Digestive and Liver Disease 55 (2023) 350–359

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Alimentary Tract

Differences between childhood- and adulthood-onset eosinophilic esophagitis: An analysis from the EoE connect registry

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https://doi.org/10.1016/j.dld.2022.09.020

ARTICLE INFO

Article history:
Received 20 February 2022
Accepted 30 September 2022
Available online 22 October 2022

Keywords:
Adult
Children
Cohort studies
Eosinophilic esophagitis
Practice patterns, registries

ABSTRACT

Background: Direct comparisons of childhood- and adulthood-onset eosinophilic esophagitis (EoE) are scarce.
Aim: To compare disease characteristics, endoscopic and histological features, allergic concomitances and therapeutic choices across ages.
Methods: Cross-sectional analysis of the EoE CONNECT registry.
Results: The adulthood-onset cohort (those diagnosed at ≥18y) comprised 1044 patients and the childhood-onset cohort (patients diagnosed at <18 y), 254. Vomiting, nausea, chest and abdominal pain, weight loss, slow eating and food aversion were significantly more frequent in children; dysphagia, food bolus impaction and heartburn predominated in adults. A family history of EoE was present in 16% of pediatric and 8.2% of adult patients ($p<0.001$). Concomitant atopic diseases did not vary across ages. Median±IQR diagnostic delay (years) from symptom onset was higher in adults (2.7 ± 6.1) than in children (1 ± 2.1; $p<0.001$). Esophageal strictures and rings predominated in adults ($p<0.001$), who underwent esophageal dilation more commonly ($p = 0.011$). Inflammatory EoE phenotypes were more common in children ($p = 0.001$), who also presented higher eosinophil counts in biopsies ($p = 0.015$) and EREFS scores ($p = 0.017$). Despite PPI predominating as initial therapy in all cohorts, dietary therapy and swallowed topical corticosteroids were more frequently prescribed in children ($p<0.001$).
Conclusions: Childhood-onset EoE has differential characteristics compared with adulthood-onset, but similar response to treatment.

1. Introduction

Eosinophilic Esophagitis (EoE) is a chronic inflammatory immunity-driven esophageal disease resulting from a local exposition of food or airborne swallowed antigens [1]. Epidemiological studies have documented a steadily increase from childhood to adolescence, with peaks in the age groups 20–24 years old and 35–39 years old. Although these were the ages with the highest number of EoE diagnoses [2], an increased incidence of EoE at pediatric age has recently been reported [3]. At present, the causes determining the onset of the disease in each individual patient are unknown. However, the concomitance of several Th2-mediated atopies with EoE, several environmental factors [4], some genetic risk variants and prenatal and early life exposure [5] potentially modifying abundance and composition of gut microbiome [6], point towards dysregulated interactions between bacteria and mucosal immunity in susceptible individuals as leading causes of EoE [7].

Although EoE is considered a single disease across the age range, differences have been reported among children and adults, especially in clinical presentation and endoscopic features [8–11]. However, most of the differences found between childhood-onset and adulthood-onset EoE come from the comparison of clinical and epidemiological data in independent patient series (pediatric *vs*. adult patients). Currently, data comparing the evolution of childhood-onset EoE with that of adulthood-onset EoE is only available in a small number of population cohorts [2,11–14], none of which have prospectively explored patients of all age ranges in a European setting. Results regarding the use of the different available therapeutic approaches, as well as the need for endoscopic dilation according to the age at diagnosis, are controversial [8,9]. Most series also have some limitations such as the retrospective inclusion of the data. Therefore, further updated information from population cohort studies is greatly needed to assess whether pediatric age-specific EoE presents a distinct phenotype at debut, and requires a different management compared to adults.

EoE CONNECT, a prospectively maintained registry, provides access to a large population-based cohort of EoE European patients, and is suitable for comparing the characteristics of EoE patients diagnosed during childhood with those diagnosed during adulthood. Through this large multi-center European study, we aimed to compare the characteristics of the disease, the diagnostic delay, the first-line therapeutic approach and response in patients diagnosed at pediatric age (<18 years) *versus* those diagnosed in adulthood. Our results will help to understand the differences between childhood-onset and adulthood-onset EoE.

2. Methods

2.1. Study population and grouping

The study sample comprised patients diagnosed with EoE based on the criteria of the Evidence-based guidelines [15] and the AGREE conference [16] and included in the EoE CONNECT registry.

For this cross-sectional analysis, patients included on the registry from 2015, when EoE CONNECT was rolled out, to 2021 were evaluated. The childhood-onset cohort comprised EoE patients diagnosed at <18 years of age, and the adulthood-onset cohort EoE patients diagnosed at ≥18 years. Variations in clinical presentation, endoscopic findings, and use of different therapies for EoE as first-line treatment have been reported across childhood and adolescence age ranges [17–19], our study therefore evaluated differences in EoE among younger patients (<12 years old at diagnosis) and teenagers (12 to 17 years at diagnosis). Elderly EoE patients have generally not been reported in the literature and whether they might constitute a different disease group, with their own characteristics (potentially a more benign disease course), has not yet been fully investigated [20]. For this reason, patients diagnosed in adulthood were also sub-classified into two groups: younger adulthood-onset EoE (18-59 years at diagnosis) and older ('elderly') adulthood-onset EoE (≥60 years at diagnosis). Patients were observed from diagnosis of EoE up to the date of their last registered visit.

2.2. EoE connect registry

EoE CONNECT is a registry of EUREOS, the European Consortium for Eosinophilic Diseases of the GI Tract (www.eureos.online). The database prospectively records clinical characteristics, outcomes and treatment of patients recruited at different sites across Europe. The definitions, detailed study protocol and operational procedures of EoE CONNECT have been published elsewhere [21]. To be included in the registry, patients are required to have a confirmed diagnosis of EoE based on the following criteria [15,16]: (1) symptoms of esophageal dysfunction, (2) a peak eosinophil count ⩾15 per high-power field (HPF; 400× magnification) at any

esophageal level, and (3) exclusion of other systemic and local causes of esophageal eosinophilia. Patients fulfilling the above-mentioned criteria who are responsive to proton pump inhibitor (PPI) therapy can be included in EoE CONNECT. Patients with EoE and concomitant gastroesophageal reflux disease (GERD) can be included if the diagnosis of EoE and GERD has been established based on accepted diagnostic criteria. After registration, physicians from attending EoE centers can voluntarily include their patients' data in the registry. At the time of data extraction (4th October 2021), the registry contained 1452 patients from 24 sites. EoE CONNECT has been approved by Ethics Committees at all participating centers; and written informed consent to participate in the EoE CONNECT project has been obtained from all patients or their legal guardians.

