ORIGINAL PAPER

DOI: http://dx.doi.org/10.15403/jgld-7110

Time Trends and Impact on Treatment Outcomes of Psychiatric Diagnoses in Patients with Eosinophilic Esophagitis

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Received: 31.03.2026
Accepted: 04.06.2026

ABSTRACT

Background & Aims: While mental illness is common in eosinophilic esophagitis (EoE), it is unknown whether psychiatric diagnosis frequency has varied over time or impacts treatment outcomes. We aimed to determine time trends in psychiatric diagnoses in EoE and whether such diagnoses affect EoE treatment outcomes.
Methods: In this retrospective cohort study of newly diagnosed EoE patients, medical records were examined to determine psychiatric diagnoses and psychoactive medication use. For patients who also had treatment with either a topical corticosteroid (tCS) or diet elimination and had a follow-up endoscopy with biopsy, histologic, endoscopic, and symptom responses were assessed. We evaluated time-trends in psychiatric diagnoses over >2 decades and compared tCS and diet elimination treatment response between patients with and without psychiatric diagnoses.
Results: Of 1291 newly diagnosed patients with EoE, 29% had a concomitant psychiatric diagnosis (18% depression; 24% anxiety) and 25% were on psychiatric medications. Over the 2-decade study timeframe, there was a slight overall increase in psychiatric diagnoses. However, diagnoses spiked in 2020 to >50% during the coronavirus disease 2019 (COVID-19) pandemic. There was no worsening in response rates for those with psychiatric diagnoses for either tCS or diet elimination treatment.
Conclusions: Psychiatric diagnoses demonstrate a slight increase in EoE over the past 2 decades, though rates spiked during the COVID-19 pandemic, substantiating the burden of depression and anxiety during this time. Interestingly, the presence of a psychiatric disorder did not impact treatment outcomes to either tCS or diet elimination, so either option is viable in EoE patients with these diagnoses.

Key words: EoE – eosinophilic esophagitis – mental health – topical steroids – diet elimination.

Abbreviations: COVID-19: coronavirus disease 2019; EoE: eosinophilic esophagitis; EREFS: EoE Endoscopic Reference Score; eos/hpf: eosinophils per high-power field; ESS: endoscopic severity score; PTSD: post-traumatic stress disorder; SNRI: serotonin norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; tCS: topical corticosteroid; UNC: University of North Carolina.

INTRODUCTION

Eosinophilic esophagitis (EoE) is a clinicopathologic condition characterized by eosinophilic-predominant esophageal inflammation and is diagnosed by the presence of at least 15 eosinophils per high-power field (eos/hpf) on esophageal biopsies following the exclusion of alternative etiologies of esophageal eosinophilia [1, 2]. The prevalence of EoE is rapidly increasing, and it is no longer considered a rare disease [3]. Presenting symptoms, particularly in adolescents and adults, include dysphagia and food impaction, which can significantly impact the health-related quality of life lives of affected patients [4-6]. Eosinophilic esophagitis is also a chronic condition that progresses from inflammation to fibrostenosis in most patients, particularly with delay in diagnosis or inadequate treatment [7].

As the literature expands on EoE, the burden of mental illness in patients with EoE is increasingly recognized. Our group demonstrated a high proportion of concomitant psychiatric diagnoses and medication use in adults and children with EoE [8]. Other studies show that individuals with EoE are at greater risk of developing psychiatric disorders later in life [9] and corroborate the increased prevalence of psychiatric disorders and use of psychotropic drugs [10,

11]. Additionally, the burden of psychiatric illness has been suggested to potentially affect treatment outcomes and adherence when co-existing with EoE and other chronic illnesses [12-14].

Currently, it is not known whether psychiatric diagnoses vary over time in patients with EoE, and a dearth of information remains regarding impact on treatment efficacy in EoE. As a consequence, there remains a lack of knowledge surrounding treatment decisions for patients that also carry a psychiatric diagnosis. Therefore, we aimed to assess whether psychiatric diagnoses impact EoE-related treatment outcomes and examined time trends in the diagnosis of psychiatric conditions in a large cohort of patients with EoE.

METHODS

We conducted a retrospective cohort study utilizing the University of North Carolina (UNC) EoE Clinicopathologic Database through 2023. This resource includes data on patients who were newly diagnosed with EoE at UNC [15-20]. The UNC IRB approved this study.

