysis.

Continuous variables were summarized as mean ± standard deviation (SD) or median and interquartile range (IQR), depending on distributional characteristics. Categorical variables were reported as counts and percentages.

Temporal trends in annual EoE diagnoses were evaluated for the 2014-2024 period using the Mann-Kendall non-parametric test for trend assessment, with Sen's slope quantifying the average annual change. Linear regression was also performed to confirm the trend; the limited number of annual time points may affect the stability of trend estimates.

Diagnostic delay was categorized into five intervals: ≤ 1 year, 1-2 years, 3-6 years, 7-10 years, and > 10 years. For the 2014-2024 period, delays were further aggregated into short (≤ 2 years), medium-long (3-10 years), and very long (> 10 years) groups to facilitate trend analysis. Due to the retrospective design, diagnostic delay could only be assessed among patients who received a confirmed diagnosis; cases with recent symptom onset but not yet diagnosed were not captured, limiting the maximal observable delay for recent diagnosis years.

Associations between categorical variables, including type 2 comorbidities, were explored using Chi-square tests. When expected cell counts were < 5, Fisher's exact test was used instead.

Three separate univariate logistic regression models were fitted with year of diagnosis as the independent variable to assess temporal trends in each diagnostic delay category. Odds ratios (OR), 95% confidence intervals (CI), and P-values are reported. Sensitivity analyses including age and sex as additional covariates were performed and yielded comparable results; therefore, the main analyses focus solely on year of diagnosis.

Descriptive analyses were performed to characterize type 2 comorbidity burden, prevalence, and co-occurrence patterns, as well as previous specialist evaluations and seasonal changes in clinical manifestations. Associations with sex were explored where appropriate, with categorical variables compared using chi-square tests.

A two-sided P-value < 0.05 was considered statistically significant.

Ethical approval

The study was approved by the local ethics board (approval no. 26258_OSS). All procedures adhered to the Declaration of Helsinki and applicable local regulations.

Results

Demographic data, trends in diagnosis and diagnostic delay

A total of 295 patients were included in the analysis (**table I**). The cohort comprised 233 males (79.0%) and 62 females (21.0%). The median age at diagnosis was 36.0 years (IQR 23.0-47.5; range: 5-84 years), with a mean of 36.4 ± 15.4 years. The age distribution supported the use of median and IQR as robust measures of central tendency and spread.

The year of diagnosis ranged from 2000 to 2024. Annual counts of diagnoses increased over time, with 20 cases recorded before 2014 and a peak of 47 diagnoses in 2023. To evaluate trends, we focused on a 10-year period from 2014 to 2024. Mann-Kendall non-parametric analysis revealed a significant upward trend in new diagnoses over this period ($S = 41.0$, $Z = 3.11$, $p = 0.002$) and Sen's slope estimated an average annual increase of 4.17

Table I *- Demographic, clinical and diagnostic characteristics in EoE patients.*

Characteristic	n (%) or value
Age, years	
Median (IQR)	36.0 (23.0–47.5)
Mean ± SD	36.4 ± 15.4
Range	5–84
Skewness	0.49
Sex	
Male	233 (79.0%)
Female	62 (21.0%)
Number of diagnoses	
Before 2014	20 (6.8%)
2014-2019	67 (22.7%)
2020-2024	196 (66.4%)
2025	12 (4.1%)
Diagnostic delay	
<1 year	61 (20.7%)
1–2 years	62 (21.0%)
3–6 years	75 (25.4%)
7–10 years	30 (10.2%)
>10 years	67 (22.7%)
Diagnostic pathway	
Another specialist before diagnosis	108 (36.6%)
Seasonality	
No effect	244 (82.7%)
Consistent with inhalant sensitization	29 (9.8%)
Seasonal change	22 (7.5%)
Presence of type 2 comorbidity	
Yes	246 (83.4%)
No	49 (16.6%)

Table II *- Trends in diagnostic delay over the 2014–2024 period.*

Diagnostic delay group	OR (95%CI)	P-value
≤2 years	0.93 (0.85–1.03)	0.155
3–10 years	0.99 (0.90–1.09)	0.877
>10 years	1.12 (0.99–1.26)	0.067

OR: odds ratio for year; 95%CI: confidence interval of the OR.

cases. Linear regression confirmed this trend (slope = 4.36/year, $p < 0.001$) (**figure 1**).

Diagnostic delay varied widely across the cohort. Only 20.7% of patients were diagnosed within the first year, whereas more than one in five patients (22.7%) experienced a delay exceeding 10 years. The remaining patients had intermediate delays.

To assess whether the increase in diagnoses over the past decade was accompanied by earlier recognition, diagnostic delay categories were aggregated into three groups for analysis over the 2014-2024 period: short (≤ 2 years), medium-long (3-10 years), and very long (> 10 years). No significant temporal changes were observed in any of the delay groups (all $p > 0.05$) (**table II**, **figure 2**). Sensitivity analyses including age and sex as covariates confirmed the robustness of the temporal trends. A modest association of male sex with very long diagnostic delay (> 10 years) was observed; however, this is likely a chance finding given the small number of patients in this subgroup and the multiple comparisons performed.

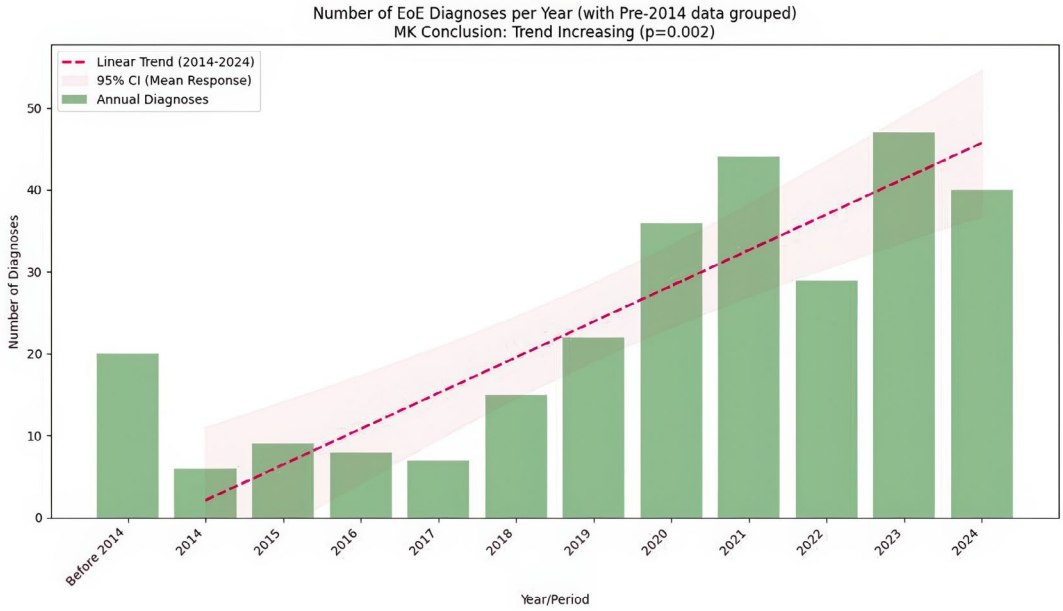
Type 2 comorbidity burden

Type 2 comorbidities were highly prevalent in this cohort, with 246 patients (83.4%) presenting at least one such condition, whereas only 49 (16.6%) had none (**figure 3A**).

Among patients with ≥ 1 type 2 comorbidity, AR was most prevalent (n = 226, 91.9%), followed by FA (n = 129, 52.4%). The FA group included both patients with IgE sensitization (n = 47, 36.4%) and those with clinically confirmed FA (n = 82, 63.6%). Among patients with clinically relevant manifestations, the most frequent was oral allergy syndrome (n = 43, 52.4%), followed by anaphylaxis (n = 21, 25.6%) and urticaria/angioedema (n = 18, 22.0%). Among the other type 2 conditions, BA occurred in 73 patients (29.7%), AD in 38 (15.5%), and CRSwNP in 5 (2.0%). Approximately one-third of patients (n=85, 34.6%) had a single type 2 comorbidity, most frequently AR. Most patients presented with multiple comorbidities (n = 161, 54.7%): 109 (44.3%) with two, 40 (16.3%) with three, and 12 (4.9%) with four. The mean number of type 2 comorbidities per patient was 1.91, and 65.4% of patients exhibited multiple type 2 comorbidities (≥ 2). Among patients with multiple type 2 comorbidities, several patterns were more evident. The most frequent combinations included AR with FA (n = 72, 29.3%), and AR with BA (n = 29, 11.8%); the most frequent triad was AR with BA and FA (n = 16, 6.5%). CRSwNP and AD occurred only in the presence of other comorbidities: BA and AR were most frequently associated with CRSwNP, whereas AR, BA, or FA were most common with AD (**table III**, **figure 3B**).

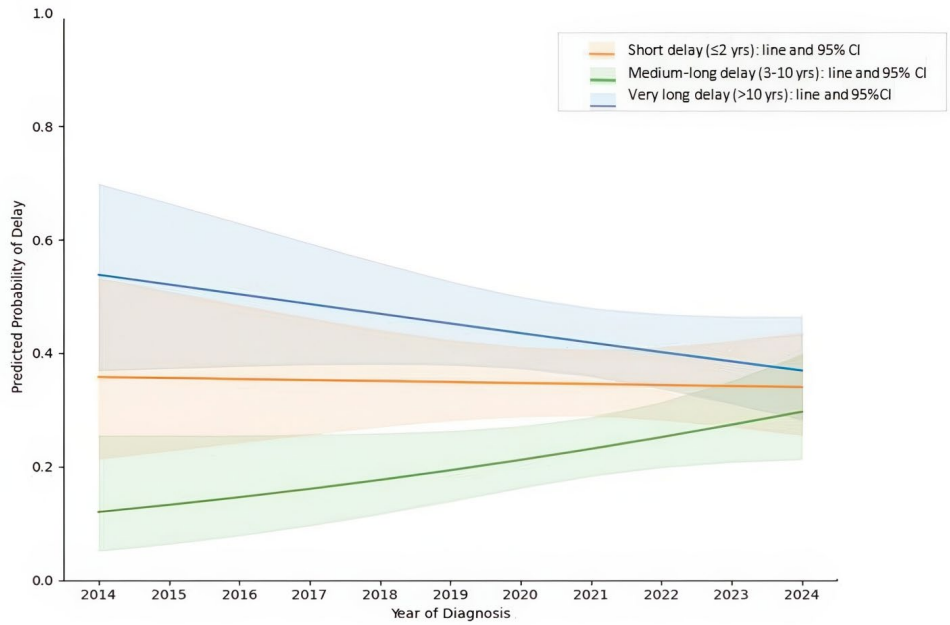
No significant sex differences were observed in the number or pattern of comorbidities ($\chi^2 = 8.70$, df = 12, $p = 0.728$). Finally, to explore whether the presence of at least one type 2 comorbidity influenced diagnostic delay across the three categories described above, a Chi-square test was performed, and no significant association was observed ($\chi^2 = 3.30$; df = 2; $p = 0.192$).