2.3. Data collection

The data collected includes patient sex, date and age at diagnosis, endoscopic features, EoE phenotype (inflammatory, structuring or mixed), peak eosinophil count at diagnosis, presence of persistent or seasonal concomitant atopic manifestations and any family background of EoE, all of which were assessed at the time of EoE diagnosis. In addition, detailed information of treatment for EoE was also retrieved from the EoE CONNECT registry: use of PPI, dietary modifications, and swallowed topic corticosteroids (STC) mono-therapies; and response to therapy (including both clinical and histological) were considered. Finally, the need for endoscopic dilation and date of each dilation session was evaluated.

2.4. Definitions

Endoscopic features are registered in EoE CONNECT according the EREFS classification system [22]: Total EREFS (0–9) is calculated by summing the severity scores of the five individual major components (Edema 0–1, Rings 0–3, Exudates 0–2, Furrows 0–1 and Strictures 0–1), and the minor finding of crepe paper esophagus (mucosal fragility or laceration upon passage of endoscope, 0–1), with higher scores indicating more severe endoscopic findings. There are two phenotypic forms of the disease, an inflammatory and a fibrostenotic type [23]. Normal esophageal diameter, whitish exudates, edema, and linear furrows constitute the inflammatory form, whereas fixed rings, strictures, and esophageal narrowing characterize the fibrostenotic type [24]. As actively maintained eosinophilic inflammation tend to progress into fibrous remodeling, with collagen deposition and stricture formation [25], a proportion of patients present with mixed endoscopic features of these two phenotypes.

Symptoms in EoE CONNECT are measured in adults and adolescents by the Dysphagia Symptoms Score (DSS), a non-validated measuring instrument developed by Alex Straumann and colleagues in 2010 [26]. Briefly, DSS assesses frequency of dysphagia, ranging from none (0) to several times per day (5); the intensity of dysphagia, ranging from unhindered swallowing (1) to long-lasting complete obstruction requiring endoscopic intervention (5); and the duration of dysphagia, ranging from no attacks (0) to lasting up to endoscopic removal of the impacted food (5). Total scores range from 1 to 15. Subjective symptom intensity reported by either children or parents is considered for younger children. As a second point of clinical evaluation, EoE CONNECT includes an assessment by physicians of symptoms from the initiation of a therapy for EoE, to capture the short-term effectiveness of any intervention.

Active disease in EoE CONNECT is defined as a peak eosinophilic infiltrate by >15 cells per high power field (hpf) at any esophageal level together with >5 points in the DSS.

Response to therapy is evaluated independently according to clinical, endoscopic and histological criteria. A decrease of more than 50% in baseline DSS after therapy is considered clinical remission in older children and adults. A symptomatic improvement ≤50% from baseline is considered as a clinical response. For younger children, any subjective improvement in symptoms reported by either children or parents is considered as clinical remission.

Histological remission is defined as an eosinophil peak count below the diagnostic threshold of 15 cells per hpf at all esophageal levels after therapy.

2.5. Treatment policy

All participating centers are considered as having expertise in managing EoE and are associated with EUREOS; an aim of which is to disseminate knowledge on EoE through a broad communication and informative program. Consequently, the therapeutic strategy for EoE in EoE CONNECT participating sites is based on international guidelines [15,27], thus, first-line anti-inflammatory therapies are selected according to patients' characteristics and preferences. Endoscopic dilation is performed for esophageal strictures (either at disease diagnosis or in combination with effective anti-inflammatory therapy), narrow caliber esophagi, or persistent symptoms, despite histological and endoscopic remission.

2.6. Statistical analysis

Mean, median, standard deviation (SD) and interquartile ranges (IQR) were calculated for continuous variables. Mean and SD were used for variables with a normal distribution and median and IQR for those with a non-normal distribution. Normality was evaluated using the Kolgomorov-Smirnov test. Comparisons were performed with Student *t*-test for normal distributed variables and Mann-Whitney test for non-normal distributed ones. Percentages were calculated for categorical variables, which were compared between groups using Chi-square ($\chi 2$) or Fisher's exact tests. Analyses were carried out using PASW 18.0 statistical analysis software (SPSS Inc, Chicago, IL, USA) and GraphPad Prism version 5.0 (GraphPad Software, San Diego, CA, USA). Statistical significance was considered when $p<0.05$.

3. Results

3.1. Demographic characteristics

A total of 1298 patients diagnosed with EoE who had both date of birth and date of diagnosis registered in EoE CONNECT were included in our study. Adulthood-onset cohort (≥18 years at diagnosis) comprised 1044 patients (80.4%), while childhood-onset cohort (<18 years at diagnosis) comprised 254 patients (19.6%). Within these age groups we also defined two subgroups of patients with special characteristics, which comprised 129 adolescent patients (12 to 17 years) and 52 older patients diagnosed over 60 years of age. Demographic and main clinical characteristics of these patient cohorts are detailed in Tables 1 and 2.

No gender differences were observed between adults and children (Table 1), with male sex being predominant in all age groups (84.1% in children and 76.8% in adults; $p = 0.142$). However, the male:female (M:F) ratio tended to reduce as age at diagnosis increased, the proportion of women being significantly higher among older patients ($p = 0.019$) (Table 2 and Fig. 1A).