The electronic medical record of each newly diagnosed EoE patient was examined to determine confirmed psychiatric diagnoses and psychoactive medication use. Psychiatric diagnoses included depression, anxiety, bipolar disorder, post-traumatic stress disorder (PTSD), and schizophrenia. Any psychiatric medication [e.g. selective serotonin reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitor (SNRI), tricyclic antidepressant, neuroleptic, benzodiazepine, buspirone, and other (e.g. trazodone, pregabalin, gabapentin, mirtazapine)] with a documented prescription was recorded as well. Additionally, demographics, presenting symptoms, symptom response, and endoscopic findings were collected. We also examined when the psychiatric diagnosis was made in relation to the EoE diagnosis, but we were only able to obtain these data from 2018 to 2023 due to limitations in documentation.

For the subset of patients who also had treatment with either a topical corticosteroid (tCS) or diet elimination and had a follow-up endoscopy with biopsy, a range of treatment outcomes were assessed. Histologic response was defined as <15 eos/hpf, with additional assessment of thresholds of ≤6 and <1 eos/hpf [21-23]. Endoscopic response was assessed using the EoE Endoscopic Reference Score (EREFS; score range 0-9) for those seen after 2013 and with an endoscopic severity score (ESS, score range 0-5 with 0/1 assigned for presence/absence of each of the EREFS findings) for all patients [24-26]. As validated patient-reported outcomes are not used clinically at our center, we extracted global symptom response from the chart. Global symptom response was defined as yes or no in accordance with patient description of disease activity at follow-up clinic visit or endoscopy as provided by the clinician in the chart. Global endoscopic response was recorded as yes or no per the endoscopist's assessment in the chart. EoE treatment at our center follows guideline recommendations [5]. For topical steroids, doses range from 1-2 mg per day for budesonide and 880-1760 mcg per day for fluticasone, depending on patient age. Endoscopy is repeated in 8-12 weeks to assess response. For diet therapy, empiric elimination is most commonly used with repeat endoscopy in 6-8 weeks.

For analysis, descriptive statistics summarized patient characteristics. We calculated the proportion of EoE patients each year over >2 decades with a concomitant psychiatric diagnosis in order to assess time-trends, and compared tCS and diet elimination treatment response between patients with and without psychiatric diagnoses. For the pre/post treatment comparisons of patients with psychiatric diagnoses to those without psychiatric diagnoses, means were compared with paired t-tests and proportions were compared with McNemar's test. Analysis was performed with Stata (version 12; College Station, TX).

RESULTS

Of 1291 newly diagnosed patients with EoE, the mean age was 28.0±18.8, with 40% younger than 18 years of age, 67% male, and 85% white. Concomitant atopy was frequent (seen in 60%), as were symptoms of dysphagia (76%) and food impaction (33%). Baseline EREFS was 3.6±1.9, with 28% requiring esophageal dilation at baseline and the peak eosinophil count was 65.4±45.8 eos/hpf at diagnosis.

In our population, 29% had at least one concomitant psychiatric diagnosis (18% depression; 24% anxiety; 2% bipolar; <1% schizophrenia) and 25% were on at least one psychiatric medication. Over the study period, rates of anxiety consistently remained higher than depression, and trends fluctuated with a slight overall increase in adults (Fig. 1A). Children followed the same trends though psychiatric diagnoses were overall more prevalent in adult populations (Fig. 1B). There was a spike in mental illness diagnoses in 2020 when >50% of people newly diagnosed with EoE had a concomitant psychiatric diagnosis (Fig. 1A), the spike being more prominent among children than adults (Fig. 1B). This trend coincides with the onset of the COVID-19 pandemic. Use of psychiatric medications followed a similar trend. For patients from 2018 forward with data on timing of psychiatric diagnoses available (n=170), 34 (21%) were diagnosed after the EoE diagnosis and 135 (79%) were diagnosed prior to their EoE diagnosis.

