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Analysis of the Association between Eosinophilic Esophagitis and MASLD: Retrospective, Observational, Cohort Analysis of the National Inpatient Sample 2016-2020

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ABSTRACT

Background & Aims: Eosinophilic esophagitis (EoE) is a chronic immune-mediated inflammatory condition. Associated pathologies for EoE are similar to those with metabolic-dysfunction-associated steatotic liver disease (MASLD). This study assesses whether an association exists between MASLD and EoE.
Methods: We used National Inpatient Sample (NIS) 2020 data to identify adult patients. ICD-10 codes were used to identify patients with MASLD and EoE. The relationship between MASLD and EoE was assessed by multivariate analysis after adjusting for confounding factors, such as patient demographics, hospital characteristics, Charlson comorbidity index, obesity, obstructive sleep apnea (OSA), diabetes, hypertension (HTN), hyperlipidemia (HLD), inflammatory bowel disease (IBD), celiac disease (CD), gastroesophageal reflux disease (GERD), smoking, alcohol use, and irritable bowel syndrome (IBS).
Results: Out of 26 million patients, 4,820 had a diagnosis of EoE. The majority of the patients were between 18 and 44 years of age (47.82%), male (54.05%), had private insurance (50.1%), and were in the highest income quartile (29.25%). A higher incidence of MASLD was noted in the EoE group than those without (6.1% vs.2.9%, $p<0.001$). After adjusting for confounding factors, MASLD had 2.38 times higher odds of having EoE (95% CI-1.82-3.11, $p<0.001$). Other factors noted to be associated with higher odds of EoE included younger age, Caucasian race, IBS, GERD, IBD, and CD.
Conclusions: Our study reports a novel finding that MASLD and EoE are associated. Future prospective studies are needed to confirm and understand the clinical significance of this relationship and how one disease affects the other.

Key words: eosinophilic esophagitis – metabolic-dysfunction-associated steatotic liver disease – national inpatient sample.

Abbreviations: AD: atopic dermatitis; CCI: Charlson-Deyo comorbidity index; CD: celiac disease; EoE: eosinophilic esophagitis; EGID: eosinophilic gastrointestinal disease; GERD: gastroesophageal reflux disease; HTN: hypertension; HLD: hyperlipidemia; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; LDL: low-density lipoprotein; MCTD: mixed connective tissue disease; MASLD: metabolic-dysfunction-associated steatotic liver disease; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; NSAID: non-steroidal anti-inflammatory drug; NIS: National Inpatient Sample; OSA: obstructive sleep apnea; TH2: T helper-2.

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic immune-mediated inflammatory condition, with symptoms ranging from vomiting and dysphagia to food impaction and feeding difficulties [1]. The gold standard of diagnosis is esophageal biopsy, demonstrating 15 eosinophils per high-powered field after excluding other diseases such as gastroesophageal reflux disease (GERD) and achalasia [1]. Studies have reported a delay in the diagnosis of EoE as these symptoms can be relatively benign and common in the adult population, and the affected patients attempt to modify their behavior in response to such symptoms with some improvement [2]. It has been noted that the incidence of EoE is increasing. This increase was initially attributed to increased awareness and testing. However, this pathology's true incidence has also been trending upward over the last two decades [2]. The incidence is reported to be 5-10

cases per 100,000, and prevalence is estimated at 0.5-1 per 1000 [2]. The annual cost of this disease has been estimated to be as high as $1.4 billion in the US [3]. The rising incidence of EoE has gathered increasing interest as eosinophilic gastrointestinal disease (EGID) [4]. Although uncommon, the diagnosis of diseases in this spectrum is on the rise.