Weight at birth was similar between patients with childhood and adulthood onset EoE. However, a difference was observed between pediatric patient subgroups, with those diagnosed at the

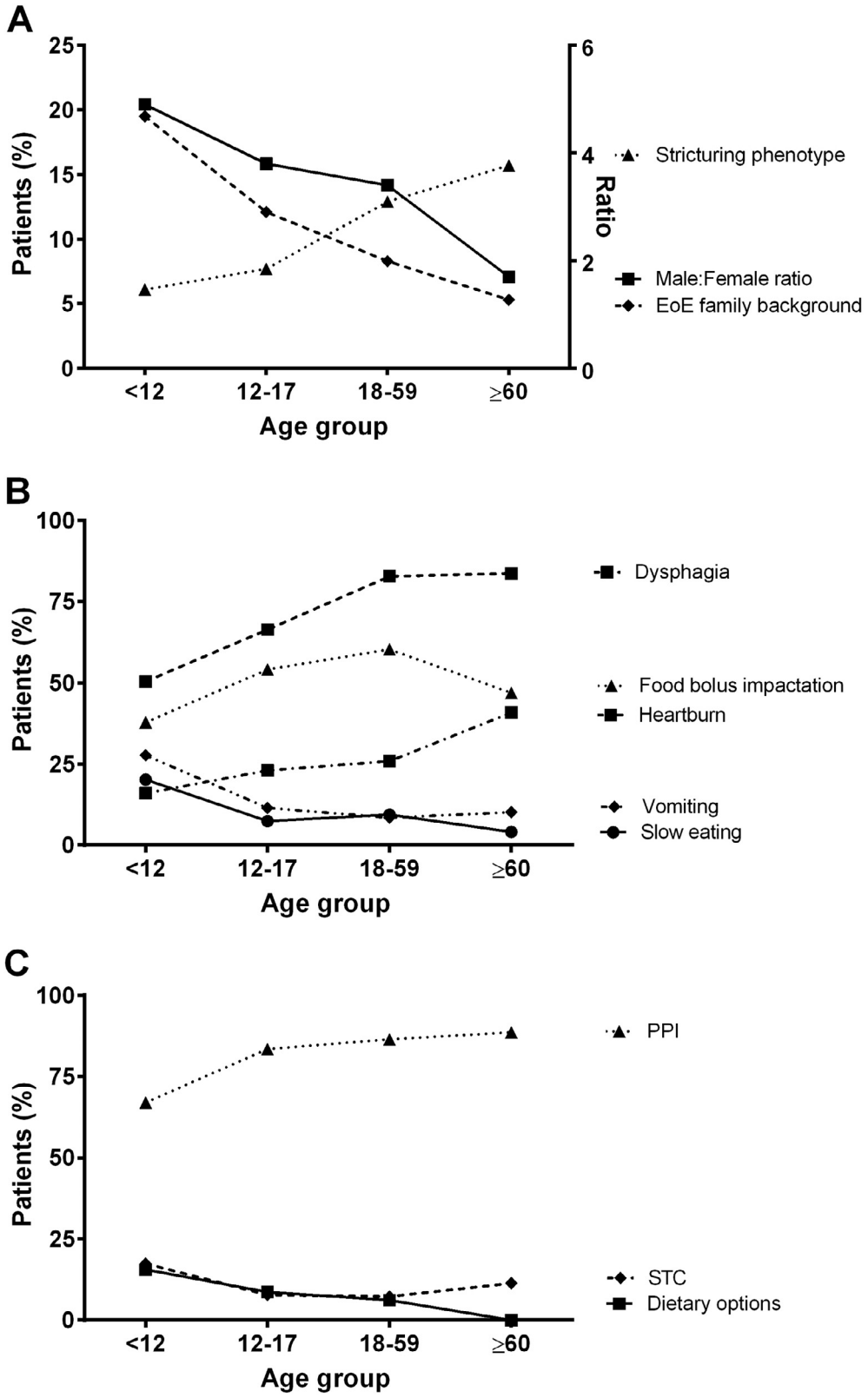

Fig. 1. Proportion of patients for each age group in demographic parameters and EoE phenotype, showing a decreased/increased trend with age of diagnosis (A), in symptoms reported (B), and in first-line treatment choice (C). PPI: proton-pump inhibitors; STC: swallowed topical corticosteroids.

Table 1
Demographic, clinical characteristics and atopic comorbidities at the time of diagnosis, and response to first-line treatment of a series of adult and pediatric patients with EoE registered in EoE CONNECT.