Figure 1 *- Annual distribution of eosinophilic esophagitis diagnoses and linear trend from 2014 to 2024.*



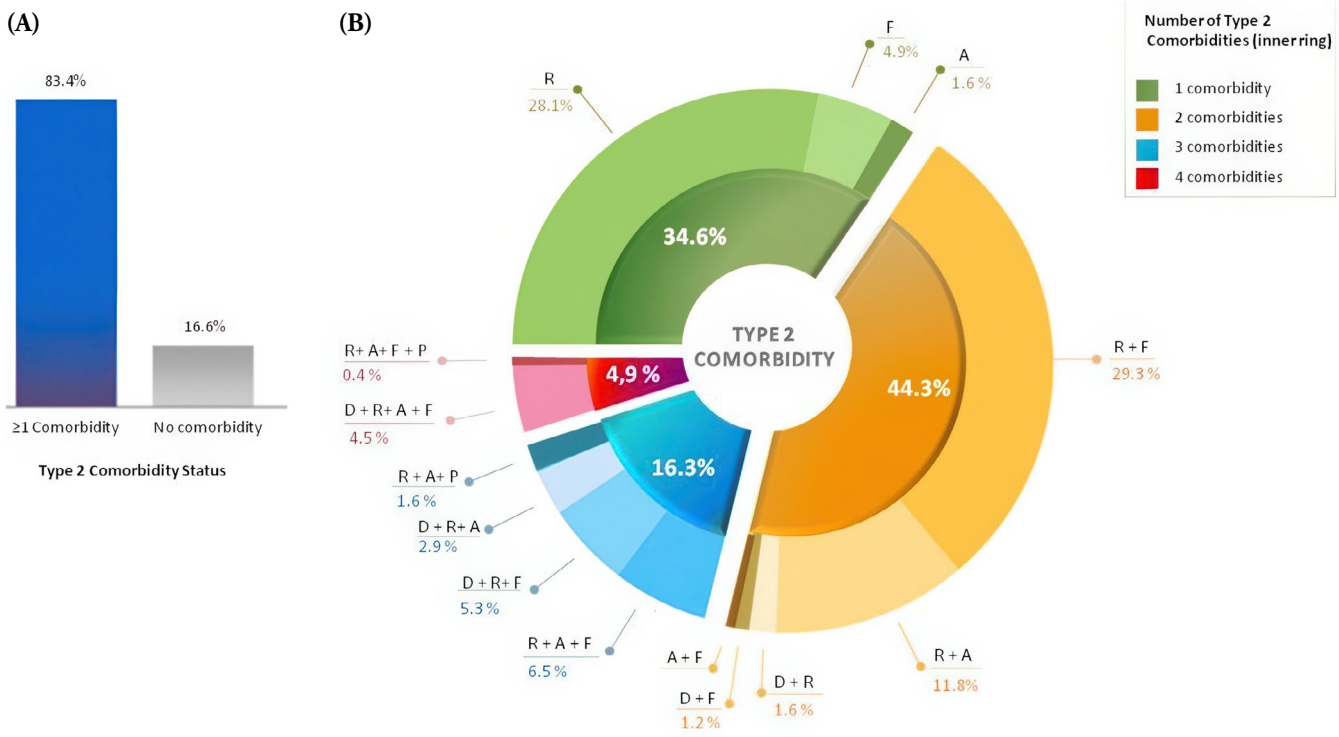
Bars represent the number of new EoE diagnoses per year, with all diagnoses recorded before 2014 aggregated into a single "Before 2014" category. The dashed line shows the linear trend in annual diagnoses from 2014 to 2024, and the shaded area represents the 95% confidence interval (CI) for the mean predicted values of this trend.

Figure 2 *- Trends in predicted probabilities of diagnostic delay across groups (2014–2024).*



Predicted probabilities of diagnostic delay are shown for three aggregated groups: short delay (≤ 2years), medium-long delay (3-10 years), and very long delay (> 10 years). Lines represent predicted probabilities from multiple logistic regression models for each group over the years 2014 to 2024, with shaded areas indicating 95% confidence intervals (CIs).

Figure 3 *- Distribution of Type 2 comorbidity and comorbidity burden.*



(A) Proportion of patients with and without type 2 comorbidities in the study cohort (n = 295); **(B)** Distribution of individual type 2 comorbidities and their combinations among patients with ≥ 1 type 2 comorbidity. The inner ring represents comorbidity burden, categorized according to the presence of one, two, three, or four comorbidities. The outer ring displays specific comorbidity combinations with corresponding prevalence. Comorbidities are displayed using single-letter abbreviations for figure clarity and correspond to the two-letter abbreviations used throughout the text: R: allergic rhinitis (AR); F: food allergy, including food sensitization (FA); A: bronchial asthma (BA); D: atopic dermatitis (AD); P: chronic rhinosinusitis with nasal polyps (CRSwNP).

Additional observations

Additional observations regarding the diagnostic pathway and symptom patterns, which involve allergist expertise and supplement the analysis of type 2 comorbidities, were recorded.

A substantial proportion of patients (n = 108, 36.6%) underwent at least one additional specialist evaluation (gastroenterology, allergy, or pediatrics) prior to the correct diagnosis of EoE, reflecting the complexity of symptom attribution. Seasonal variation in symptom severity was uncommon: most patients (n = 244, 82.7%) reported no seasonal influence on symptoms, whereas a minority described patterns consistent with inhalant sensitization (n = 29, 9.8%) or seasonal symptom fluctuations related to seasonal transitions (n = 22, 7.5%).

These findings, although secondary, illustrate other aspects of EoE that particularly engage allergist expertise: seasonal symptom patterns are best evaluated in an allergological context, whereas prior specialist consultations highlight the challenges in achieving timely recognition of EoE.

Discussion and conclusions

In this retrospective multicenter study of seven Italian allergy referral centers specialized in EoE management, we observed a substantial increase in diagnoses over recent years, consistent with previous reports. To our knowledge, this study represents one of the largest multicenter cohorts of EoE patients evaluated in allergy referral centers in Italy and provides a detailed characterization of the burden and patterns of type 2 comorbidities in this population.

This rapid rise, making EoE one of the most common causes of dysphagia, likely reflects a combination of factors, including greater awareness among healthcare providers, broader use of endoscopic techniques, and updated diagnostic criteria (2018), which now include proton-pump inhibitor-responsive EoE within the disease spectrum (20). On the other hand, the long-standing increase in type 2 allergic diseases – including AR, BA, and FA – may provide context for the rising EoE incidence.

Despite improved recognition, diagnostic delay remains substantial, with over 20% of patients experiencing delays exceeding 10 years. This delay is likely multifactorial and may reflect patient coping strategies (*e.g.*, avoiding specific foods, drinking liquids with meals, eating slowly) and empirical proton pump inhibitor therapy, both of which can minimize symptoms, particularly in the absence of major bolus impaction.

Additionally, reliance on invasive diagnostic procedures requiring esophageal biopsies, the lack of reliable non-invasive biomarkers, and the need for differential diagnosis with other conditions, such as gastroesophageal reflux and FA, further complicate early recognition.

In our cohort, a notable proportion of patients (36.6%) underwent at least one specialist evaluation (allergist, gastroenterologist, or pediatrician) before receiving the diagnosis. Interestingly, the presence of at least one type 2 comorbidity was not associated with earlier detection of EoE.

Beyond diagnostic delay, the overall complexity of EoE management is further compounded by the potential coexistence of type 2 comorbidities, with which EoE shares common type 2-mediated inflammatory pathways. In our cohort, 83.4% of patients had at least one comorbidity, approximately two-thirds (65.5%) had ≥ 2, and 21.2% had ≥ 3 concomitant type 2 conditions. The presence of multiple type 2 comorbidities highlights the need for multidisciplinary management and may influence therapeutic decision-making.

These findings highlight the need for a systematic assessment of type 2 comorbidities in patients with EoE, as their coexistence may influence disease burden, multidisciplinary management, and therapeutic decision-making.

Given the frequent coexistence of multiple type 2 comorbidities, biologic therapies targeting key drivers of type 2 inflammation may play a particularly relevant role in EoE. Dupilumab, which specifically inhibits the IL-4/IL-13 axis, is now approved for EoE and is also widely used in other type 2-mediated diseases, including AD, BA, and CRSwNP. The integration of biologic therapies into EoE management may benefit from a comprehensive assessment of each patient's type 2 comorbidity profile, supporting a precision-medicine approach.

Several limitations should be acknowledged. First, the retrospective design relies on medical records and clinician-completed questionnaires, which may introduce incomplete or missing data. Second, patients with comorbidities may have been preferentially referred to these centers, potentially leading to an overestimation of comorbidity prevalence. However, this bias is likely limited given the well-established association with EoE. In addition, in the participating centers, allergological evaluation was likely requested in all patients with confirmed EoE, regardless of previous suspicion of allergic disease.

Finally, as an observational study, our findings describe associations but cannot establish causality. Future prospective studies are needed to clarify how the burden of type 2 comorbidities influences long-term outcomes and therapeutic strategies in patients with EoE.

In conclusion, the frequent coexistence of type 2 comorbidities further amplifies the complexity of managing EoE, highlighting the need for a coordinated, multidisciplinary approach. Within

Table III *- Distribution of type 2 comorbidities among patients with ≥1 comorbidity (n = 246) in patients with EoE.*

Type 2 comorbidities	n	%
Number of type 2 comorbidities/combination		
1 comorbidity	85	34.6%
AR	69	28.1%
FA	12	4.9%
BA	4	1.6%
2 comorbidities	109	44.3%
AR + FA	72	29.3%
AR + BA	29	11.8%
AD +AR	4	1.6%
AD + FA	3	1.2%
BA + FA	1	0.4%
3 comorbidities	40	16.3%
AR + BA + FA	16	6.5%
AD + AR + FA	13	5.3%
AD + AR + BA	7	2.9%
AR + BA + CRSwNP	4	1.6%
4 comorbidities	12	4.9%
AD + AR + BA + FA	11	4.5%
AR + BA + FA + CRSwNP	1	0.4%
Prevalence of individual type 2 comorbidity		
AR	226	91.9%
FA	129	52.4%
Food sensitization	47	36.4%
Food allergy	82	63.6%
with oral allergy syndrome	43	52.4%
with urticaria/angioedema	18	22.0%
with anaphylaxis (of other degree)	21	25.6%
BA	73	29.7%
AD	38	15.5%
CRSwNP	5	2.0%

Percentages may not total 100% due to rounding. AR: allergic rhinitis; FA: food allergy, including food sensitization; BA: bronchial asthma; AD: atopic dermatitis; CRSwNP: chronic rhinosinusitis with nasal polyps.

this framework, allergists play a central role throughout the continuum of care: in the pre-diagnostic phase, they facilitate early recognition and guide patients through appropriate diagnostic pathways; post-diagnosis, they contribute to detailed phenotyping and collaborate closely with other specialists to support the integration of biologic therapies into personalized treatment strategies. In addition, they work alongside nutritionists to develop targeted elimination diets in patients with concomitant food allergies.

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None.

