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

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KEY WORDS

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

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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 management in patients with EoE.

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.

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-4R α 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 corresponding gastroenterology centers and the histopathology 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 $\pm$ 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 $\pm$ SD	36.4 $\pm$ 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.

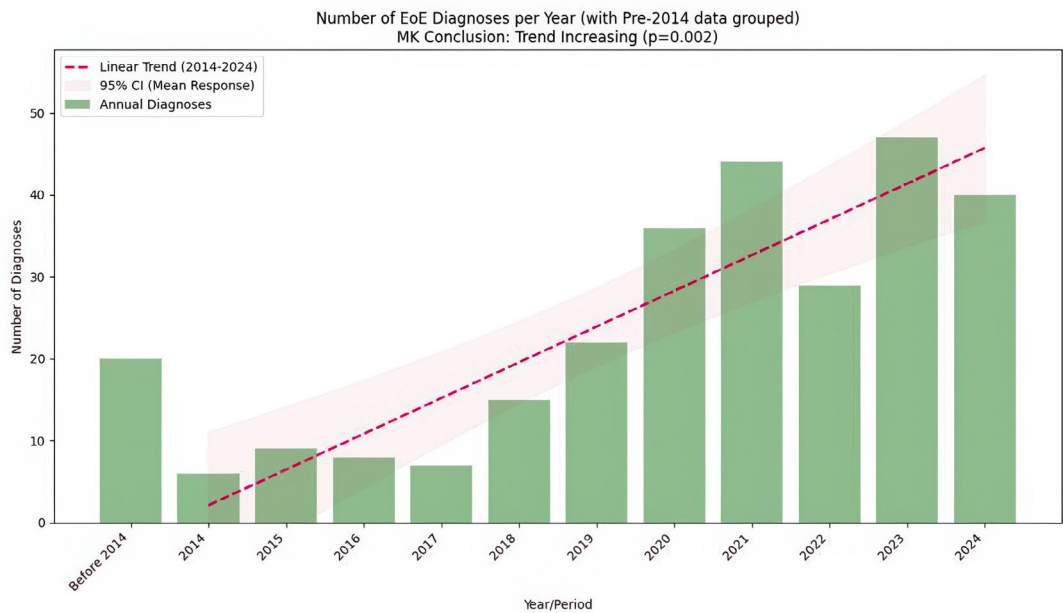
Type 2 comorbidity burden

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**).

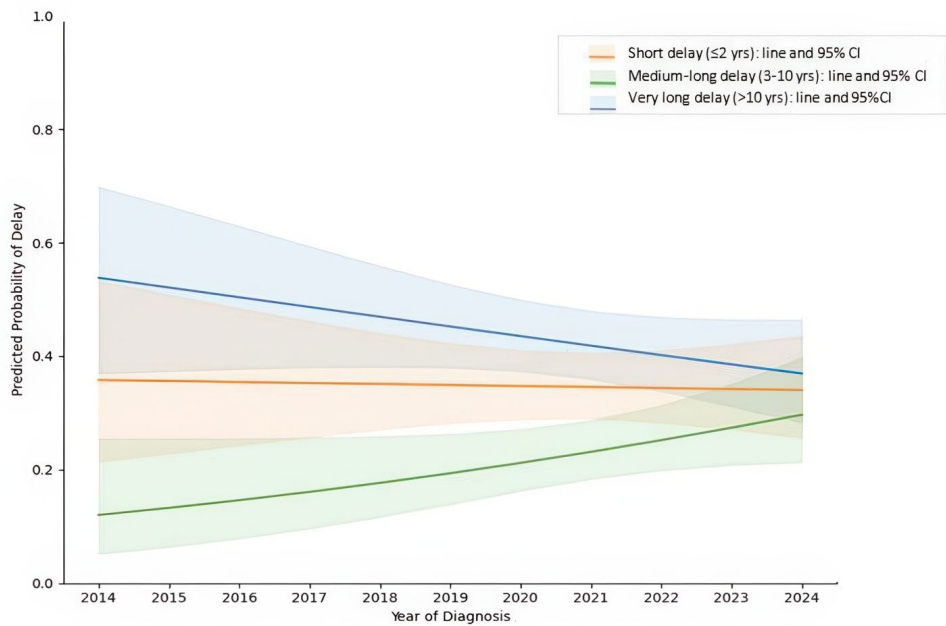
No significant sex differences were observed in the number or pattern of comorbidities ($\chi^2 = 8.70$, $df = 12$, $p = 0.728$). Finally, to explore whether the presence of at least one type 2 comorbidity influenced diagnostic delay across the three categories described above, a Chi-square test was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