		Total (n = 1298)	**Pediatrics** (n = 254)	**Adults** (n = 1044)	**p**
Mean age at diagnosis, years (SD; rank)		33.0 (15.2; 0.7–89.7)	11.9 (3.9; 0.7–17.9)	38.2 (12.2; 18.0–89.7)	<0.001
Diagnostic delay (years, median ± IQR, [n])		2.1 ± 5.5, [1104]	1 ± 2.1 [209]	2.7 ± 6.1 [895]	<0.001
Sex	Male, n (%)	1008 (77.7)	206 (84.1)	802 (76.8)	0.142
	Female, n (%)	290 (22.3)	48 (18.9)	242 (23.2)	
Family EoE background	Yes, n (%)	104 (9.8)	36 (16)	68 (8.2)	<0.001
	No, n (%)	954 (90.2)	189 (84)	765 (91.8)	
Weight at birth, Kg (median ± IQR [n])		3.3 ± 0.6 [447]	3.4 ± 0.6 [147]	3.2 ± 0.6 [330]	0.485
EREFS score at baseline (median ± IQR [n])		2 ± 3 [1122]	3 ± 2 [210]	2 ± 3 [912]	0.017
EREFS sub-score	Inflammation	1 ± 2	2 ± 2	1 ± 2	<0.001
	Fibrosis	1 ± 2	0 ± 1	1 ± 2	<0.001
EoE phenotype	Inflammatory, n (%)	894 (74.5)	195 (84.1)	699 (72.2)	0.001
	Stricturing, n (%)	142 (11.8)	16 (6.9)	126 (13)	
	Mixed, n (%)	164 (13.7)	21 (9.0)	143 (14.8)	
Peak of eosinophils/hpf (median ± IQR [n])		40 ± 40 [971]	50 ± 50 [175]	40 ± 35.7 [796]	0.015
Concomitant atopies					
Rhinitis	Seasonal, n (%)	454 (80.4)	104 (83.9)	350 (79.4)	0.265
	Persistent, n (%)	111 (19.6)	20 (16.1)	91 (20.6)	
Asthma	Seasonal, n (%)	233 (70.2)	61 (77.2)	172 (68)	0.117
	Persistent, n (%)	99 (29.8)	18 (22.8)	81 (32)	
Conjunctivitis	Seasonal, n (%)	272 (91)	71 (93.4)	201 (90.1)	0.388
	Persistent, n (%)	27 (9)	5 (6.6)	22 (9.9)	
Dermatitis	Seasonal, n (%)	84 (52.5)	29 (50.9)	55 (53.4)	0.760
	Persistent, n (%)	76 (47.5)	28 (49.1)	48 (46.6)	
Treatment used for EoE and effectiveness					
First-line anti-inflammatory treatment[a]	Dietary treatment, n (%)	79 (7.1)	27 (12.1%)	52 (5.9)	<0.001
	PPI, n (%)	933 (84.4)	169 (75.4)	764 (86.6)	
	STC, n (%)	94 (8.5)	28 (12.5)	66 (7.5)	
Clinical response rate to any first-line treatment	Yes, n (%)	810 (73.9)	162 (73.3)	648 (74.1)	0.820
	No, n (%)	286 (26.1)	59 (26.7)	227 (25.9)	
Clinical response to FED	Yes, n (%)	45 (80)	13 (86.7)	32 (78.0)	0.708
	No, n (%)	11 (20)	2 (13.3)	9 (22.0)	
Clinical response to PPI	Yes, n (%)	630 (73)	115 (72.8)	515 (72.7)	>0.999
	No, n (%)	236 (27)	43 (27.2)	193 (27.3)	
Clinical response to STC	Yes, n (%)	60 (80)	17 (73.1)	43 (82.7)	0.532
	No, n (%)	15 (20)	6 (26.1)	9 (17.3)	
Histological response rate to any first-line treatment	Yes, n (%)	510 (50.1)	94 (45.2)	416 (51.4)	0.113
	No, n (%)	508 (49.9)	114 (54.8)	394 (48.6)	
Histological response to FED	Yes, n (%)	28 (48)	8 (47.0)	19 (47.5)	>0.999
	No, n (%)	30 (52)	9 (53.0)	21 (52.5)	
Histological response to PPI	Yes, n (%)	413 (50)	68 (45.6)	345 (50.7)	0.279
	No, n (%)	417 (50)	81 (54.4)	336 (49.3)	
Histological response to STC	Yes, n (%)	35 (63)	10 (52.6)	25 (67.6)	0.383
	No, n (%)	21 (37)	9 (47.4)	12 (32.4%)	
Endoscopic dilation rate, n (%)		84 (6.5)	8 (3.3)	76 (7.9)	0.011
Number of dilation sessions/patient (median ± IQR)		1 ± 1	1.5 ± 1	1 ± 1	0.603

EoE: eosinophilic esophagitis; SD: standard deviation; IQR: inter-quartile range; FED: food-elimination diet; PPI: proton-pump inhibitors; STC: swallowed topical corticosteroids; EREFS: edema, rings, exudates, furrows and stricture; hpf: high power field;.
[a] First-line treatment: only single therapy treatments were included in the analysis.

youngest ages (before 12 years) presenting significantly lower birth weight (3.3 *vs.* 3.5 kg; $p = 0.033$) (Table 2).

A family background of EoE was present in 9.8% of patients registered in EoE CONNECT overall, with this proportion being significantly higher among children compared to adults (16 *vs.* 8.2%; $p<0.001$) and showing a decreasing trend with age (Fig. 1A).

3.2. EoE symptoms

Overall, 1236 out of the 1298 patients included (95.2%) had at least one symptom of EoE registered, with no differences between children (94.9%) and adults (95.3%). Details on the 17 potential symptoms of EoE that are included in EoE CONNECT is shown in Table 3. Compared to adults, the childhood-onset cohort more frequently presented vomiting, chest pain, abdominal pain, slow eating, weight loss, aversion to food and nausea. In contrast, dysphagia, food bolus impaction, and heartburn were significantly more common among adults.

Differences in clinical manifestations in adolescents and older adults were assessed exclusively for those symptoms with an overall frequency of 10% or higher, in order to avoid low numbers affecting statistical significance (Table 4). Patients diagnosed with EoE at 60 or older suffered from heartburn more commonly than the younger adults (40.8% *vs.* 25.9%; $p = 0.021$); while EoE patients diagnosed during adolescence had more dysphagia (66.4% *vs.* 50.4%; $p = 0.012$) and food bolus impaction (54.1% *vs.* 37.8%; $p = 0.011$) that younger children, who, in contrast, presented vomiting (27.7% *vs.* 11.5%; $p = 0.001$) and slow eating (20.2% *vs.* 7.4%, $p = 0.004$) with higher frequency. Furthermore, the frequency of dysphagia and heartburn tended to increase with age at EoE diagnosis (Fig. 1B).

3.3. Concomitant allergic diseases

Rhinitis, asthma, conjunctivitis and dermatitis were the four main concomitant atopic conditions reported by patients. No differences were found regarding the persistent or seasonal presenta-

Table 2
Demographic and clinical characteristics at the time of diagnosis and response to treatment of different age sub-groups of EoE patients registered in EoE CONNECT.