For patients treated with tCS, there were no differences in treatment outcomes based on presence of psychiatric diagnoses. For example, histologic responses (<15 eos/hpf) were 59% and 53%, respectively, for those without and with psychiatric diagnosis (p=0.19). Post-treatment endoscopic features, EREFS, ESS, and global symptom response were also similar (Table I). For those treated with diet, there were trends towards improved histologic responses (<15 eos/hpf) in those with concomitant psychiatric diagnoses (48%) vs those without (37%; p=0.08), but symptomatic and endoscopic responses were similar (Table I). There were also no differences in histologic response to tCS among those with a psychiatric diagnosis regardless of whether they were on psychiatric medications. For example, histologic response to topical steroids was 44% in those with a psychiatric diagnosis and not on medications and 45% in those on medications (p=0.97); there was only 1 person on psychiatric medications who underwent diet elimination (a non-responder).

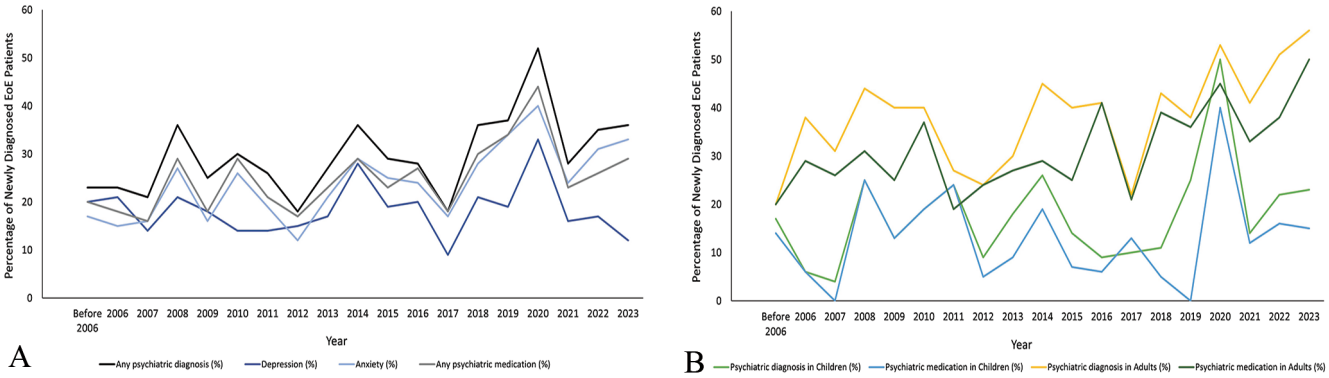

Fig. 1. Time trends in psychiatric diagnosis in patients newly diagnosed with EoE. (A) Time trends in any psychiatric diagnosis, depression, anxiety, and any psychiatric medication in the overall cohort. (B) Time trends in psychiatric diagnoses and medications stratified by adults and children. In both panels, the clear spike in 2020-2021 related to COVID-19 is clear.

Table I. Treatment response to topical steroids and diet elimination

	Topical Steroids			Diet Elimination		
	No psychiatric diagnosis (n = 366)	Any psychiatric diagnosis (n = 156)	p	No psychiatric diagnosis (n = 212)	Any psychiatric diagnosis (n = 77)	p
Type of steroid used (n, %)			0.15			
Fluticasone	110 (30)	56 (36)		--	--	--
Budesonide	256 (70)	100 (64)		--	--	--
Mean steroid dose (mcg ± SD)	1599 ± 712	1800 ± 744	0.004	--	--	--
Type of diet (n, %)						
Targeted	--	--	--	46 (22)	16 (21)	0.85
Empiric	--	--	--	130 (61)	43 (56)	0.40
Elemental	--	--	--	13 (6)	2 (3)	0.70
Post-treatment peak eosinophil count (mean eos/hpf ± SD)	24.1 ± 37.2	25.8 ± 36.5	0.62	43.7 ± 48.1	37.9 ± 53.7	0.34
p value vs baseline	< 0.001	< 0.001		< 0.001	< 0.001	
Histologic response (n, %)						
<15 eos/hpf	215 (59)	82 (53)	0.19	78 (37)	37 (48)	0.08
≤6 eos/hpf	188 (51)	73 (47)	0.34	58 (27)	33 (43)	0.01
<1 eos/hpf	113 (31)	43 (28)	0.45	25 (12)	15 (19)	0.09
Global symptom response (n, %)*	105 (77)	35 (73)	0.55	126 (64)	48 (67)	0.68
Post-treatment endoscopic findings (n, %)						
Normal	82 (22)	36 (23)	0.57	82 (24)	16 (21)	0.52
Exudates	80 (23)	48 (32)	0.03	65 (31)	26 (34)	0.63
Rings	151 (42)	73 (48)	0.26	98 (46)	43 (56)	0.16
Edema	105 (29)	45 (30)	0.98	58 (27)	21 (27)	0.97
Furrows	160 (45)	73 (48)	0.52	120 (57)	38 (49)	0.26
Stricture	106 (30)	50 (33)	0.52	62 (30)	27 (35)	0.44
Narrowing	61 (17)	22 (14)	0.45	41 (19)	18 (23)	0.46
Crepe-paper mucosa	4 (1)	0 (0)	0.19	2 (1)	2 (3)	0.29
Dilation	101 (28)	51 (34)	0.24	61 (29)	28 (36)	0.23
Stricture diameter (before dilation; mean mm ± SD)	13.9 ± 2.8	14.8 ± 2.2	0.10	13.5 ± 3.2	14.6 ± 3.8	0.20
Candida	23 (7)	11 (7)	0.75	--	--	--
Global endoscopic response (n, %)**	264 (72)	106 (69)	0.42	118 (56)	41 (53)	0.63
Post-treatment endoscopic severity (mean scores ± SD)						
EREFS***\	2.1 ± 1.9	2.5 ± 2.0	0.12	2.3 ± 2.0	2.5 ± 2.9	0.43
p value vs baseline	< 0.001	< 0.001		< 0.001	0.02	
ESS	1.7 ± 1.4	1.9 ± 1.7	0.15	1.9 ± 1.5	2.0 ± 1.5	0.57
p value vs baseline	< 0.001	< 0.001		< 0.001	< 0.001	