Eosinophilic esophagitis and asthma are frequently found as comorbid conditions in the atopic spectrum of disease [5]. They share pathophysiology driven by T helper-2 (TH2) cells and have a similar treatment that involves systemic steroids and biological therapy [5]. A retrospective analysis conducted by Benninger et al. [6] to determine the prevalence of atopic diseases in EoE revealed that the incidence of asthma, allergic rhinitis, atopic dermatitis (AD), and food allergies was 22.2%, 32.9%, 15.6%, and 13.2% respectively in the year before the diagnosis. Within 12 months of diagnosis, these percentages increased to 44.7%, 27.1%, 25.2%, and 16.9%, respectively [6]. The data regarding the association between EoE and celiac disease (CD) is conflicting, with some studies showing an association, mostly in the pediatric population [7-10]. Although a systematic review by Lucendo et al. [7] failed to establish support for the relationship between EoE and CD, a study by Dharamraj et al. [9] established an incidence of 10.7% in their cohort of children. A study conducted on children in Australia determined the prevalence of esophageal eosinophilia in 8.2% of children with CD who underwent concurrent esophageal biopsy, but this was limited by the fact that not all children could undergo esophageal biopsies [8]. An adult population-based study by Ludvigsson et al. [10] also found no increased risk of CD in patients with EoE.

Obesity has also been found to exacerbate the TH2-driven inflammatory response in EoE [11]. Thus, obesity is considered a risk factor for the development and worsening of the disease, and weight loss is a potential treatment method [11]. An experimental model with male BALB/c mice analyzed obesity by various parameters, including but not limited to glucose, total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides, which were all increased in the experimental subjects [11].

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease and also the leading cause of liver-associated mortality and morbidity [12]. Studies have estimated NAFLD to affect nearly 30% of the worldwide adult population, with incidence increasing from 22% to 37% from 1991 to 2019 [13]. Due to a greater appreciation of the metabolic and cardiovascular derangements contributing to non-alcoholic liver disease, metabolic dysfunction-associated liver disease (MASLD) has since been introduced, bringing greater emphasis to the associated comorbidities contributing to disease development, as opposed to simply being non-alcoholic. Due to its increasing prevalence and impact on the prognosis of patients with liver disease, further studies are required to highlight various associations with MASLD.

Interestingly, associated pathologies such as obesity, CD, and inflammatory bowel disease (IBD) have been well-established for MASLD worldwide [14-16]. Lamb et al. [17], in their study of 350 patients, reported no statistically significant association between the two. Still, a trend towards an increased incidence of fatty liver and cirrhosis on imaging was reported in patients with EoE compared to the control group [17]. In this study, we use the nationally available public database to assess if an association exists between MASLD and EoE. We further evaluated the association between other comorbidities and EoE.

METHODS

Data Source

A retrospective, observational cohort analysis utilized the Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample (NIS) years 2016 to 2020. The NIS is the nation's largest database of inpatient hospital stays [18]. It collects data from a 20% stratified sample of hospitals in 37 states in the United States and has been reliably used to estimate disease burden and outcomes. Each hospitalization is de-identified and maintained in the NIS as a unique entry. We did not require institutional review board (IRB) approval as it is publicly available de-identified data.

Study Population

The International Classification of Diseases 10th Version, Clinical Modification (ICD-10 CM) diagnosis codes were used to identify all patients admitted in 2020. Patients under 18 and those with missing demographics and mortality data were excluded from the analysis. In total, 26.4 million cases met the inclusion criteria. Patients were stratified into two groups: those with and without the diagnosis of EoE.

Definition of MASLD

Patients were classified to have MASLD if they had ICD-10 codes for liver disease without mention of alcohol (ICD-10: I85.xx, K65.2, K72.1x, K72.9x, K74.0-2, K74.6x, K75.8x, K75.9, K76.0, K76.6-9, K77, R18.x). We then excluded patients with other chronic liver diseases and chronic liver disease with mention of alcohol or alcohol use disorder. A similar approach has been used by Hirode et al. [19] to identify patients with a diagnosis of MASLD. Due to the inpatient nature of the population database, the specific diagnostic method utilized to evaluate hepatic steatosis was unable to be assessed.