Contributions

LF, AF: conceptualization, data curation, formal analysis, writing – original draft, writing – review & editing, supervision, validation. DB, MBB, FB, GC, DG, EP, RBP, DV: supervision, validation, writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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ORIGINAL ARTICLE

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Marko Barešić[1], Boris Karanović[1], Ljerka Čulav[2], Dijana Perković[3], Jasminka Milas-Ahić[4], Srđan Novak[5], Željka Kardum[4,6], Ana Marija Masle[4], Daniel Victor Šimac[5], Marijana Matijaš[3], Branimir Anić[1]

Prevalence, clinical characteristics and the burden of disease of the Croatian adult patients with HAE: nationwide survey analysis

[1]Division of Clinical Immunology and Rheumatology, Department of Internal Medicine, University of Zagreb, School of Medicine, University Hospital Center Zagreb, Zagreb, Croatia
[2]Department of Otorhinolaryngology, Šibenik General Hospital, Šibenik, Croatia
[3]Division of Rheumatology, Allergology and Clinical Immunology, Department of Internal Medicine, University of Split, School of Medicine, University Hospital Center Split, Split, Croatia
[4]Division of Rheumatology, Clinical Immunology and Allergology, Department of Internal Medicine, University of Osijek, School of Medicine, University Hospital Center Osijek, Osijek, Croatia
[5]Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, University of Rijeka, School of Medicine, University Hospital Center Rijeka, Rijeka, Croatia
[6]Department of Internal Medicine, General Hospital Zadar, Zadar, Croatia

Key words

Hereditary angioedema types I and II; surveys and questionnaires; patient reported outcome measures; prevalence; epidemiology.

Corresponding author
Boris Karanović
Division of Clinical Immunology and Rheumatology,
Department of Internal Medicine
University of Zagreb
School of Medicine
University Hospital Center Zagreb
Kišpatićeva 12, Zagreb, Croatia
ORCID: 0000-0002-5884-1190
E-mail: boris.karanovic@gmail.com

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Impact statement

This study offers valuable real-world insights into the epidemiological, demographic, and clinical features of Croatian HAE patients, thereby enhancing the limited existing data on HAE from Croatia and Southeast Europe.

Summary

Background. *Hereditary angioedema (HAE) is a rare genetic disorder with variable prevalence, characterized by recurrent swelling in various parts of the body, including potential laryngeal attacks, significantly affecting patients' quality of life.* ***Methods.*** *A nationwide, cross-sectional survey study was conducted between December 2023 and June 2024, targeting adults (aged 18 and older) in partnership with the HAE Hrvatska patient organization. The patients filled out different HAE-related questionnaires. Descriptive statistics were used to analyze and summarize the data.* ***Results.*** *The prevalence of HAE in Croatia is estimated to be 3.10 per 100,000 people. The majority were females, patients with positive family history, and type 1 HAE. The median diagnostic delay was 13 years, with initial attacks typically occurring in adolescence, but diagnosis was often not established until young to middle adulthood. Regarding quality of life, approximately 51% reported a significant impact. Fatigue was prevalent, with 46.9% of patients experiencing mild to moderate levels, and 22.4% suffering from severe fatigue. Most patients reported minimal depression, and 37.7% presented with moderate to severe anxiety. Among employed individuals, a median presenteeism of 20% indicated productivity loss while at work, in contrast to generally minimal absenteeism.* ***Conclusions.*** *Recent more substantial diagnostic efforts and increased awareness are contributing factors to the higher observed prevalence of HAE in Croatia, mainly due to the sustained work of a dedicated patient organization and a well-developed network of national HAE experts. Patients still experience a high disease burden, impaired quality of life, and difficulties with daily activities, which trends are also observed in other HAE cohorts worldwide.*

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Introduction

Hereditary angioedema (HAE) is an orphan disease characterized by recurrent swelling episodes, primarily linked to C1 inhibitor (C1-INH) deficiency or dysfunction resulting in excessive bradykinin production (1). HAE follows an autosomal dominant inheritance pattern, often affecting multiple members within the same family. The two most common forms, HAE types 1 and 2, account for approximately 90% of cases and are caused by mutations in the SERPING1 gene, which encodes the C1-INH protein. Nevertheless, approximately 20% of patients are diagnosed with *de novo* mutations (2). The most infrequent form is HAE with normal C1-INH levels (HAE-nC1-INH), which is linked to mutations in F12, PLG, ANGPT1, KNG1, MYOF, HS3ST6 and recently described genes CPN1 and DAB2IP (3). As with many other rare diseases, the precise global prevalence of HAE is unclear, and reported estimates vary, typically ranging from 1:50,000 to 1:150,000 according to different epidemiological studies (4, 5). It is plausible that the observed variability in the reported prevalence of HAE is significantly influenced by differences in diagnostic resources and clinical awareness of medical professionals across regions, potentially contributing to both underestimation and occasional misclassification of cases (6). Founder effects, consanguinity and isolated gene pools can lead to higher frequencies of specific variants, as observed for mutations in F12, PLG and other genes (7). Beyond healthcare providers, non-medical subjects like patient advocacy groups and patient organizations are also instrumental in gathering essential data concerning individuals with HAE and their caregivers.

HAE is characterized by a high and multifaceted burden on patients, their families, and healthcare systems. This burden extends far beyond the physical symptoms of the attacks themselves (8). Patient-reported outcome measures (PROMs) are standardized, validated questionnaires that serve as tools that directly capture a patient's perception of their own health status, experiences, and burden of disease. PROMs can be generic and measure broad aspects of health-related quality of life that are applicable to a wide range of conditions and populations, and condition-specific, designed to measure outcomes relevant to a particular disease (9). Over time, angioedema and HAE-specific PROMs (HAE-PROMs) have been developed and put into use to monitor and manage patients with HAE (10). Most commonly used PROMs include: Angioedema Control Test (AECT) (11), Angioedema Activity Score (AAS) (12), Angioedema Quality of Life Questionnaire (AE-QoL) (13), Hereditary Angioedema Activity Score (HAE-AS) (14), and Hereditary Angioedema Quality of Life (HAE-QoL) (15). PROMs are valuable clinical tools for follow-up and can be of aid in the comprehensive assessment of patients, ultimately helping to develop improved therapeutic strategies. Due to intellectual property rights and the complexities of translation and cultural validation, not all HAE-specific PROMs are universally available or widely adopted in routine clinical practice outside of research settings, emphasizing the need for improved implementation strategies (10).

While data on HAE in Croatia appear limited, several significant medical publications have emerged over time. Notably, these include the national guidelines for the diagnosis and treatment of HAE, published in 2014 (16), and a 2019 national study that specifically identified Croatian pediatric HAE patients (17). In our current study, we are reporting results from a nationwide survey analysis conducted by Croatian HAE experts, aimed at elucidating up-to-date epidemiological data (primarily prevalence) and the comprehensive disease burden experienced by adult patients (18 years and older). The study did not include pediatric patients, as the PROMs used were not suitable and standardized for this age group's ability to self-report. The survey's data collection was performed before the first-line long-term prophylactic (LTP) treatments, lanadelumab and berotralstat, received regulatory approval and reimbursement in Croatia.

Materials and methods

Population of Croatia

The population of Croatia is 3,871,833, as reported by the official Croatian Bureau of Statistics and the 2021 census (18), which positions the country among the smaller ones of the 27 EU member countries by population. Point prevalence was used to determine the proportion of individuals with HAE since this epidemiological measure captures both new and existing cases, and is typically expressed as 1:100,000 inhabitants.

Patients with HAE

In our study cohort, all patients presented with typical recurrent angioedema. Patients with mast cell-mediated and medication-induced angioedema were excluded. Those with HAE types 1 and 2 exhibited low C4 and low functional C1-INH (with low/normal antigenic C1-INH levels), while patients with HAE-nC1-INH had normal C1-INH levels. Most HAE type 1 and 2 patients had a confirmed SERPING1 mutation. Among patients presenting with HAE-nC1-INH, none of the individuals analyzed demonstrated a known non-SERPING1 mutation, some of them being negative for all known non-SERPING1 mutations, while others haven't been tested yet due to objective technical limitations. Therefore, a subset of our cohort remained genetically uncharacterized. As a result, they were collectively classified as HAE with unknown mutation (HAE-UNK). No patients with acquired angioedema were included although in everyday clinical practice we actively search for such patients by C1q testing. Croatian HAE patients receive diagnosis, treatment, and follow-up care at their respective regional medical centers, as centralization into a single medical center is not obligatory. A significant number of Croatian individuals

affected by HAE, together with their caregivers, are affiliated with HAE Hrvatska, the Croatian patient organization, which is a constituent of the broader global non-profit organization, HAE International.

A cross-sectional, observational patient survey was conducted by leading Croatian HAE experts in partnership with HAE Hrvatska, from December 2023 to June 2024. This survey exclusively included adult patients (aged 18 years or older), who voluntarily completed the face-to-face survey after providing their written informed consent for participation. In a single point of time, the patients anonymously provided their demographics, general data about HAE history and treatment and filled out different questionnaires. In the study we used both angioedema and HAE specific questionnaires such as AECT and AE-QoL, in addition to standardized generic questionnaires not exclusively associated to HAE such as FACIT-FATIGUE, EQ-5D-5L, WPAI:GH, Beck's Depression and Anxiety Inventory (12, 13, 19-23). To facilitate participation, patients had the option to complete the surveys during their follow-up appointments or at home, submitting them afterwards or sending them to their treating physician. The survey targeted all adult HAE patients in Croatia. However, participation was limited to those who were members of the HAE Hrvatska organization or were in active follow-up at their hospital centers. A total of fifty-seven adult patients voluntarily completed the questionnaire.

Sufficient data security measures have been implemented. Subsequent processing and the application of descriptive statistics were carried out using Microsoft Office Excel. The study was approved by the Ethics committee of University Hospital Centre Zagreb, Zagreb, Croatia (approval number: 8.1-24/86-2; 02/013 AG) and was carried out according to the principles of the Declaration of Helsinki. Informed consent was obtained from the patients included in the survey.

Results

Fifty-seven Croatian HAE patients took part in the study. The median age of the participants was 47, with half of the individuals falling between 36 and 54 years old, and their ages spanning from 19 to 78. Most patients were female (40; 70.2%), living in urban areas (44; 77.2%), and having a secondary level of education (41; 71.9%). Thirty-seven (64.9%) were diagnosed with HAE type 1, 8 (14%) with HAE type 2, and 12 (21%) with HAE-nC1-INH with unknown non-SERPING1 mutation (HAE-UNK). A positive family history was present in 44 (77.2%) of the patients, with a median of one child (range: 0-8) per patient. The median patient's age at their first HAE attack was 15 years (IQR 10-23; range: 1-47), while the median age at diagnosis was 26 years (IQR 19-39; range: 3-60). This indicates a median diagnostic delay of 13 years (IQR 6-20), with a range from 5 years before the first symptom to 43 years after the initial swelling. The most common localization of the first HAE symptom was the extremities, affecting 25 participants (43.9%), followed by face in 16 participants (28.1%), and abdomen in 14 participants (24.6%). Larynx was the first symptom localization for 2 participants (3.5%), while 7 participants (12.3%) experienced their first symptoms in other locations. It is worth noting that the percentages sum to more than 100%, indicating that some participants experienced their first symptoms in more than one localization. The most common localizations of HAE attacks were the extremities (33; 57.9%) and abdomen (30; 52.6%), followed by the face (19; 33.3%), larynx (12; 21.1%), and tongue (5; 8.8%). Again, some participants experienced their most common symptoms in multiple localizations. Stress was the most frequently reported trigger, affecting 37 participants (67.3%) followed by physical injury and menstrual cycle in 23 participants (40.4%) and 17 participants (29.8%), respectively. Medication was identified as a trigger in 5 participants (8.8%). Notably, 9 participants (15.8%) reported no specific trigger. Some participants identified more than one trigger for their HAE attacks. The median number of HAE attacks during the 3 months prior to participation was 2, with an IQR of 1-6 and a total range of none to 70 attacks. For ODT, most patients used icatibant (31; 54.4%) and intravenous C1-INH concentrates (21, 36.8%). Regarding the current LTP, it is essential to clarify that the study was conducted before the introduction of first-line LTP with lanadelumab and berotralstat in Croatia. Twenty-six patients (45.6%) were not treated by any LTP medication, while 19 patients (33.3%) were using danazol. For those on danazol, the median dose was 150 mg daily (IQR: 100-275 mg), with a range of 50-600 mg. Additionally, tranexamic acid and intravenous C1-INH concentrates were used in 5 (8.8%) and 12 patients (21.1%), respectively. In some patients, more than one drug was used concurrently. Baseline demographic characteristics, clinical features, and treatment data are shown in **table I**.