		Pediatrics			**Adults**		
		below 12 (n = 125)	**12 to 17** (n = 129)	**p**	**18 to 59** (n = 992)	**over 60** (n = 52)	**p**
Mean age at diagnosis, years (SD; rank)		8.5 (2.4; 0.7–11.9)	15.1 (1.6; 12.2–17.9)	<0.001	36.7 (10.5; 18.0–59.8)	66.1 (6.0; 60.0–89.7)	<0.001
Diagnostic delay in years (median ± IQR, [n])		1.0 ± 2.1 [96]	1.0 ± 2.8 [113]	0.149	2.7 ± 6.2 [851]	1.7 ± 4.3 [44]	0.143
Sex	Male, n (%)	104 (83.2)	102 (79.1)	0.401	769 (77.5)	33 (63.5)	0.019
	Female, n (%)	21 (16.8)	27 (20.9)		223 (22.5)	19 (36.5)	
Male:Female ratio		4.9:1	3.8:1		3.4:1	1.7:1	
Family EoE background	Yes, n (%)	23 (19.5)	13 (12.1)	0.149	66 (8.3)	2 (5.3)	0.762
	No, n (%)	95 (80.5)	94 (87.9)		729 (91.7)	36 (94.7)	
Weight at birth, Kg (median ± IQR [n])		3.3 ± 0.7 [89]	3.5 ± 0.8 [58]	0.033	3.2 ± 0.6 [322]	3.5 ± 0.8 [8]	0.639
EREFS score at baseline (median ± IQR [n])		3 ± 2 [105]	3 ± 2 [105]	0.948	2 ± 3 [867]	2 ± 2.5 [45]	<0.001
EREFS sub-score	Inflammation	2 ± 2	2 ± 2	0.057	1 ± 2	0 ± 2	0.003
	Fibrosis	0 ± 0	0 ± 1	0.008	1 ± 2	1 ± 2	0.047
EoE phenotype	Inflammatory, n (%)	102 (88.7)	93 (79.5)	0.105	663 (72.3)	36 (70.6)	0.838
	Stricturing, n (%)	7 (6.1)	9 (7.7)		118 (12.9)	8 (15.7)	
	Mixed, n (%)	6 (5.2)	15 (12.8)		136 (14.8)	7 (13.7)	
Peak of eosinophils/hpf (median ± IQR [n])		50 ± 50 [90]	50 ± 53.5 [85]	0.967	40 ± 39 [757]	35 ± 26 [39]	0.053
First-line anti-inflammatory treatment[a]	Dietary treatment, n (%)	17 (15.6)	10 (8.7)	0.015	52 (6.2)	0 (0)	0.158
	PPI, n (%)	73 (67.0)	96 (83.5)		725 (86.5)	36 (88.6)	
	STC, n (%)	19 (17.4)	9 (7.8)		61 (7.3)	5 (11.4)	
Clinical RR to first-line treatment	Yes, n (%)	85 (78.7)	77 (68.1)	0.076	610 (73.6)	38 (82.6)	0.174
	No, n (%)	23 (21.3)	36 (31.9)		219 (26.4)	8 (17.4)	
Histological RR to first-line treatment	Yes, n (%)	47 (45.6)	47 (44.8)	0.900	387 (50.6)	29 (64.4)	0.071
	No, n (%)	56 (54.4)	58 (55.2)		378 (49.4)	16 (35.6)	

EoE: eosinophilic esophagitis; SD: standard deviation; IQR: inter-quartile range; PPI: proton-pump inhibitors; STC: swallowed topical corticosteroids; EREFS: edema, rings, exudates, furrows and stricture; hpf: high power field; RR: response rate.
[a] First-line treatment: only single therapy treatments were included in the analysis.

Table 3
Frequency of symptoms associated with eosinophilic esophagitis in pediatric and adult patients.

Symptom	**Overall (n = 1236)**	**Pediatrics (n = 241)**	**Adults (n = 995)**	**p**
Abdominal pain, n (%)	73 (5.9)	33 (13.7)	40 (4.0)	**<0.001**
Chest pain, n (%)	139 (11.2)	41 (17.0)	98 (9.8)	**0.002**
Choking, n (%)	111 (8.9)	20 (8.3)	91 (9.1)	0.680
Diarrhea, n (%)	28 (2.3)	7 (2.9)	21 (2.1)	0.457
Depressive mood, n (%)	7 (0.6)	0 (0)	7 (0.7)	0.357
Dysphagia, n (%)	965 (78.1)	141 (58.5)	824 (82.8)	**<0.001**
Epigastric pain, n (%)	110 (8.9)	21(8.7)	89 (8.9)	0.910
Failure to thrive, n (%)	105 (8.5)	26 (10.8)	79 (7.9)	0.155
Food aversion, n (%)	28 (2.3)	15 (6.2)	13 (1.3)	**<0.001**
Food bolus impaction, n (%)	704 (57.0)	111 (46.1)	593 (59.6)	**<0.001**
Heartburn, n (%)	312 (25.2)	47 (19.5)	265 (26.6)	**0.022**
Nausea, n (%)	37(3.0)	14 (5.8)	23 (2.3)	**0.004**
Regurgitation, n (%)	153 (12.4)	24 (10.0)	129 (13.0)	0.204
Sleep disturbances, n (%)	18 (1.5)	3 (1.2)	15 (1.5)	>0.999
Slow eating, n (%)	124 (10.0)	33 (13.7)	91 (9.1)	**0.035**
Vomiting, n (%)	132 (10.7)	47 (19.5)	85 (8.7)	**<0.001**
Weight loss, n (%)	41 (3.3)	16 (6.6)	25 (2.5)	**0.001**

Table 4
Frequency of symptoms associated with EoE and differences according to age at the time of diagnosis in age-related subgroup of patients. Only symptoms with an overall frequency ≥10% are considered.

	Pediatrics			**Adults**		
	below 12 (n = 119)	**12 to 17** (n = 122)	**p**	**18 to 59** (n = 946)	**over 60** (n = 49)	**p**
Chest pain, n (%)	25 (21)	16 (13.1)	0.103	91 (9.6)	7 (14.3)	0.320
Dysphagia, n (%)	60 (50.4)	81 (66.4)	0.012	783 (82.8)	41 (83.7)	0.870
Food bolus impaction, n (%)	45 (37.8)	66 (54.1)	0.011	570 (60.3)	23 (46.9)	0.064
Heartburn, n (%)	19 (16.0)	28 (23.0)	0.171	245 (25.9)	20 (40.8)	0.021
Regurgitation, n (%)	11 (9.2)	13 (10.7)	0.714	120 (12.7)	9 (18.3)	0.272
Slow eating, n (%)	24 (20.2)	9 (7.4)	0.004	89 (9.4)	2 (4.1)	0.307
Vomiting, n (%)	33 (27.7)	14 (11.5)	0.001	80 (8.5)	5 (10.2)	0.602