Study Variables

We collected information on patient demographics such as age (divided into three groups; <44 years, 45–64 years, and >65 years), gender, race, primary insurance, and median income quartile. Hospital characteristics such as region, bed size, and rural/urban location, pre-specified by HCUP, were also collected. We further collected information regarding common comorbidities associated with MASLD, such as diabetes, hypertension (HTN), obesity, obstructive sleep apnea (OSA), hyperlipidemia (HDL), GERD, and IBD. We also collected information on tobacco use and conditions related to EoE, mixed connective tissue disorders (MCTD), AD, asthma, and CD. We used the Charlson-Deyo Comorbidity Index (CCI) to assess the comorbidity burden. It is a well-validated index based on ICD 10-CM codes meant to be used in large administrative data to predict mortality and hospital resource use [20].

Study Outcomes

Our study aims to assess if an association exists between MASLD and EoE. We also assessed the relationship between EoE and other factors reported in the literature.

Statistical Analysis

We used hospital-level discharge weights to generate national estimates. Chi-square was used to compare categorical variables, while an independent sample t-test was used for continuous variables. Univariate and Multivariate logistic regression was performed. We adjusted for patient demographics, hospital comorbidities, CCI, smoking, diabetes, HTN, obesity, OSA, HLD, GERD, MCTD, AD, asthma, CD, and IBD. The unadjusted odds ratios were calculated with a 95% confidence interval. A type I error of <0.05 was considered statistically significant. Data analysis was done using STATA 17.0 (Texas).

RESULTS

A total of 26,432,832 patients were admitted in 2020. Of these, 4,820 (0.018%) patients had EoE. The majority of the patients in the EoE group were between 18 and 44 years of age (47.82%), male (54.05%), had private insurance (50.1%), and were in the highest income quartile (29.25%). Patients with EoE had a higher prevalence of MASLD, GERD, OSA, IBD, asthma, AD, CD, MCTD, and IBS compared to patients without EoE. A complete list of demographic differences and comorbidities between patients with EoE and those without is presented in Table I.

Table I. Comorbidities and demographic differences between patients with and without EoE

Demographics	Absence of EoE, n (%)	Presence of EoE, n (%)	p
Age category			<0.001
18-44	7,533,926 (28.5)	2,305 (47.8)	
45-64	7,298,996 (27.6)	1,445 (30)	
>65	11,595,090 (43.9)	1,070 (22.2)	
Gender			<0.001
Male	11,510,706 (43.6)	2,605 (54.1)	
Female	14,917,306 (56.5)	2,215 (46)	
Race			<0.001
White	17,391,612 (65.8)	3,920 (81.3)	
Black	4,170,666 (15.8)	365 (7.6)	
Hispanic	3,126,595 (11.8)	345 (7.2)	
Asian/Pacific Islander	755,040 (2.9)	50 (1)	
Native American	180,755 (0.68)	10 (0.21)	
Other	803,345 (3.04)	130 (2.7)	
Primary expected payer			<0.001
Medicare	12,352,079 (46.7)	1,335 (27.7)	
Medicaid	4,949,095 (18.7)	690 (14.3)	
Private	7,093,397 (26.8)	2,415 (50.1)	
Uninsured	1,114,716 (4.2)	200 (4.2)	
Median household income			<0.001
Lowest quartile	8,084,715 (30.6)	905 (18.8)	
Second quartile	7,178,683 (27.1)	1,155 (24)	
Third quartile	6,044,072 (22.9)	1,350 (28)	
Highest quartile	5,120,542 (19.4)	1,410 (29.3)	
Charlson Comorbidities			<0.001
0	8,895,473 (33.7)	1,940 (40.3)	
1	4,997,520 (18.9)	1,415 (29.4)	
2	3,581,665 (13.6)	625 (13)	
>3	8,953,354 (33.9)	840 (17.4)	
Underlying comorbidity			
MASLD	755,615 (2.9)	295 (6.1)	<0.001
GERD	4,976,005 (18.8)	1,570 (32.6)	<0.001
HLD	8,698,165 (32.9)	1,190 (24.7)	<0.001
Smoking	9,624,180 (36.4)	1,345 (27.9)	<0.001
Diabetes	7,534,160 (28.5)	625 (13)	<0.001
HTN	15,049,406 (56.9)	1,905 (39.5)	<0.001
Obesity	4,934,194 (18.7)	815 (16.9)	0.16
OSA	1,967,415 (7.4)	400 (8.3)	0.33
IBD	291,310 (1.1)	255 (5.3)	<0.001
Asthma	1,827,790 (6.9)	1,045 (21.7)	<0.001
AD	6,905 (0.03)	10 (0.2)	<0.001
CD	36,830 (0.1)	80 (1.7)	<0.001
MCTD	356,145 (1.4)	140 (2.9)	<0.001
IBS	249,580 (0.9)	170 (3.5)	<0.001