AECT was used for assessing disease control, indicating poorly controlled disease with a median in both 4 week and 3-month AECT measuring 8, ranging from 1 to 16, IQR 5-15 for 4-week AECT and 0 to 16, IQR 5-12 for a median 3 month AECT, respectively. According to AE-QoL, 28 patients (51.0%) reported significant effect, 19 patients (34.5%) experienced no effect, and 8 patients (14.5%) reported a small to moderate impact on their quality of life.

When analyzing FACIT-fatigue, 15 patients (30.6%) reported very little to no fatigue, 23 patients (46.9%) experienced mild to moderate levels of fatigue, and 11 patients (22.4%) reported severe fatigue. Anxiety testing (BAI) reported 17 patients (32.1%) with minimal anxiety, 16 patients (30.2%) with mild anxiety, 6 patients (11.3%) with moderate anxiety and 14 patients (26.4%) severe anxiety. Depression testing (BDI) revealed minimal depression in 38 patients (76.0%), mild depression in seven patients (14.0%), moderate depression in four patients (8.0%), and severe depression in 1 patient (2.0%). Nineteen (33.9%) patients were

Table I *- Baseline demographic characteristics, clinical features and treatment of the Croatian HAE patients.*

Variable		Value
Gender	Male, n (%)	17 (29.8)
	Female, n (%)	40 (70.2)
Age	Median (IQR), (range)	47 (36-54),(19-78)
Place or residence	Rural, n (%)	13 (22.8)
	Urban, n (%)	44 (77.2)
Level of education	Primary education, n (%)	0
	Secondary education, n (%)	41 (71.9)
	Tertiary Education, n (%)	16 (28.1)
HAE type	HAE type 1, n (%)	37 (64.9)
	HAE type 2, n (%)	8 (14.0)
	HAE-nC1-INH (HAE-UNK), n (%)	12 (21.0)
Positive family history of HAE, n (%)		44 (77.2)
Number of children, median (IQR), (range)		1 (0-2),(0-8)
Age at the first attack in years, median (IQR), (range)		15 (10-23),(1-47)
Age at diagnosis in years, median (IQR), (range)		26 (19-39),(3-60)
Delay in diagnosis in years, median (IQR), (range)		13 (6-20),(-5-43)
Localization of the first symptoms of HAE	Extremities, n (%)	25 (43.9)
	Face, n (%)	16 (28.1)
	Abdomen, n (%)	14 (24.6)
	Larynx, n (%)	2 (3.5)
	Other, n (%)	7 (12.3)
Most common localization of HAE attacks	Extremities, n (%)	33 (57.9)
	Face, n (%)	19 (33.3)
	Abdomen, n (%)	30 (52.6)
	Tongue, n (%)	5 (8.8)
	Larynx, n (%)	12 (21.1)
Triggers of HAE attack	None, n (%)	9 (15.8)
	Stress, n (%)	37 (67.3)
	Menstrual cycle, n (%)	17 (29.8)
	Physical injury, n (%)	23 (40.4)
	Medication, n (%)	5 (8.8)
Number of HAE attacks during the past 3 months	Median (IQR), (range)	2 (1-6),(0-70)
Current ODT	Icatibant, n (%)	31 (54.4)
	C1-INH (pd + r), n (%)	21 (36.8)
Current LTP	None, n (%)	26 (45.6)
	Danazol, n (%)	19 (33.3)
	Danazol dose (mg), median (IQR), (range)	150 (100-275),(50-600)
	Tranexamic acid, n (%)	5 (8.8)
	C1-INH (pd + r), n (%)	12 (21.1)

HAE: Hereditary angioedema; IQR: Interquartile range; ODT: On-demand treatment; LTP: Long-term prophylaxis; C1-INH: C1-inhibitor; HAE-UNK: HAE with unknown mutation; HAE-nC1-INH: HAE with normal C1-INH levels.

Table II *- Patient reported outcome measures (PROMs) of the Croatian HAE patients.*

Variable		Value
AECT 4 week, median (IQR), (range)		8 (5-15),(1-16)
AECT 3 month, median (IQR), (range)		8 (5-12),(0-16)
AE-QoL	No effect on QoL, n (%)	19 (34.5)
	Small to moderate effect on QoL, n (%)	8 (14.5)
	Large effect on QoL, n (%)	28 (51.0)
FACIT-Fatigue	None or minimal fatigue: >40, n (%)	15 (30.6)
	Mild to moderate fatigue: >21 to ≤40, n (%)	23 (46.9)
	Severe fatigue: ≤21, n (%)	11 (22.4)
The Beck Anxiety Inventory (BAI)	Minimal anxiety (0-7), n (%)	17 (32.1)
	Mild anxiety (8-15), n (%)	16 (30.2)
	Moderate anxiety (16-25), n (%)	6 (11.3)
	Severe anxiety (26-63), n (%)	14 (26.4)
The Beck Depression Inventory (BDI)	Minimal depression (0-13), n (%)	38 (76.0)
	Mild depression (14-19), n (%)	7 (14.0)
	Moderate depression (20-28), n (%)	4 (8.0)
	Severe depression (29-63), n (%)	1 (2.0)
WPAI:GH	Worker / Employee, n (%)	19 (33.9)
	Absenteeism (%), median (IQR), (range)	0 (0-8),(0-100)
	Presenteeism (%), median (IQR), (range)	20 (0-50),(0-100)

AECT: Angioedema Control Test; IQR: Interquartile range; AE-QoL: Angioedema Quality of Life Questionnaire; FACIT: Functional Assessment of Chronic Illness Therapy; WPAI:GH: Work Productivity and Activity Impairment Questionnaire: General Health.

employed with median absenteeism of 0%, and median presenteeism of 20%.

Results of the Croatian HAE patients PROMs are presented in **table II**.

The health status, based on the EQ-5D-5L domains, is presented as follows: for mobility, nearly half of the respondents (49.1%) reported no problems, while 29.1% experienced slight problems. Moderate, severe, and extreme problems accounted for 9.1%, 9.1%, and 3.6% respectively. In self-care, an overwhelming majority (83.6%) reported no problems, with only small percentages experiencing slight (7.3%), moderate (7.3%), or severe (1.8%) problems.

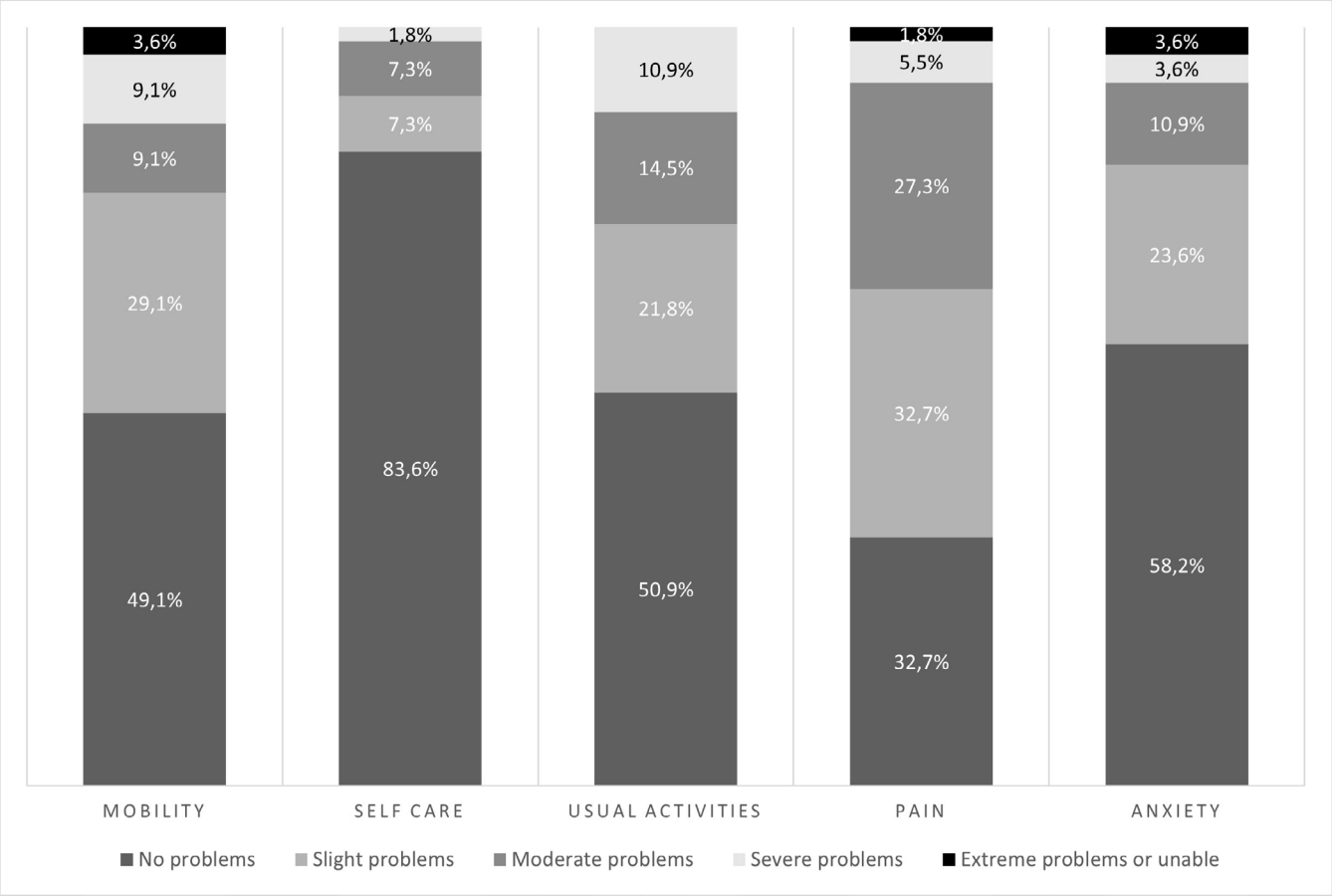
Usual activities show a more varied distribution. While 50.9% reported no problems, 21.8% had slight problems, 14.5% faced moderate problems, and 10.9% experienced severe problems. Pain is a significant issue, with only 32.7% reporting no problems. A nearly equal proportion (32.7%) experienced slight pain, while 27.3% reported moderate pain. Severe pain was reported by 5.5% and extreme pain by 1.8%. Finally, for anxiety, 58.2% reported no problems, suggesting that a majority do not experience significant anxiety. However, a considerable portion did report some anxiety: 23.6% with slight problems, 10.9% with moderate problems, and 3.6% with severe problems. Extreme anxiety or being unable was reported by 3.6%, indicating that anxiety affects a notable segment of the population.