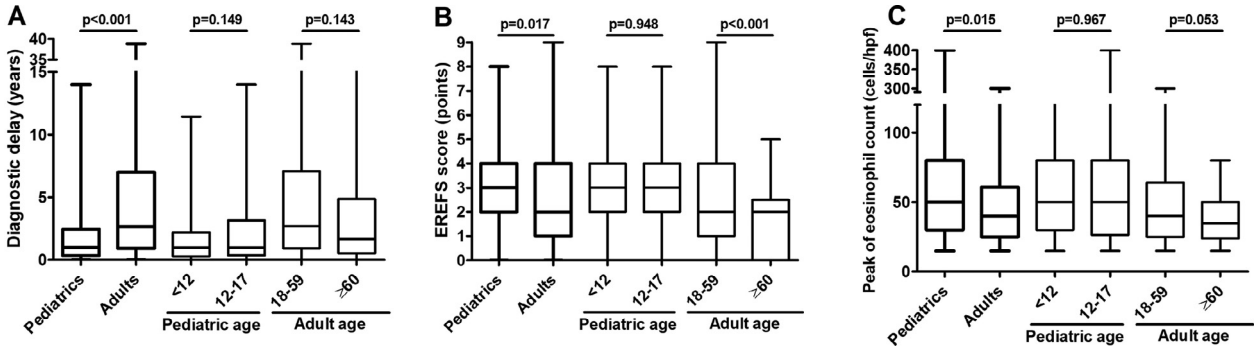

Fig. 2. Box plots for diagnostic delay (years passed from symptom onset to receiving an EoE diagnosis) (A), EREFS (edema, rings, exudates, furrows and stricture) score calculated at diagnosis endoscopy (B) and peak of eosinophil count per high power field (maximum number of eosinophils in biopsies taken for EoE diagnosis) (C).

tion of these between children and adults (Table 1). Likewise, no differences were found when adolescents and older adults subgroups were compared with small children and younger adults (data not shown).

3.4. Diagnostic delay

EoE symptoms onset data was available for 1104 patients in our study (85%), thus allowing diagnostic delay to be calculated. The median ± IQR diagnostic delay for EoE in our cohort was 2.1 ± 5.5 years, and was significantly longer for adults than for children (2.7 ± 6.1 *vs.* 1 ± 2.1 years; $p<0.001$). No significant differences were observed within patient subgroups (Table 2 and Fig. 2A).

3.5. EREFS score, phenotype and peak eosinophil counts

The EREFS score was evaluated in 1122 patients, including 912 adults and 210 pediatric patients. Overall median ± IQR EREFS scores were higher in children than in adults (3 ± 2 vs 2 ± 2; $p = 0.017$), with older adults at diagnosis showing an even lower EREFS score compared to younger adults ($p <0.001$) (Tables 1 and 2) (Fig. 2B).

While pediatric patients mostly presented higher median ± IQR scores for inflammatory features (edema, furrows and/or exudates) (2 ± 2 *vs.* 1 ± 2; $p<0.001$), fibrotic components of EREFS (rings and/or strictures) were more prevalent among adults (1 ± 2 *vs.* 0 ± 1; $p<0.001$), thus contributing to adults presenting significantly higher prevalence of structuring (13.0% *vs.* 6.9%) and mixed phenotypes (14.8% *vs.* 9.0%) than children at the time of EoE diagnosis ($p<0.001$). A trend towards increasing prevalence of structuring phenotypes with age at EoE diagnosis was also found (Fig. 1A).

Differences in peak of eosinophil counts per hpf were also evaluated in patients of different ages. Pediatric patients overall presented higher median ± IQR peak eosinophil densities at esophageal biopsies than adults (50 ± 50 *vs.* 40 ± 35; $p = 0.015$). Older adults tended to present less peak eosinophil counts than younger adults (40 ± 39 *vs.* 35 ± 26; $p = 0.053$) (Fig. 2C).

In accordance with these results, we observed that the increase in the percentage of stricturing phenotypes throughout the patient ages was inversely correlated with the maximum eosinophil counts in esophageal biopsies (Spearman Rho=−0.115; $p<0.001$).

3.6. Choice of first-line treatment and efficacy to induce remission

We found differences in the choice of first-line therapy for the treatment of children and adults with EoE in real-world practice (Table 1). Thus, dietary therapies were used more frequently overall in children (12.1% *vs.* 5.9%) and STC (12.5% *vs.* 7.5%) than in adults ($p<0.001$). Both therapies were used with a significantly higher frequency among those children under 12 years of age at the time of diagnosis compared to adolescents (Table 2). A trend to reduce the use of dietary therapies as the initial intervention to induce EoE remission across patients' age at diagnosis was noticed, while the opposite occurred with PPI therapy (Fig. 1C).

The effectiveness of the three first-line treatment options to induce clinical and histological responses was not different between children and adults (Table 1). Nor did we find variances when different age subgroups of patients were compared (Table 2). In addition, no differences were detected in the effectiveness of empirical food elimination diets (EFED was the most common dietary intervention used), PPI and STC between children and adults, although the number of patients with fully assessed clinical and histological response was low, especially for children treated with EFED and STC (Table 1).

Finally, we analyzed the endoscopic dilations carried out in children and adults (either as a single procedure or combined with other anti-inflammatory therapy). This procedure was performed more commonly among adults (76 patients, 7.9%) than among children (8 patients, 3.3%; $p = 0.011$). However, in patients who required endoscopic dilation, the median ± IQR number of dilations per patient did not differ between age groups (Table 1).

4. Discussion

The present series is, to our knowledge, the largest available comparing subjects with EoE diagnosed in childhood and adulthood. The prospective collection of data allowed us to obtain key updated knowledge on the differences between pediatric and adult-onset EoE with respect to: the symptoms, endoscopic features and histological activity at diagnosis, the use of the different treatment options and the response in terms of histological and clinical improvement. The standardized data collection of EoE CONNECT also allowed us to make direct comparisons between patients of different age groups in order to better define the natural history of EoE and its characteristics across ages. Our results complement those provided by previous series of patients of all ages [28], as well as provide an overview of EoE, compared to recent works focused exclusively on younger patients [29].

Symptoms associated with EoE as well as endoscopic features evolved across the age range, with notable differences even within different age groups. As recently described, EoE presentation is heterogeneous in the pediatric age and findings vary from small children to adolescents [29]. Fibrotic features progressively develop with age, leading to a significantly higher risk of structuring EoE and the need for endoscopic dilation. Differences in first-line therapies to treat EoE patients were noted when pediatric and adult patients were compared, with the response to these therapies being similar in patients independent of age.