EREFS: EoE Endoscopic Reference Score; eos/hpf: eosinophils per high-power field; ESS: endoscopic severity score; SD: standard deviation; *available for n=136 and 48; n=197 and 72; defined as yes or no in accordance with patient description of disease activity at follow-up clinic visit or endoscopy as provided by the clinician in the chart; **defined as yes or no per the endoscopist's assessment in the chart; ***available for n=202 and 90; n=189 and 71.

DISCUSSION

This study demonstrates a substantial and persistent burden of psychiatric disease among patients with EoE, with nearly one-third of newly diagnosed patients having a concomitant psychiatric diagnosis and one-quarter receiving psychiatric medications. These findings corroborate prior reports demonstrating higher rates of anxiety and depression in patients with EoE compared with the general population [8, 10, 11]. Beyond confirming this association, our analysis adds to existing literature and extends prior results demonstrated in Reed et al. [8] which initially detailed the burden of psychiatric comorbidities in EoE. by characterizing longitudinal trends over nearly two decades.[8] We observed a gradual but sustained increase in prevalence of psychiatric diagnoses among patients with EoE, rising from approximately 23% before 2006 to 36% by 2023, with anxiety consistently more common than depression across age groups. Although psychiatric diagnoses were more prevalent among adults than children, both populations followed similar temporal patterns. Finally, we assessed whether a concomitant psychiatric condition impacted treatment outcomes, and counter to our expectation, we found response rates to tCS and dietary elimination were similar regardless of psychiatric comorbidity.

The finding of frequent concomitant psychiatric conditions in patients with EoE has important clinical implications. Psychiatric comorbidity may influence symptom perception, health-related quality of life, and healthcare utilization by patients with EoE [8, 27]. Interestingly, there was a pronounced spike in psychiatric diagnoses in 2020, where more than half of patients newly diagnosed with EoE also had a psychiatric diagnosis. Children newly diagnosed with EoE demonstrated a particularly prominent increase in psychiatric diagnoses and medications at this time. This increase parallels global trends showing a marked rise in anxiety and depression during the COVID-19 pandemic [28-31]. General proposed contributors include social isolation, uncertainty, disruptions in routine medical care, and heightened health-related stress [32-34]. Patients with EoE may have been particularly vulnerable during this period due to delays in diagnostic evaluation, prolonged symptom burden prior to care, medical setting anxiety, and increased time for symptom rumination during periods of isolation. We have associated data that procedure cancelations and subsequent delays in care led to the development and progression of strictures as well [35]. The parallel time trends observed in psychiatric disease within the EoE population suggest that broader societal stressors may amplify mental health vulnerability in individuals managing chronic gastrointestinal symptoms.