AD: atopic dermatitis; CD: celiac disease; EoE: eosinophilic esophagitis; eosinophilic gastrointestinal disease; GERD: gastroesophageal reflux disease; HTN: hypertension; HLD: hyperlipidemia; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; MCTD: mixed connective tissue disease; MASLD: metabolic-dysfunction-associated steatotic liver disease; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; OSA: obstructive sleep apnea.

A statistically significant positive association was noted between MASLD and EoE on univariate analysis (aOR=-2.21, 95%CI: -1.70 - -2.88, p<0.001). The association remained statistically significant after adjusting for confounding factors (aOR=-2.38, 95%CI:-1.82 - -3.11, p<0.001). Other factors noted to be associated with higher odds of EoE included private insurance (aOR=-1.39, 95%CI:-1.12 - -1.72, p<0.001), highest income quartile (aOR=-1.76, 95%CI: - 1.44 - -2.14, p<0.001), GERD (aOR=-2.29, 95%CI: -1.44 - -2.14, p<0.001), IBS (aOR=-2.41, 95%CI: -1.67 - -3.49, p<0.001) and IBD (aOR=-2.88, 95%CI: -2.18 - -3.8, p<0.001).

Atopic dermitits was associated with 4.31 higher odds of having EoE (aOR=-4.31, 95%CI: -1.06 - -17.53, p<0.001). Smoking (aOR=-0.64, 95%CI: -0.55 - -0.74, p<0.001) and obesity (aOR=-0.79, 95%CI: -0.66 - -0.95, p<0.001) were associated with lower odds of EoE.

The multivariate regression results are provided in Fig. 1 and Table II.

DISCUSSION

In our study, patients with MASLD had 150% higher odds of having EoE than patients without MASLD. There is a lack of prior studies evaluating the relationship between EoE and MASLD or similar pathologies such as NAFLD.