Results of assessment of participants' health status according to EQ-5D-5L is shown in **figure 1**.

Regarding patient perception of treatment success, the median satisfaction level is 9 out of 10, with an interquartile range (IQR) of 7-10 and a full range of 1-10. This suggests that while there's a broad spectrum of experiences, the majority of patients are highly satisfied with their treatment outcomes.

Patients' most frequently reported concern (50.9% of patients) is the fear of passing HAE to their children. This is followed by fear of failure to meet business responsibilities (42.1%) and neglecting social activities (35.1%). Fear of dying due to an HAE attack is a concern for 33.3% of patients, while a small percentage (15.8%) reported no concerns or fears. This highlights the significant impact HAE has on patients' personal, professional, and family lives.

Figure 1 *- Results of assessment of participants' health status according to EQ-5D-5L.*



In terms of suggestions for improving medical care, the overwhelming majority of patients (72.2%) emphasized the need for improved education and training of healthcare professionals. This indicates a perceived gap in the knowledge and skills of medical staff regarding HAE. Additionally, a substantial portion (46.3%) suggested improved education of the general population, which could potentially lead to greater awareness, understanding, and support for individuals with HAE. A smaller percentage (14.8%) recommended improved communication with their leading physician.

Patients' subjective personal perspectives and perceptions of HAE are summarized in **table III**.

While specifying the exact number of HAE patients in Croatia is challenging, we utilized data that, to the best of the authors knowledge, is reliable and relevant. The Croatian patient organization HAE Hrvatska, the solely and the most important patient advocacy group in Croatia, reported 120 individuals with HAE, holding the up-to-date register of members/patients known to be associated with the organization. Among them, 98 are adults (aged 18 or older) and 22 are minors (aged 18 or younger). The majority of these individuals receive regular follow-up care at their regional medical centers.

The data provided by HAE Hrvatska offers the most accurate and consistent representation of real-world figures. Taking these estimates into account, and considering Croatia's total population of 3,871,833 reported by the 2021 census, the point prevalence is estimated at 3.10 per 100,000 people or 1.55 per 50,000 people.

Discussion and conclusions

Recognizing the scarcity of recent epidemiological data, especially concerning prevalence, and the lack of comprehensive insights into the disease burden among adult HAE patients (≥18 years of age) from Croatia, the Croatian HAE experts undertook a nationwide survey analysis. The primary objective of this investigation was to assess the current status of HAE in Croatia, encompassing

Table III - *Patients' subjective personal perspectives and perceptions of HAE.*

Variable		Value
Patient's subjective perception of treatment success (0 = highly dissatisfied; 10 = highly satisfied), median (IQR), (range)		9 (7-10), (1-10)
Patients' deepest concerns / fears	No concerns / fears, n (%)	9 (15.8)
	Neglecting social activities, n (%)	20 (35.1)
	Failure to meet business responsibilities, n (%)	24 (42.1)
	Fear of dying due to HAE attack, n (%)	19 (33.3)
	Fear of passing HAE to their children, n (%)	29 (50.9)
Patients' suggestions for improving medical care	Improved communication with leading physician, n (%)	8 (14.8)
	Improved education and training of healthcare professionals, n (%)	39 (72.2)
	Improved education of general population, n (%)	25 (46.3)

IQR: Interquartile range; HAE: Hereditary angioedema.

aspects such as diagnostic delays, treatment accessibility, and the overall patient-reported quality of life and disease burden. The study utilized a survey design. Survey research is a widely used quantitative research method involving the systematic collection of data from a sample of individuals through their responses to questions. As a versatile tool, it can provide insights into perceptions, measure behaviors, the severity of the disease, and identify trends within the observed group. While primarily quantitative, surveys can also incorporate qualitative elements through open-ended questions to gain a deeper understanding of the context. Surveys can take different forms, including face-to-face and web-based methods. Web surveys appear to be more practical for participants, but according to some authors, they have an 11% lower response rate compared to other modes, a finding that appears robust and not due to publication bias (24). Another study confirmed that the web survey had a significantly lower unit response rate (18.0%) compared to the face-to-face survey (43.1%), with differences most evident among older and less educated. Although the web survey was nearly three times more cost-effective per completed questionnaire, its lower and more selective response could introduce bias (25). Due to identified shortcomings, we opted for face-to-face surveys for our study, which the patients completed during their follow-up visits or at home, subsequently returning them to their leading physician.

Prevalence

HAE is classified as an orphan disease, with global prevalence estimates ranging from 1:50,000 to 1:150,000 people. A recent systematic review and meta-analysis, encompassing 11,245 HAE cases from 24 studies between 2000 and 2024, reported a pooled worldwide prevalence of 1.22 cases per 100,000 people (95%CI 0.91-1.53). The review noted lower prevalence in Asia and Africa compared to Europe and North America, with HAE type 1 being the most common and a slight female predominance (4). Prevalence figures vary by countries and regions, often due to diagnostic and expert access and the methodology of the analyzed data. Specific national studies further illustrate this variation. In the United States, HAE prevalence is estimated between 1.84 and 2.67 per 100,000 people, with claims-based data suggesting 2.43 to 2.67 per 100,000 and expert-reviewed records showing 1.84 to 2.13 per 100,000 (26). Mexican authors, using a mixed-methods approach, estimated a prevalence of 0.9 per 50,000 inhabitants (27). Similarly, a study in the Asia Pacific region reported a minimal prevalence of 0.02 per 100,000, attributing variability to limited access to diagnostic tests and therapies (28). South Australia identified 35 individuals, yielding a prevalence of 1 in 52,400 (29). Finland experienced a significant increase in HAE type 1 and 2 prevalence, rising from 0.8 to 2.6 per 100,000 persons by 2021, with 103 new diagnoses over a decade, and a mean incidence of 0.16 per 100,000. The higher Finnish prevalence, where patients were often diagnosed at a mean age of 39 years after misdiagnosis, may stem from a founder effect, genetic isolation, and improved diagnostic practices (6). In the United Kingdom, a survey identified 1152 patients, providing a minimum prevalence rate of 1:59,000 (30). Meanwhile, Latvia reported a point prevalence of 0.53 per 100,000 inhabitants from 10 diagnosed patients between 2006 and 2022 (31), while Belarus estimated a minimal prevalence of 1:148,000 for HAE due to C1-INH deficiency (32). The detected minimal prevalence of HAE in Spain is 1.09:100,000, a figure that is likely an underestimate due to the disease's rare nature and potential for patient misdiagnosis (33).

While primarily focused on genotype-phenotype association, novel SERPING1 mutations and drug prophylaxis, studies from Croatia's neighboring countries, Slovenia, Serbia and Hungary, also provided estimated HAE prevalence rates of 0.95, 1.00 and 1.98:100,000, respectively (34, 35).

National HAE experts, utilizing data from the Croatian HAE patient organization, estimated the point prevalence of HAE in pediatric and adult patients at 3.10 per 100,000 people (1.55 per 50,000). The prevalence of HAE in different countries and regions is shown in **table IV**.

Variations in HAE prevalence across countries and populations are common and vary according to different sources and published papers. In all likelihood, reported differences result from the disease's rarity and the challenge of misdiagnosing, underdiagnosing, or overdiagnosing affected individuals. Delayed diagnosis increases the risk of life-threatening laryngeal attacks and unnecessary interventions. Disease is often underreported due to overlapping symptoms with other conditions. Insufficient disease awareness often leads to undetected cases, especially in patients who present with *de novo* mutation within their family. The emphasis should be put on the fact that accurate prevalence estimates are crucial for future planning of patient care, especially as new treatment options emerge. In Croatia, similar to the data from Finland, Hungary and the US, the elevated observed prevalence of HAE can be attributed to enhanced diagnostic initiatives and heightened national awareness, primarily facilitated by a dedicated patient organization and a well-established network of national HAE experts. However, further efforts are needed to elucidate and confirm our estimated prevalence, as the absence of an official HAE Registry in Croatia currently limits comprehensive data collection and validation.

Burden and quality of life

PROMs are essential healthcare tools that directly capture a patient's perspective on their health, symptoms, functional abilities, disease burden, and quality of life. Despite their recognized benefits in clinical practice and research, PROMs have limitations. These include potential lack of comprehensiveness, as they may not capture all relevant aspects of a patient's experience. Furthermore, PROM scores can be influenced by various external factors unrelated to the assessed intervention, such as individual pain levels, psychological state, social circumstances, baseline functional status, age, sex, comorbidities, and personality traits. The reliability and validity of PROMs are also vulnerable to incomplete questionnaires or missing data. Nevertheless, their significant advantages in providing patient-centered insights typically outweigh these disadvantages, leading to their frequent use in daily clinical and research settings (9).

Reported patient demographics show some variation and represent only a portion of HAE patients, as not all individuals with HAE participated in published studies. The Croatian study reported a female predominance (70.2%) and HAE type 1 as most common (64.9%), followed by HAE-nC1-INH (21%) and HAE type 2 (14%). This differs slightly from the Canadian study where HAE type 1 was 46% and HAE-nl-C1-INH 43% (37), but is similar to another Canadian report with 57% HAE type 1 and 26% HAE

Table IV *- Prevalence of HAE in different countries and regions.*

Country / Region	Prevalence per 100,000 people	Reference
Worldwide	1.22	(4)
USA	1.84-2.67	(26)
Mexico	1.8	(27)
Asia Pacific	0.02	(28)
South Australia	1.91	(29)
Finland	0.8-2.6	(6)
United Kingdom	1.69	(30)
Spain	1.09	(33)
Latvia	0.53	(31)
Belarus	0.68	(32)
Serbia	1.00	(35)
Slovenia	0.95	(34)
Hungary	1.98	(36)
Croatia (our study)	3.10	-

type 2 (38). Portuguese reference center found a high prevalence of HAE type 2 (39).

By comparing the Croatian results with other published data, a significant diagnostic delay is a consistent theme across multiple studies. In Croatia, the median diagnostic delay for HAE was 13 years, mainly due to a lack of awareness among general medical practitioners. However, recent efforts by HAE experts and patient organization have significantly improved the diagnostic journey for patients, leading to more timely and accurate diagnosis. Similar delays are reported by Canadian (average 10-11 years) (38) and Indian authors (median 10 years) (40). German group reported an even longer mean diagnostic delay of 18.1 years (41), while Finnish colleagues noted a mean diagnostic age of 39 years due to misclassification (6). The Brazilian center also highlighted significant delays, particularly for those without a family history (42). Most Portuguese patients experienced initial symptoms before adulthood, around 12.6 years old (35), the Brazilian family study found a mean HAE diagnosis age of 16.7 years (36). These differences underscore a global lack of awareness among healthcare providers, leading to prolonged suffering and unnecessary treatments, as seen in cited published reports. Implementing targeted education for primary care physicians, conducting cascade testing in families, offering newborn screening to high-risk families, and running dedicated awareness campaigns are crucial steps to both shorten diagnostic delays and improve patient outcomes.