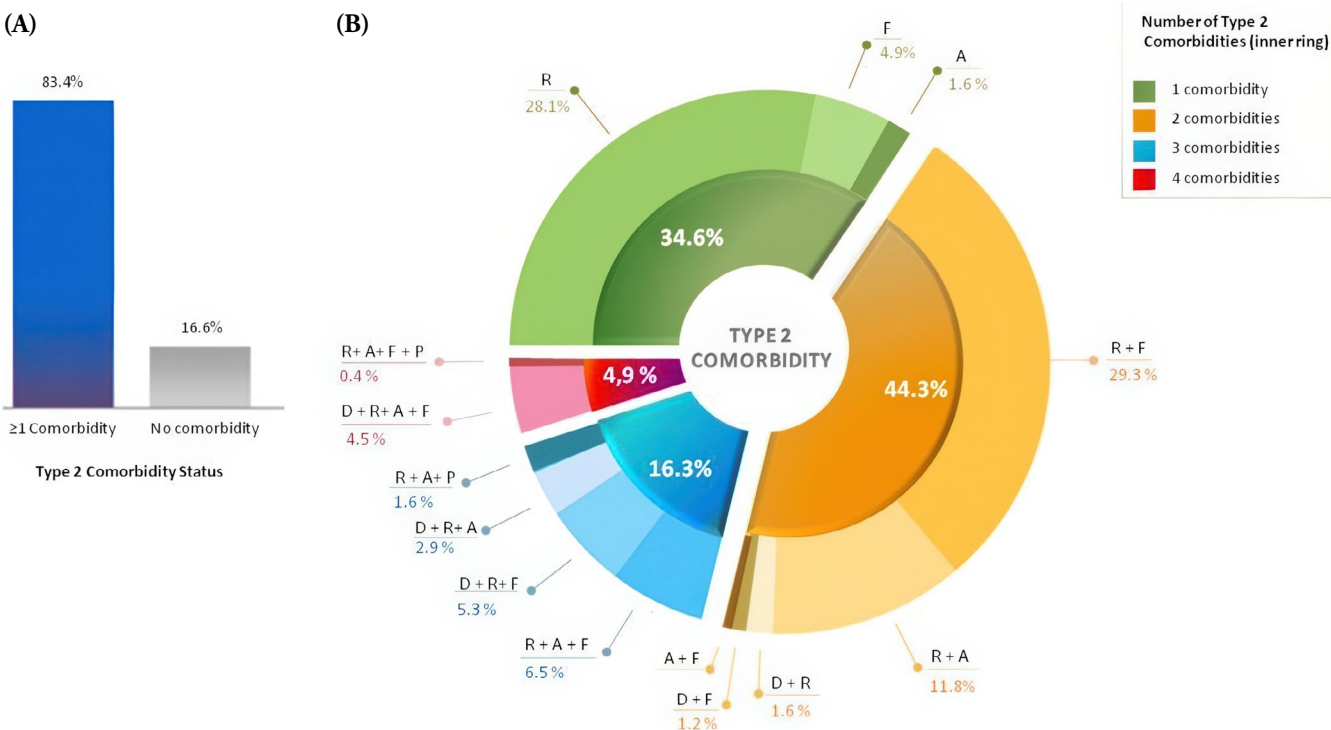
Bars represent the number of new EoE diagnoses per year, with all diagnoses recorded before 2014 aggregated into a single “Before 2014” category. The dashed line shows the linear trend in annual diagnoses from 2014 to 2024, and the shaded area represents the 95% confidence interval (CI) for the mean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

Fundings

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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