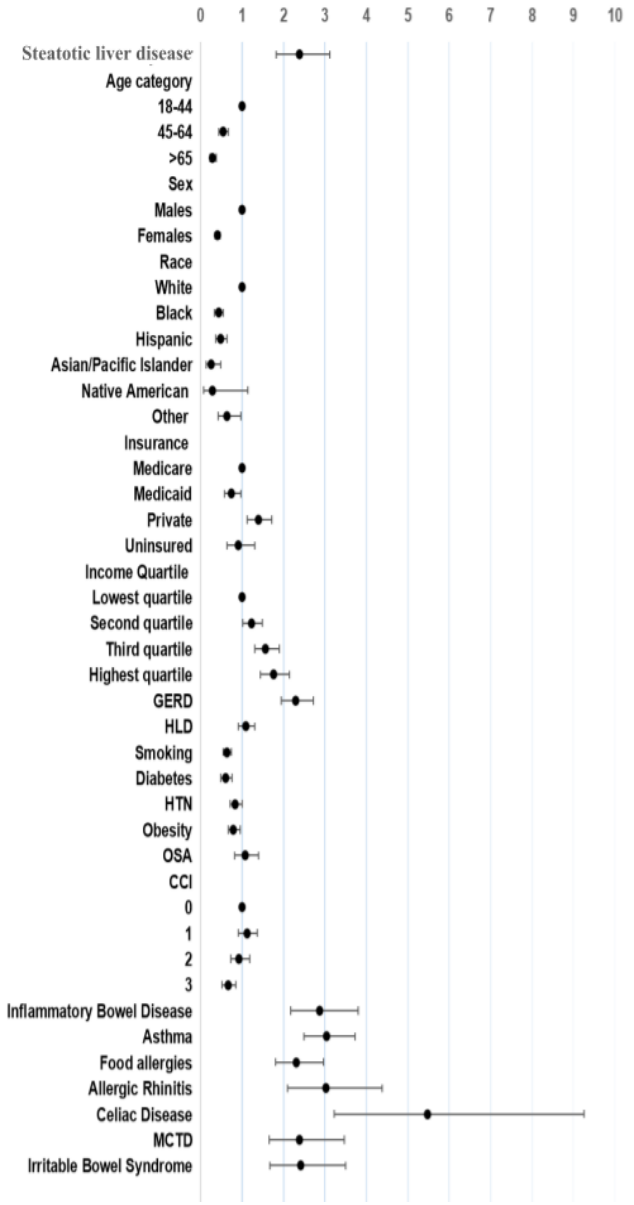

Fig. 1. Results of multivariate regression analysis depicting the association of EoE with various diseases and factors. CCI: Charlson comorbidity index. For the rest of abbreviations see Table I.

Table II. Results of multivariable analysis depicting the association of eosinophilic esophagitis with various patient characteristics and comorbidities

	Odds Ratio	95% Confidence Interval	p
Fatty Liver	2.38	1.82-3.11	<0.001
Age category			
18-44	Ref		
45-64	0.54	0.44-0.66	<0.001
>65	0.29	0.22-0.37	<0.001
Gender			
Males	Ref		
Females	0.41	0.35-0.47	<0.001
Race			
White	Ref		
Black	0.43	0.33-0.55	<0.001
Hispanic	0.48	0.36-0.63	<0.001
Asian/Pacific Islander	0.25	0.13-0.49	<0.001
Native American	0.29	0.07-1.14	0.076
Other	0.63	0.42-0.97	0.034
Insurance			
Medicare	Ref		
Medicaid	0.74	0.57-0.97	0.028
Private	1.39	1.12-1.71	0.002
Uninsured	0.91	0.63-1.31	0.618
Income quartile			
Lowest quartile	Ref		
Second quartile	1.23	1.01-1.50	0.036
Third quartile	1.57	1.30-1.90	<0.001
Highest quartile	1.76	1.44-2.14	<0.001
GERD	2.29	1.94-2.72	<0.001
HLD	1.09	0.91-1.30	0.342
Smoking	0.64	0.55-0.74	<0.001
Diabetes	0.61	0.49-0.75	<0.001
HTN	0.84	0.71-1.00	0.051
Obesity	0.79	0.66-0.95	0.012
OSA	1.07	0.82-1.39	0.627
CCI			
1	1.12	0.91-1.37	0.286
2	0.93	0.73-1.19	0.559
3	0.67	0.52-0.85	0.001
Inflammatory bowel disease	2.88	2.18-3.80	<0.001
Asthma	3.04	2.49-3.73	<0.001
Atopic dermatitis	4.31	1.06-17.53	0.041
Food allergies	2.31	1.80- 2.96	<0.001
Allergic rhinitis	3.03	2.10-4.38	<0.001
Celiac disease	5.47	3.23-9.25	<0.001
Mixed connective tissue disorder	2.39	1.65-3.46	<0.001
Irritable bowel syndrome	2.41	1.67-3.49	<0.001

For abbreviations see Table I.

A prior study by Lamb et al. [17] evaluated possible common risk factors for NAFLD and EoE of obesity, hyperlipidemia, and hyperglycemia. They did not find a significant association between EoE and MASLD regarding those risk factors. However, they noted a trend toward an increased incidence of fatty liver on imaging in patients with EoE compared to those who were controlled [17]. Although hypothesized to be associated with common comorbidities, a significant association was found between EoE and MASLD even after adjusting for confounding factors.