Attack localization and frequency also show similarities. In Croatia, extremities (57.9%) and abdomen (52.6%) were the most common attack sites, aligning with Canadian (38), Mexican (27), and German (41) findings where abdominal pain and cutaneous swelling were prevalent. Laryngeal involvement, a life-threatening symptom, was reported in 21.1% of Croatian patients as a common attack localization and 3.5% as the first symptom. This is consistent with Mexican data (27.5% severe laryngeal edema) (27) and Brazilian findings (significant laryngeal involvement in a quarter of respondents) (42). The high frequency of attacks is a recurring burden, with 35% of Canadian participants experiencing more than five attacks in six months (38), and acute episodes predominantly moderate to severe (77.0%) in Mexico (27). The Croatian data, indicated by a median AECT of 8, also suggests poorly controlled disease, as seen in the Dutch (36% poorly controlled by AECT) (43) and the Australian study emphasizing continued significant burden despite effective ODT (29).

Regarding healthcare utilization, Croatian patients reported median absenteeism of 0% and presenteeism of 20%, which reflects the impact of the disease on work, although less detailed than the general statement in the USA data about absenteeism and presenteeism for both patients and caregivers (44). Brazilian patients averaged 16.8 emergency visits annually (45), and Mexican patients averaged 7.6, pointing to the significant acute care burden (27). The median number of HAE attacks among Croatian patients in the 3 months preceding the survey was 2, with a range extending from 0 to 70 attacks. A significant portion of these patients were utilizing ODT such as icatibant and intravenous C1-INH concentrates.

The impact on quality of life is reported as an important issue in almost every published paper. Fifty-one percent of Croatian participants reported a significant effect on their quality of life (AE-QoL), with only 14.5% reporting small to moderate impact. This aligns with the Japanese study, which found significant impairment in health-related quality of life and a direct correlation between higher attack frequencies and increased impairment in daily life and work productivity (46). The USA data broadly states that HAE patients often experience reduced quality of life due to stress, anxiety, and depression (47). The Dutch study explicitly linked angioedema attacks to a significant drop in EQ-5D-5L utility values (43). While the South Australian study indicated generally satisfactory disease control with prophylactic therapies leading to high patient satisfaction, this is presented as a positive outcome of effective management, rather than a reflection of the inherent disease burden without adequate treatment (48). The overall picture indicates that HAE profoundly affects patients' quality of life across diverse geographical regions.

Psychological comorbidities according to Croatian participants are reported as a prominent problem, anxiety testing (BAI) showing 26.4% of patients experience severe anxiety, and 30.2% mild anxiety. Depression testing (BDI) revealed 8.0% with moderate depression and 2.0% with severe depression. This is similar to the USA data, which reported an increased prevalence of depression in female HAE-C1INH participants and generally stated that HAE patients often experience significant emotional impairment due to stress, anxiety, and depression (47). The German survey also highlighted the significant burden due to anxiety of unpredictable swelling attacks (49). The Japanese study explicitly linked elevated scores on AE-QoL domains (fatigue/mood and fears/shame) to higher anxiety levels (46). These consistent findings emphasize the critical need for psychological support as part of comprehensive HAE management.

Treatment approaches also vary, particularly concerning LTP. In Croatia, 54.4% participants were on LTP, with danazol being the most common (33.3%), compared to 45% of patients on LTP in the UK (predominantly danazol) (30) and 69% on C1-INH in Canada (38). The Croatian study was conducted before the introduction of modern first-line LTP, which explains the high proportion of patients on danazol, further emphasizing the disease burden in this cohort compared to regions with better access, where modern LTPs led to high patient satisfaction (29). The Croatian experience of self-administration of intravenous C1-INH at home proved to be an excellent way to reduce the pressure of Emergency room visits. Stress was the most frequently reported trigger in Croatia (67.3%), consistent with Por-

tuguese findings, highlighting the psycho-social aspects of disease management (39). Modern LTP in comparison with older therapies (like attenuated androgens) has significantly improved efficacy, provided a favorable safety profile, and a better quality of life for patients.

Recently conducted international survey among HAE experts concluded similar significant unmet needs and barriers to treatment, leading to a call for improved access to care, better education for physicians and patients, and increased collaboration among stakeholders (50).

In conclusion, global HAE studies consistently highlight delayed diagnoses, misdiagnosis, and the impact of the disease on quality of life, work productivity, and psycho-social aspects, a tendency also observed in Croatian data. The median 13-year diagnostic delay reported in Croatian patients, consistent with global trends, highlights the critical need for improved recognition and more efficient diagnostic patient pathways. With the recent approval and reimbursement of first-line long-term prophylactic therapies, such as lanadelumab and berotralstat, as well as other emerging treatments, significant improvements in quality of life and reductions in disease burden are expected in Croatia and worldwide.

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Contributions

MB: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing – original draft, writing – review & editing. BK: data curation, formal analysis, investigation, methodology, project administration, resources, software, validation, visualization, writing – review & editing. LČ, ŽK, DVŠ, MM: methodology, resources, writing – review & editing. DP, JMA, SN, BA: validation, visualization, writing – review & editing. AMM: investigation, writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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LETTER TO THE EDITOR

Eur Ann Allergy Clin Immunol Vol 58, N.5, 230-232, 2026

Inês Filipa da Costa Farinha[1], António Celso Dias Pereira[2,3], Frederico Eugénio de Castro Soares Regateiro[1,2,4], Ana Maria Pego Todo-Bom Ferreira da Costa[1,2], Emília Maria Antunes Gomes de Faria[1]

Selective Immunoglobulin M deficiency: an underestimated immunodeficiency

[1]Department of Allergy and Clinical Immunology, Coimbra Hospital and University Centre, Coimbra, Portugal
[2]Faculty of Medicine of the University of Coimbra, Coimbra, Portugal
[3]Immunoallergology, Coimbra Surgical Center, Coimbra, Portugal
[4]ICBR, Coimbra Biomedical and Clinical Research Institute, University of Coimbra, Coimbra, Portugal

Key words

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Corresponding author
Inês Filipa da Costa Farinha
Department of Allergy and Clinical Immunology
Coimbra Hospital and University Centre
Praceta Prof. Mota Pinto s/n
3000-075 Coimbra, Portugal
ORCID: 0000-0002-0427-8814
E-mail: ines_farinha9@hotmail.com

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To the Editor,

selective Immunoglobulin M deficiency (sIgMD) is a subtype of inborn error of immunity (IEI) defined by the European Society for Immunodeficiencies (ESID) as an isolated decrease in serum immunoglobulin (Ig)M concentration greater than 2 standard deviations from normal, while the remaining immunoglobulins, as well as T-lymphocytes and antibody response to vaccinations are normal, in the absence of external factors (1-3). Janssen *et al.* (2) classified sIgMD as 'true' if all ESID criteria were met, 'possible' when ESID criteria are not fulfilled completely – because data on IgG subclasses and/or vaccination responses are lacking – or 'unclassified primary antibody deficiency' when other abnormalities in antibodies are also present, *i.e.*, IgG-subclass deficiency, below-normal levels of IgG or IgA and/or impaired vaccination responses (1, 2). A prevalence of 0.07-2.1% in Immunology and Immunodeficiency clinics has been reported (6). Clinically, sIgMD associates with increased susceptibility to infections, allergic diseases, autoimmune disorders and malignancies (2-7). However, low IgM has been incidentally observed in asymptomatic patients (6, 7). The therapeutic approach aims to manage and prevent infections, address associated conditions and provide supportive care (8, 9). Only small cohorts sIgMD patients have been described (5) and the knowledge about this entity is limited. We performed a retrospective characterization of selective IgM deficiency patients followed in our Allergy and Clinical Immunology Department from 2015 to 2020. We included 13 patients with an average age at diagnosis of 41 years. Seven

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patients had IgM serum levels < 0.17g/L, while the remaining patients had levels between 0.22-0.31g/L. None of the patients presented T cells defects (number and phenotypes). CD19+ B cells numbers were normal in 5 out of 9 patients, a lower proportion than those observed by Castagnoli *et al*. (10) in a pediatric cohort and Lucuab-Fegurgur *et al*. (8) in an adult cohort. The response to pneumococcal and tetanus vaccination were evaluated in 3 patients and were normal in all. Detailed immunoglobulin levels and T- and B-cell counts are presented in **table I(Suppl)**. Therefore, three patients fully met the ESID criteria for sIgMD and ten patients had 'possible' sIgMD, namely due to lack of evaluation of the vaccination response. **Table I** summarizes the demographic characteristics and the referral reasons. None of the patients had a family history of IEI. The most frequent clinical manifestations were infections (in 12 patients), mainly respiratory, usually successfully treated with conventional courses of antibiotics, although an 86-year-old patient developed severe fatal pneumonia with sepsis. Seven patients presented with atopic diseases, 4 with autoimmune manifestations, and 2 with serological autoimmune markers without clinical expression. Over a median follow-up period of 7.5 years, three patients developed neoplastic or premalignant conditions. None of the patients progressed to another IEI. The infectious and non-infectious manifestations are shown in **table II**. No patient was treated with replacement human immunoglobulin. Recognizing the significance of this frequently overlooked IEI is crucial, prompting clinicians to maintain heightened vigilance and conduct thorough follow-ups for potential complications. A summary of the laboratory investigations for suspected selective IgM deficiency is provided in **table II(Suppl)**. Our findings support other international studies in which most patients with sIgDM mostly present with recurrent respiratory tract infections and a significant proportion of patients develop also autoimmune and allergic diseases (5-7, 11). Previous reports observed that about a quarter of the patients with sIgMD progress to another IEI (3), but we did not found progression in any of our patients over the course of 7.5 years average follow-up. Additionally, it is worth noting that none of the more than 50 patients with antibody deficiencies (mostly CVID) followed in our department progressed from an initial state of sIgMD (unpublished data). In contrast to the 25% of asymptomatic patients reported in another series (3), 92% of our patients had symptoms that are probably related to sIgMD. This is the first series of sIgMD Portuguese patients published. The knowledge of this often-undervalued immunodeficiency is critical and additional multicenter studies and/or national registry are necessary for a better phenotypic characterization and the identification of prognostic factors of this immunological entity to help guide management decisions.

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IFCF: investigation, data curation, methodology, writing - original draft, conceptualization, visualization. ACDP: resources; writ-

Table I *- Demographic characteristics and reasons for referral of patients with selective IgM deficiency.*

Id	Gender	Diagnosis age	Current age	Referral reasons
1	F	19	✞ 86 pneumonia	Selective IgM deficiency
2	M	28	41	Rhinorrhea
3	F	70	81	IEI suspicion
4	M	51	58	IEI suspicion
5	M	41	46	Recurrent folliculitis
6	F	51	59	Chronic rhinosinusitis
7	M	15	21	Recurrent ENT infections
8	F	67	70	Selective IgM deficiency
9	M	7	13	Recurrent infections
10	F	28	32	Urticaria
11	F	30	37	Atopic dermatitis
12	F	42	46	Asthma
13	M	47	52	Recurrent angioedema

F: female; M: male; ENT: Ear, nose and throat; IEI: Error of Immunity.