In a recent review, Visaggi et al. [10] analyzed the main differences between children and adults with EoE at the time of diagnosis, and provided indirect evidence that endoscopy in children usually shows an inflammatory-predominant pattern while adults more frequently show fibrostenotic phenotype. A recent paper based on data from pEEr (European Pediatric Eosinophilic Esophagitis Registry) of ESPGHAN also found that endoscopic findings of fibrosis, in especial esophageal rings, were more common in adolescents, whereas exudates were more frequent in younger children [29]. A retrospective EoE cohort recruited across 10 sites at USA also documented that a larger proportion of pediatric EoE patients had an inflammatory phenotype at endoscopy, while more adults had a fibrostenotic phenotype than did pediatric individuals [28]. This difference is clearly supported by our study, in which a fibrostenotic phenotype was almost twice as frequent in adults compared to children. This fact is potentially related with a longer course of subclinical disease among adults, and with a more prolonged diagnostic delay from symptoms onset. Lack of care of more than 2 years in patients with EoE has been recently associated with signs of increased disease activity and progression to fibrostenosis [30]. An untreated EoE has been associated with the formation of esophageal strictures [31] and the risk for a fibrostenotic phenotype appears to double for every 10-year increase in age [32], indicating a progressive disease.

Disease phenotype could also determine disease complaints, with most children having been reported to present with nausea, vomiting, anorexia, abdominal pain, failure to thrive and heartburn [9,10,29,33]. In contrast, dysphagia and food impaction are considered typical for adult-onset EoE, as already reported in additional large series [11,28]. Our data demonstrated that, dysphagia and food bolus impaction are also reported by approximately half of pediatric patients (59% and 46%, respectively). Both symptoms were significantly more common among adolescents than in children diagnosed below 12 years of age, completely reproducing the results from pEEr [28]. Vomiting and slow eating were present in 1 out of 4 and 1 out of 5 children, respectively, and both symptoms were significantly more common in younger children compared to adolescents. Consequently, adolescents displayed more dysphagia and food bolus impaction and less vomiting and slow eating than children diagnosed under 12 years old, thus making them more similar to adults in terms of EoE symptoms (Supplementary Table 1). In addition, younger children, especially under 8 years of age, were less able to express symptoms, and the presence of dysphagia might be usually inferred by indirect symptoms such as slow eating of food aversion.

Among adults, our data confirm dysphagia to solids, food impaction and heartburn as the most common symptoms, which appeared significantly more frequently than in the whole pediatric group. In contrast, adults diagnosed over 60 years presented heartburn more frequently than younger adults, while no changes were observed for other symptoms.

Population-based epidemiological studies have described that the vast majority of patients with EoE are between the first and the sixth decades in life [2,34,35], despite having been described in patients of all ages. Nevertheless, the incidence of EoE decreases as age increases and patient series of aged patients are minimal. As these patients are frequently excluded from trials assessing new therapies for EoE [36–38], it has been noted that their response to different treatments remains largely unknown [20]. A recent retrospective cohort study identified only 12 patients aged over 65 among those newly diagnosed and treated with STC at the EoE database of the University of North Carolina [20]. This therefore makes our series of 52 senior EoE patients the largest described to our knowledge, although our cut-off of 60 years of age was slightly different. Apart from its differences in clinical presentation compared to younger adults, and a progressive decrease in male:female ratio compared to younger ages, patients diagnosed as suffering from EoE over the age of 60 presented lower EREFS scores and peak eosinophil counts. Contrary to Ketchem et al. [20], we did not observe a longer diagnosis delay for elder patients, most likely suggesting that esophageal symptoms are considered as alarm symptoms in this patient group. Taken together with the fact that the elderly could respond better to treatment with STC [20] and probably to other therapies (we noticed a trend to improved histological response to any first-line treatment among patients aged over 60), available evidences suggests EoE in older patients represents a milder form of the disease compared to younger adults.

Importantly, our research identified that the proportion of children with a family background of EoE was significantly higher than that of adults. This could reflect either a greater awareness in families of the appearance of symptoms in a young member, or that the family grouping of cases implies greater severity of EoE and appearance at a younger age. Shorter diagnostic delays were recently associated with the presence of a family history for EoE [29]. Despite a higher role for environmental factors being recognized in the origin of EoE [39], family aggregation of EoE in population-based studies suggests a genetic contribution [40]. However, from microarray analysis on esophageal biopsies from familial and sporadic EoE patients no significant differences were found [41], however the low number of samples analyzed in this single available study (provided by only 6 family and 10 sporadic EoE patients) prevent definitive conclusions.

Our study also assessed the persistent and seasonal presentation of the four major atopic conditions associated with EoE and found no differences between children and adults. A previous observation by Vernon et al. also described a similar history of allergic rhinitis, atopic dermatitis, immunoglobulin E-mediated food allergy, and family history of atopy in children and adults with EoE [42], but a higher prevalence of asthma in children compared to adults. In fact, EoE has been shown as a late manifestation of the atopic march [43] and diagnosed after the onset of atopic dermatitis, IgE-mediated food allergy, asthma and allergic rhinitis, making it unlikely to find differences between children and adults overall. In contrast, small but statistically significant differences in the prevalence of atopic dermatitis and food allergy between children and adolescents were found in the pEEr [29]. Relevantly, our study shows that allergic rhinitis and bronchial asthma were the main atopic manifestations associated with EoE, and that their course was seasonal in the vast majority of patients. However, data on atopic manifestations were available for less than half of patients registered in EoE CONNECT, therefore they might not reflect the true prevalence of these diseases in the EoE population, despite allowing comparison between ages.