Given mixed evidence regarding treatment adherence and outcomes among patients with psychiatric comorbidities, both in chronic disease broadly and within gastrointestinal disorders [13, 14, 36-38], it might have been expected that psychiatric diagnoses would negatively impact EoE treatment response. However, our findings did not demonstrate differences in symptomatic, endoscopic, or histologic outcomes among patients treated with topical corticosteroids based on psychiatric diagnosis status. Similarly, among patients treated with dietary elimination, histologic response trended toward improvement in those with psychiatric diagnoses, counter to expectations, while symptomatic and endoscopic outcomes remained comparable. Overall, these results are reassuring and suggest that standard EoE therapies remain effective regardless of psychiatric comorbidity. This is additionally encouraging given concerns that mental illness may impair adherence or engagement with complex treatment regimens such as elimination diets [39,40]. The findings support offering both pharmacologic and dietary therapies to patients with EoE regardless of psychiatric history, and according to their preferences, as recommended by guidelines [5].

Despite providing valuable insights, this study is subject to inherent limitations. Most notably, we lacked detailed adherence data for both medical and dietary therapies as this was not consistently documented, limiting our ability to assess whether psychiatric diagnoses influenced treatment engagement rather than treatment efficacy. Our data also did not capture granular measures of EoE symptom severity with patient-reported outcomes or psychiatric disease severity, which may differentially affect outcomes. Timing analyses were further constrained by reliance on documented EoE diagnosis dates, despite the well-recognized delay between symptom onset and formal diagnosis in EoE [41-45]. Finally, although we have previously reported psychiatric diagnosis data in this cohort through 2017, that study did not report on time trends or treatment outcomes, and there is no overlap with the present analyses [8]. Strengths include the large EoE database with granular clinical and outcome data, the >2 decade time course of the data, and confirmation of psychiatric diagnosis and medication prescription in the chart.

Future studies should aim to better characterize the temporal relationship between psychiatric symptom onset and EoE symptom development, rather than diagnosis alone. Prospective investigations incorporating adherence measures and mental health screening tools may further clarify the bidirectional relationship between psychiatric disease and EoE and help identify opportunities for early intervention.

CONCLUSIONS

Concomitant psychiatric diagnoses in EoE patients are common and can either precede or follow EoE diagnosis. Time trends demonstrate a possible slight increase, though rates spiked during the COVID-19 pandemic, substantiating that more people suffered from depression and anxiety during this time. Interestingly, the presence of a psychiatric disorder did not impact treatment outcomes to either tCS or diet elimination, so either option should be considered as viable in EoE patients with these diagnoses. Given the frequency of psychiatric diagnoses in patients with EoE, providers should be cognizant that these are likely and involve mental health professionals in their multidisciplinary care plans for EoE management.

Conflicts of interest: E.S.D. reports research funding from: Adare/Ellodi, Allakos, Arena/Pfizer, AstraZeneca, Celldex, Dr. Falk Pharma, Eupraxia, Ferring, GSK, Meritage, Miraca, Nutricia, Celgene/Receptos/BMS, Phathom, Regeneron, Revolo, Sanofi, Shire/Takeda, Uniquity; consulting fees from: Abbvie, Adare/Ellodi, Alfasigma,

ALK, Allakos, Amgen, Anaptysbio, Apogee, Apollo, Aqilion, Arena/Pfizer, AstraZeneca, Bethanamist, Biocryst, Bryn, Calypso, Celgene/Receptos/BMS, Celldex, Cyted, Domain, EsoCap, Eupraxia, Dr. Falk Pharma, Ferring, GI Reviewers, GSK, Holoclara, Invea, Knightpoint, LucidDx, Nexstone Immunology/Uniquity, Nutricia, Parexel/Calyx, Phathom, Regeneron, Revolo, Robarts/Alimentiv, Roivant, Sanofi, Shire/Takeda, Target RWE, Third Harmonic Bio, Upstream Bio; and educational grants from: Allakos, Aqilion, Holoclara, Invea. C.C.R reports consulting fees from AstraZeneca and GI Reviewers. None of the other authors have disclosures.

Authors' contribution: E.S.D. conceived the study. A.A.W. and E.S.D. designed the study. All the authors collected data and interpreted the results. A.A.W and E.S.D drafted the manuscript. All the authors critically revised the manuscript. E.S.D. supervised the study. All the authors approved the final version of the manuscript.

Acknowledgments: This study was supported in part by T32 DK007634 and NIH T35 DK007386.

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