***Table II** - Infectious and non-infectious manifestations of patients with selective IgM deficiency.*

Id	Infectious manifestations	Allergic / autoimmune / malignant diseases
1	Upper respiratory infections >4/year Pneumonia with sepsis	Squamous cell carcinoma
2	Sinusitis	Bee venom anaphylaxis; chronic rhinosinusitis; house dust mite and grass sensitization
3	Upper respiratory infections 2-3/year Pneumonia	Sweet's syndrome; monoclonal gammopathy of undetermined significance
4	Chronic diarrhea and gastroenteritis	None
5	Cutaneous Infections	Asthma and rhinitis allergic to grasses; Psoriasis
6	Upper respiratory infections >5/year Pneumonia; Sinusitis	Weak positive ANA without clinical correlation
7	Upper respiratory infections >5/year Pneumonia; Sinusitis Folliculitis	None
8	Upper respiratory infections 1/year	Hypothyroidism Weak positive ana without clinical relevance
9	Upper respiratory infections >4/year	Asthma and rhinitis
10	None	Dermatographic urticaria
11	Upper respiratory infections 2/year Pneumonia	Allergic asthma and rhinoconjunctivitis; atopic dermatitis; hypothyroidism
12	Upper respiratory infections 1/year	Asthma, atopic dermatitis, rhinoconjunctivitis; food and drug allergy; breast carcinoma
13	Upper respiratory infections 1/year	Recurrent angioedema

ANA: antinuclear antibodies.

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Conflict of interests

The authors declare that they have no conflict of interests.

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LETTER TO THE EDITOR

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Angela Klain[1], Baoran Yang[2], Lorenzo Cecchi[3], Maria De Filippo[4,5], Mattia Giovannini[6,7], Alessandro Maria Marra[8], Matteo Martini[9], Gian Luigi Marseglia[4], Michele Miraglia del Giudice[1], Francesco Murzilli[10]

Regional disparities in access to epinephrine auto-injectors for children and adults in Italy

[1]Department of Woman, Child and General and Specialized Surgery, University of Campania 'Luigi Vanvitelli', Naples, Italy
[2]Allergy Clinical Immunology and Rheumatology Unit, ASST Carlo Poma, Mantua, Italy
[3]Allergy and Immunology Unit, San Giovanni di Dio Hospital, USL Toscana Centro, Florence, Italy
[4]Pediatric Unit, Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy
[5]Department of Maternal Infantile and Urological Sciences, AOU Policlinico Umberto I, Rome, Italy
[6]Allergy Unit, Meyer Children's Hospital IRCCS, Florence, Italy
[7]Department of Health Sciences, University of Florence, Florence, Italy
[8]Pulmonology Unit, ASST Rhodense, Garbagnate Milanese Hospital, Milan, Italy
[9]Allergy Unit, Department of Internal Medicine, University Hospital AOU Delle Marche, Ancona, Italy
[10]Allergy Unit, SS Filippo e Nicola Hospital, Avezzano, L'Aquila, Italy

Key words

Epinephrine auto-injector; anaphylaxis; regional disparities; Italy; reimbursement policies.

Corresponding author
Michele Miraglia del Giudice
Department of Woman, Child and General and Specialized Surgery
University of Campania 'Luigi Vanvitelli'
via Luigi de Crecchio 2
80138 Naples, Italy
ORCID: 0000-0002-8369-5957
E-mail: michele.miraglia@unicampania.it

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To the Editor,

anaphylaxis is a potentially life-threatening systemic reaction that requires rapid recognition and treatment, with adrenaline representing the first-line (1, 2). In a 2024 study, the overall incidence of anaphylaxis in France was estimated at 1.34 per 100,000 people per year, with a hospital admission rate for severe reactions of 0.08 per 100,000 per year (2). Globally, in the pediatric population, the incidence of anaphylaxis is estimated to range from 1 to 761 episodes per 100,000 people per year (3), with most cases occurring before six years of age and being influenced by the presence of atopic comorbidities. The most common triggers in children are foods, including milk, eggs, and tree nuts, whereas drug- and insect venom-induced anaphylaxis occurs more frequently in adults (4). Risk factors for severe reactions include pulmonary diseases, including asthma, and mastocytosis. Diagnosis is clinical, with no single sign or symptom being pathognomonic. However, serum tryptase levels measured in the acute phase may support the diagnosis. Reaction patterns may differ by trigger, with the skin being the most frequently affected. Most

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reactions occur within 30 min of exposure, although a delay of 4 h can be seen for specific triggers, and biphasic anaphylaxis has also been described (5). Epinephrine autoinjectors (EAI) are prescribed for at-risk individuals to facilitate prompt epinephrine administration during anaphylaxis in the community (6). In Italy, EAI are available and dispensed by the National Health System. Epinephrine halts and reverses reactions in a manner that other treatments cannot. Different EAI brands are available as doses of 150 µg, 300 µg, or 500 µg (7); however, there is limited global availability of the 500-µg dose, contributing to disparities in access at both national and international level. The European Medicines Agency (EMA) recommends patients at risk of anaphylaxis should always be prescribed two EAI and should carry both at all times (8).

Currently, there is insufficient data on the availability and reimbursement of autoinjectors across different states for both children and adults. The Italian Society of Pediatric Allergy and Immunology (SIAIP) and the Association of Italian Territorial and Hospital Allergists and Immunologists (AAIITO) have analyzed the availability of EAI for children and adults, respectively. To investigate potential regional differences, data were collected from junior and senior SIAIP and AAIITO regional representatives between June and September 2024.

EAI availability and reimbursement in Italy demonstrated marked regional disparities, affecting both pediatric and adult populations. A key issue is the absence of updated regional regulations for supply and reimbursement. Consequently, several regions still rely on heterogenous policies, leading pharmacies to dispense whichever device is available. Most regions provide two injectors per year for children. Exceptions include Sardinia and Trentino-Alto Adige (Bolzano province), which reimburse only one injector annually. Additionally, in Piedmont, Veneto, and Aosta Valley one injector is reimbursed by default, and a second provided only in specific circumstances. Reimbursement policies for adults show greater variability. Two injectors per year are reimbursed in Basilicata, Calabria, Emilia-Romagna, Lazio,

Table I *- Number of reimbursed autoinjectors in Italian regions in the pediatric and adult populations.*

Italian regions	Number of reimbursed autoinjectors	
	Children	**Adults**
Abruzzo	2/year	1-2/year
Basilicata	2/year	2/year
Calabria	2/year	2/year
Campania	2/year	1-2/year
Emilia Romagna	2/year	2/year
Friuli Venezia Giulia	2/year	1-2/year
Lazio	2/year	2/year
Liguria	2/year	1-2/year
Lombardy	2/year	1-2/year
Marche	2/year	1-2/year
Molise	2/year	1-2/year
Piedmont	1-2/year	1-2/year
Puglia	2/year	1-2/year
Sardinia	1/year	1/year
Sicily	2/year	1-2/year
Tuscany	2/year	2/year
Trentino Alto Adige – Bolzano province	1/year	1/year
Trentino Alto Adige – Trento province	2/year	1-2/year
Umbria	2/year	1-2/year
Veneto	1-2/year	2/year
Aosta Valley	1-2/year	1-2/year

Tuscany and Veneto. In Sardinia and Trentino-Alto Adige (Bolzano province), only one injector per year is reimbursed. In several regions, including Abruzzo, Campania, Friuli Venezia Giulia, Liguria, Lombardy, Marche, Molise, Piedmont, Puglia, Sicily, Trentino-Alto Adige (Trento province), Umbria, and Aosta Valley, the reimbursement for two injectors is restricted to specific circumstances, such as systemic mastocytosis, biphasic anaphylaxis, near-fatal anaphylaxis, severe anaphylaxis, severe obesity, or remote residence (**table I** and **figure 1**).

This is the first nationwide analysis addressing the availability and reimbursement of EAI in Italy, covering the pediatric and adult populations. Our work was limited by several factors, including intra-regional variability (so we described the prevailing regional trend), the reliance on data reported by regional representatives, the absence of formally published updated regional regulations in some areas, and the lack of quantitative data on prescription volumes. These issues reflect broader trends observed in low- and middle-income countries, as detailed in the World Allergy Organization survey (9). Emerging adrenaline delivery systems, such as intranasal formulations, may improve ease and readiness of use, even if knowledge gaps remain.

The role of patient associations should also be considered, as these organizations substantially contribute in improving awareness of anaphylaxis management and in promoting equitable access to EAIs. Their inclusion in national strategies together with other relevant stakeholders may facilitate policy harmonization and strengthen educational initiatives aimed at reducing regional disparities.

Without standardized policies, access to EAIs appears unreliable, potentially representing a risk for patients in emergencies. Harmonizing reimbursement policies and procurement frameworks across Italian regions is essential to ensure egalitarian and prompt access to EAI, aligning national practice with international recommendations.

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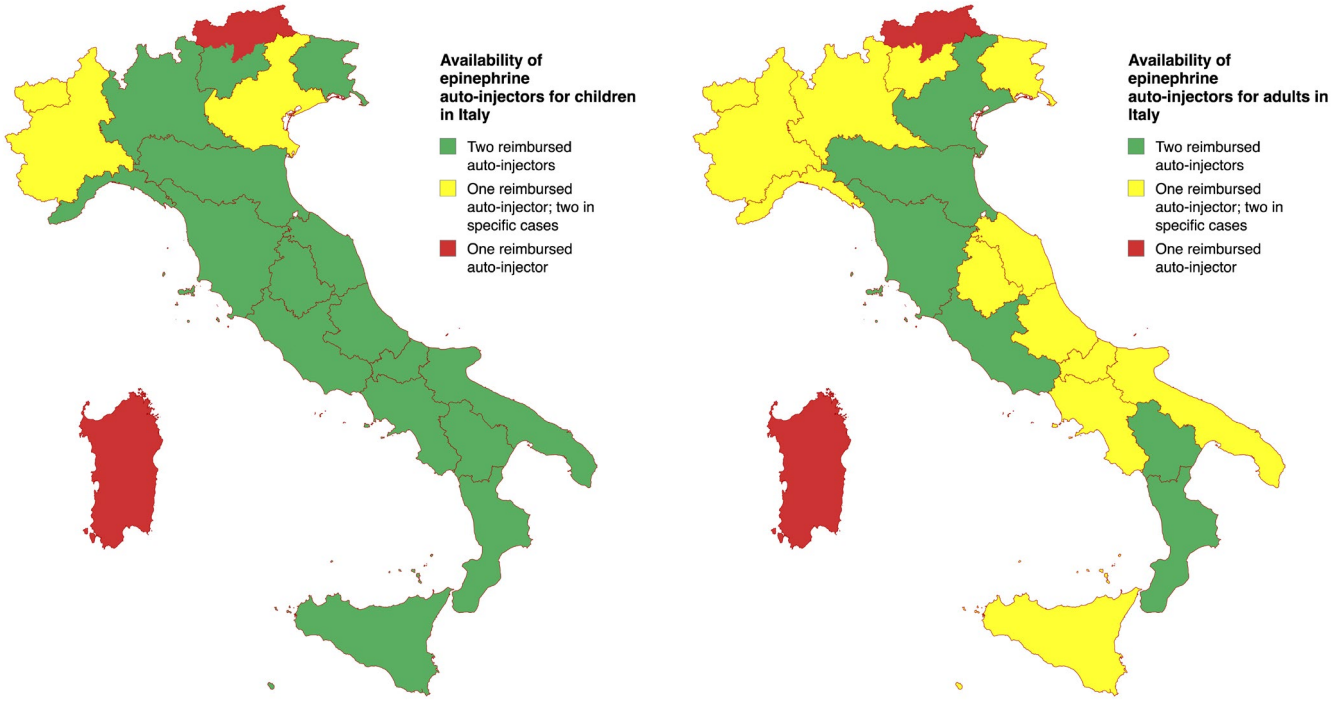
Contributions

AK, MG: conceptualization. AK, BY: writing - original draft. LC, MDF, MG, AMM, MM, GLM, MMdG, FM: writing - review & editing, investigation, formal analysis.