According to survey-based studies carried out in Europe [44,45], United States of America [46] and Australia [47] with regard to therapy, PPI represented the most commonly prescribed first-line therapy for EoE in patients of all ages. This is confirmed by registries of clinical practice [48]. However, PPI was prescribed significantly less in children overall compared to adults, and also among younger children compared to adolescents. STC and dietary therapy were preferred equally as first-line therapy for EoE in 12% of pediatric patients, and both therapies doubled in frequency its use in younger children compared to adolescents. Importantly, the effectiveness of the different therapies were not different between patients of different age groups, which reproduced the symptomatic response and histological remission rates (mostly involving adult EoE patients) already reported in previous analysis of the EoE CONNECT registry [48,49]. In contrast, response rate to PPIs in pEEr was significantly lower, likely due to the preferential inclusion of patients who failed to PPI therapy [29], following diagnostic criteria available before the 2017 clinical practice guideline [15] was released. As for endoscopic dilation, this was

used more than twice as frequently in adults compared to children, as the former presented a higher frequency of fibrostenosing EoE. However, the number of dilation procedures performed did not differ according to patients age, probably reflecting the sustained effect of endoscopic dilation when combined with an effective anti-inflammatory therapy in EoE [50,51].

A significantly shorter diagnostic delay among pediatric patients compared to adults is another relevant finding of our research. Differences in diagnostic delay from symptoms onset were previously described in a multicenter study carried out in Spain in 2012 which found a diagnostic delay of 28.04±30 months and 54.7 ± 62 months respectively for children and adults [52]. Our research shows that the diagnostic delay for EoE has been reduced by half over the last decade at European sites participating in EoE CONNECT, in agreement with recent findings from another analysis of our registry, which also documented a better diagnostic work-up of patients with EoE over time [53]. Data from pEEr just reported a diagnostic delay of around 1 year for pediatric patients with EoE overall, quite similar to EoE CONNECT results, despite it was slightly longer for smaller children. However, these figures are provided by facilities specialized in the management of patients with EoE, and could not reproduce the general situation of the issue. In general, diagnostic delay for EoE is still unacceptably long, especially among adult patients [53]. In fact, older age at the time of diagnosis has been identified to predict increased time to diagnosis in EoE [54].

Our study has some limitations. First of all, although the EoE CONNECT registry included a high number of variables, some data is not frequently registered, such as atopic conditions associated with EoE, patient weigh at birth, or peak eosinophil count; therefore, the number of patients for those analyses were lower compared to the whole cohort. Secondly, as several sites participate in EoE CONNECT, some heterogeneity in the management of EoE patients could be present and differences in practice patterns would have affected the management of patients from both the pediatric and adult cohorts within the centers. However, this is likely to have had a minor impact as most of the researchers contributing to EoE are experts in EoE and work at referral sites for EoE patients. In addition, EUREOS provides educational support for its members to overcome heterogeneity in the management of EoE patients. Thirdly, our data could no assess disease endotypes for EoE, *i.e.*, disease subtypes defined by molecular and cellular markers that might impact the identification, prognosis and response to therapy of patients with EoE [28]. Finally, since the sub-group of patients diagnosed at 60 years old or over was small conclusions should be viewed cautiously and this age group evaluated in bigger cohorts if possible in the future.

Our study has also several strengths. Firstly, to our knowledge, this is the largest study on the comparison of childhood and adulthood-onset EoE currently. Secondly, EoE CONNECT mostly includes prospectively recruited patients and information is updated on successive visits to clinic. In addition, 24 sites provided information on their patients to inform this study from the EoE CONNECT registry, which include both large university and regional hospitals, reflecting real practice.

In conclusion, the largest study cohort comparing childhood- and adulthood-onset EoE shows that patients diagnosed during childhood have differential clinical and endoscopic characteristics, and show differences in the use of first-line therapies. However, response rates to treatment were similar in patients of all ages.

Authorship statement

Guarantor of article: Alfredo J Lucendo. Specific author contributions: Alfredo J Lucendo, and Emilio J Laserna-Mendieta design and writers. Pilar Navarro, Sonsoles Tamarit-Sebastián, Ángel Arias and Emilio J Laserna-Mendieta: database monitoring and quality assessment, data extraction and analysis. Sergio Casabona-Francés, Edoardo Savarino, Isabel Pérez-Martínez, Danila Guagnozzi, Jesús Barrio, Antonia Perello A, Antonio Guardiola-Arévalo, Elena Betoré, Leonardo Blas-Jhon, Francesca Racca, Anne Lund Krarup, Carolina Gutiérrez-Junquera, Sonia Fernández-Fernández, Susana De la Riva S, Juan E Naves, Silvia Carrión, Natalia García-Morales, Valentín Roales, Juan Armando Rodríguez-Oballe, Raffaella Dainese, Alba Rodríguez-Sánchez, Maria Lluisa Masiques-Mas, Sara Feo-Ortega, Matteo Ghisa, Daria Maniero, Adolfo Suarez, Ronald Llerena Castro, Paula Gil-Simón, Luisa de la Peña-Negro, Alicia Granja Navacerrada, Javier Alcedo, Lonore Hurtado de Mendoza-Guena, Gaia Pellegatta, María Teresa Pérez-Fernández, Cecilio Santander, Sonsoles Tamarit-Sebastián, Ángles Arias y Alfredo J. Lucendo AJ participated in the collection and interpretation of data. All authors provided a critical review and relevant intellectual content to the manuscript and approved its final version.

Conflict of Interest

AJ Lucendo has served as a speaker, and/or has received research and/or education funding and/or consulting fees from Adare/Ellodi, Dr. Falk Pharma, Regeneron, Dr. Falk Pharma and EsoCap.

C. Santander received honoraria as consultant and trainer at Laborie/MMS and Medtronic Covidien AG, and received research funding from AstraZeneca, EsoCap Biotech, Regeneron Pharmaceuticals Inc., Adare Pharmaceuticals Inc., and Dr. Falk Pharma GmbH.

J. Alcedo has served as a speaker, consultant and advisory member for or has received research funding from Adare Pharmaceuticals Inc, Abbvie, MSD, Allergan, and Shire Pharmaceuticals.

C Gutiérrez-Junquera has received research funding from Dr. Falk Pharma.

The remaining authors have no conflict of interest.

Funding

EJ Laserna-Mendieta is recipient of a Juan Rodes grant (JR19/00005) and P Navarro of a Sara Borrell grant (CD19/00102), both from the Instituto de Salud Carlos III (ISCIII), Spanish Ministry of Health - Social Services and Equality, which is partly funded by the European Social Fund (period 2014–2020).

Data Availability Statement

The data that supports the findings of this study is available from the corresponding author upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2022.09.020.

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