Conflict of interests

MG reports personal fees from Sanofi, Thermo Fisher Scientific. Other authors declare no conflict of interests.

Figure 1 *- Disparities in access to epinephrine auto-injectors for children and adults in Italy.*



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LETTER TO THE EDITOR

Eur Ann Allergy Clin Immunol Vol 58, N.5, 237-239, 2026

Barbara Cristina Ramos, Carolina Sanchez Aranda, Marcia Carvalho Mallozi, Dirceu Solé, Lucila Camargo Lopes de Oliveira

Peanut allergen sensitization profile in Brazil

Division of Allergy, Clinical Immunology and Rheumatology, Department of Pediatrics, Federal University of São Paulo, São Paulo, Brazil

Key words

Peanut; sensitization; cross-reactivity.

Corresponding author
Lucila Camargo Lopes de Oliveira
Division of Allergy, Clinical Immunology and Rheumatology
Department of Pediatrics
Federal University of São Paulo
Rua dos Otonis 725
Vila Clementino, Sao Paulo (SP)
04024-002, Brazil
ORCID: 0000-0003-2065-571X
E-mail: lucila_camargo@yahoo.com

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To the Editor,

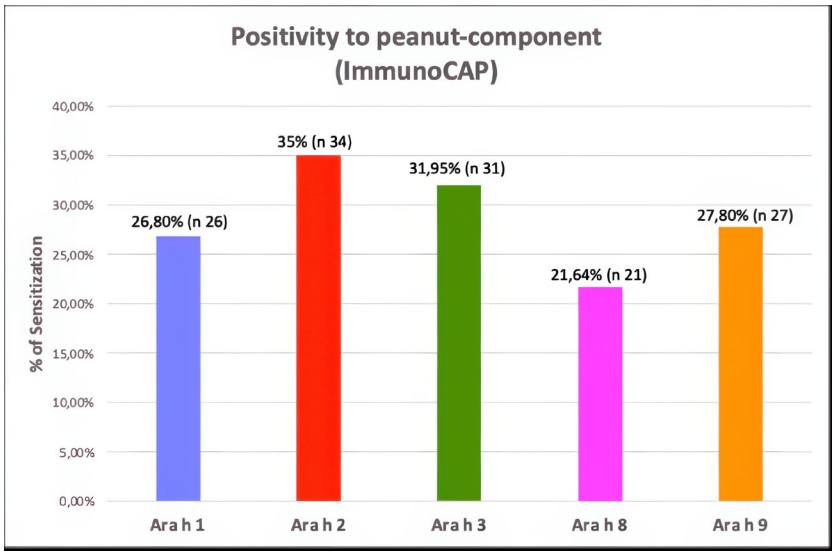
the prevalence of peanut allergy in children is around 0.2-4.5% (1) and varies geographically, with different sensitization patterns depending on genetics, lifestyle, and environmental exposure (2). The diagnosis is done by suggestive clinical history upon peanut ingestion aided by the serum allergen-specific IgE (sIgE) to peanut extract, components and basophil activation test. Nonetheless, sensitization can be present despite clinical symptoms or as a cross-reactivity phenomena (1). Allergen sensitization has also been postulated to have a predictive role in the development of clinical allergies (3).

Our objective was to describe the profile of peanut sensitization and its possible PR-10 and lipid-transfer proteins (LTP) cross-sensitization in Brazil.

Data was collected from a previous cross-sectional multicenter study (PROAL II) (3), where atopic participants (age 6 months to 18 years) had their sensitization profile compared to asymptomatic children. Participants that presented with sIgE ≥ 0.35kUA/L to whole-peanut (Pn) and/or peanut-components (Ara h 1, 2, 3, 8, and 9) were included. The ImmunoCAP® (ThermoFisher Scientific – Uppsala, Sweden) was used to determine the levels of sIgE. ImmunoCAP ISAC® of participants with atopic dermatitis (AD) and food allergy (FA) was analyzed to the same allergens. Sex, age, principal allergy condition, concomitant allergy disease were assessed. The Federal University of São Paulo Ethics Committee approved this study (No.824.156). All patients provided written informed consent. From the 470 participants, 97 (20.6%) were positive to Pn-sIgE and/or its components (age 10-204 months, median 72) (**figure 1**). Participants with positive Pn-sIgE had a mean of 5.57kUA/L, range 0.36-56.0kUA/L. As main allergy condition, 13.7% (n = 12) had asthma (A) and/or allergic rhinitis (AR), 41.3% (n = 36) had AD, 32.1% (n = 28) had FA, 3.4% (n = 3) had recurrent wheezing (RW) and 9.2% (n = 8) were healthy controls. Regarding positivity to the components, 22 (25.2%) were positive to Ara h 1, 29 (33.3%) to Ara h 2, 28 (32.1%) to Ara h 3, 17 (19.5%) to Ara h 8 and 24 (27.5%) to Ara h 9 (**figure 2**). Forty-six underwent ISAC analysis, with 37 (80%) negatives to allergens, probably due to assay's lower sensitivity. Seven (15%) were positive to one or more Ara h and two (4%) were positive to PR-10 or LTP allergens.

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Figure 1 *- Percentage of positivity to peanut-components serum-specific IgE.*



There was no difference in the levels of Pn-sIgE for the participants with AD, A/AR, FA, RW, and controls (p = 0.613).

In the 10 Pn-sIgE negative participants, but positive to peanut-components, the main allergy condition was AD (n = 7) followed by A/AR (n = 3). Four were sensitized to Ara h 1, five to Ara h 2, three to Ara h 3, four to Ara h 8 and three to Ara h 9 (**figure 2**). Only two had ISAC analysis, both without sensitization.

In our cohort, one in five had a positive Pn-sIgE and/or peanut-component sIgE. This is a higher prevalence of sensitization than the one observed in Japan (4).

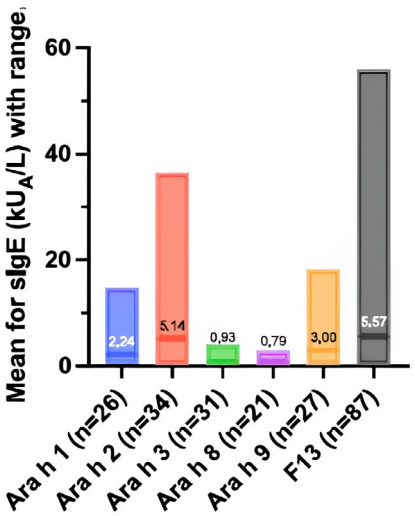
The storage proteins, Ara h1, 2, and 3 were the most prevalent in our participants, but the majority (45.9%) were only sensitized to Pn-sIgE as observed in the United States (5). These components are relevant in North/Central Europe (2). Vereda *et al.* (5) reported that two-thirds of the Spanish patients had sensitization to Ara h 9, and from those, 66% were monosensitized. Despite having 24/87 sensitized to Ara h 9, our monosensitized participants were only six. For Ara h 8 this was even less. In this cohort, there was a high proportion of AD patients that could per se increased sensitization, although healthy controls also presented with sensitization (9.2%). Component analysis by ISAC were almost all negative, including the ones to LTP and PR-10.

In conclusion, peanut sensitization among Brazilians is mostly due to primary sensitization than cross-reactivity, and that should be considered when evaluating a patient with suspected peanut allergy.

Fundings

None.

Figure 2 *- Mean and range for whole-peanut serum-specific IgE and peanut components obtained by ImmunoCAP.*



Contributions

BCR: data curation, formal analysis, investigation, writing – original draft. CSA: conceptualization, investigation, methodology, writing – review & editing. MCM: supervision, writing –

review & editing. DS: conceptualization, methodology, supervision, writing – review & editing. LCLO: conceptualization, methodology, formal analysis, investigation, writing – original draft, writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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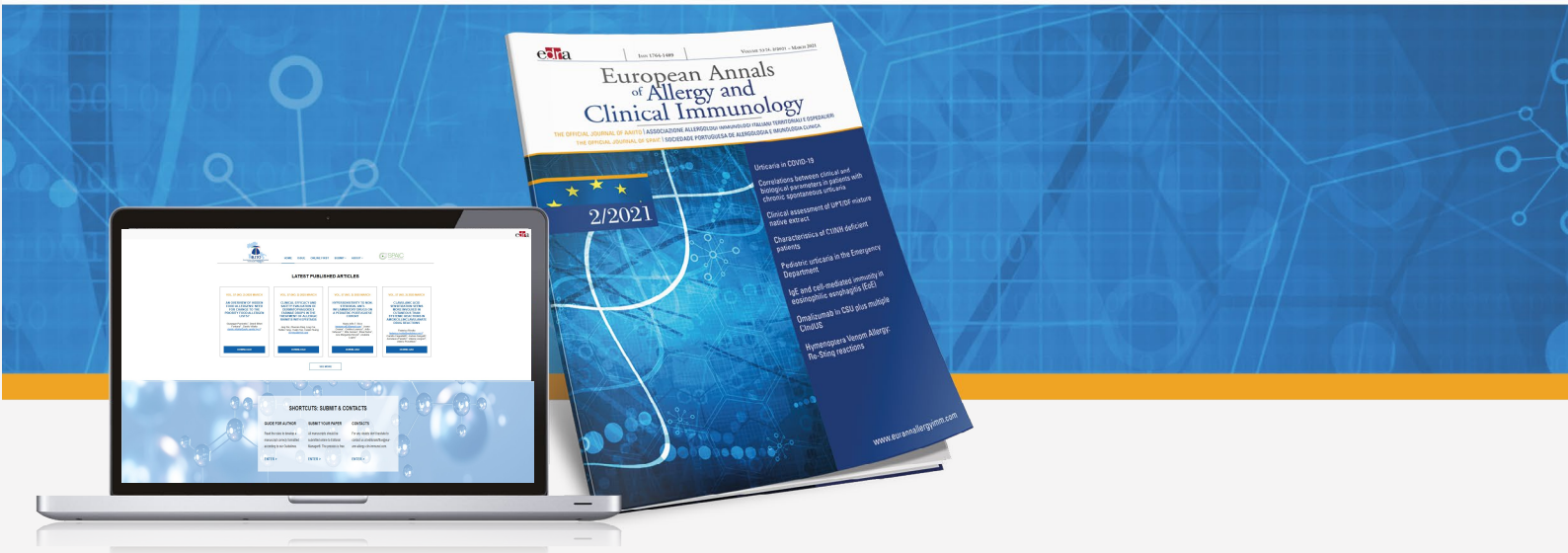
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