We hypothesize that alterations in the gut microbiome may be responsible for this association. A study by Harris et al. [21] in a sample of 70 children and adults reported an alteration in the microbiome of patients with EoE and GERD. Their study noted an increased prevalence of Haemophilus

in untreated EoE patients [21]. Patients with EoE have been found to have decreased gut microbiome diversity overall [22]. Similarly, microbiome alterations can occur in patients with non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) [23]. Studies have suggested a potential causal relationship between changes in the gut microbiota and NAFLD/NASH [23-25]. A murine model evaluating the effect of dietary fat on the development of metabolic syndrome noted that an increased flow of saturated fats in the distal intestine could trigger a change in the gut microbiota, showing an elevated Firmicutes-to-Bacteroidetes ratio [26]. Besides our study, the study of Lamb et al. [17] reported a trend toward increased EoE in patients with NASH. However, the association did not reach statistical significance, likely due to the small sample size of the patients. While the exact mechanism and association is unclear, it has been demonstrated that microbiome changes, whether esophageal or gut, exist with EoE and MASLD. These microbiome alterations may lead to downstream overexpression of cytokines, which may result in a similar pro-inflammatory change in both EoE and MASLD.

In our study, younger men and white patients had a higher incidence of EoE. Our results align with the previously published literature regarding the demographics of EoE [27, 28]. Eosinophilic esophagitis is a disease of the young. It is typically present in school-age children and young adults but can also be present in infancy [29]. The literature has reported differences based on gender [30]. These differences have been attributed to differences in molecular signatures of different aspects of EoE pathology, including epithelial barrier, eosinophils, mast cells, and proliferation [30]. Our finding that Caucasians have higher odds of having EoE aligns with the previously published literature [31, 32]. In a cohort of 660 patients with EoE, more than 83% were white, followed by African Americans [31]. A study of 208 patients has reported that African Americans have a younger age at diagnosis, while Caucasians present with more dysphagia and esophageal rings [32]. In this study, interestingly, regardless of gender, the endoscopic appearances and histological severity are similar among different races [32].

Another finding of our study is that patients with private insurance and in the highest income quartile were at higher odds of having EoE. We hypothesize that patients with private insurance and the highest income quartile have better access to healthcare and thus are diagnosed with EoE. Further research is required before a conclusion can be drawn from these findings.

Our study noted an inverse relationship between tobacco smoking and EoE. Tobacco smokers were noted to be at a 36% lower risk of having EoE. The results align with the findings by Koutlas et al. [33] in their cohort of adult patients, which reported the disease was less likely in patients who smoke cigarettes or use NSAIDs. Obesity was also associated with lower odds of having EoE. Previous studies have reported conflicting results on obesity as a risk factor for the development of EoE [34, 35]. A study by Alkhero et al. [34] noted that the association between EoE and obesity was not statistically significant. On the contrary, a study by Tanakaet et al. [35] noted a positive association between body mass index and EoE. None of the studies mentioned above adjusted for fatty liver. The association noted previously between EoE and obesity could be due to the higher incidence of fatty liver in obese patients.

Our study also noted a strong association between GERD and EoE. There is a considerable symptom overlap between GERD and EoE, although food impaction is more common in EoE [36]. Literature has suggested that EoE is considered in the differential diagnosis for patients with symptoms suggestive of GERD who do not respond to high-dose proton pump inhibitors (PPIs) [37]. Biopsy continues to be the gold standard for the diagnosis of EoE [38]. Our findings of a strong association between allergic conditions (asthma, AD, food/insect allergies, and allergic rhinitis) and MCTD align with the studies previously reported in the literature [6, 39-41].

We report that patients with a diagnosis of IBS are at higher odds of having EoE. Literature has reported that patients with non-EOE EGID can have concomitant IBS [42]. Extensive work-up for other causes of gastrointestinal symptoms is required before a diagnosis of IBS is made. Previous studies have documented that IBS patients are more sensitive to aeroallergens [43]. Interestingly, animal studies have shown that EoE can be induced by the intranasal instillation of allergens [40]. The association between EoE and IBD has been well-established and noted in our study. We report that patients with IBD have 2.88 times higher odds of having EoE than patients without IBD.

A retrospective cohort study by Fan et al. [44] on adults at a tertiary care center reported a five times higher prevalence of EoE in IBD than the general population. Studies have shown a bilateral relationship determined the incidence of EoE to be threefold to fivefold in those with IBD. In contrast, the incidence of IBD in those with EoE was threefold to sixfold [45]. Gastroenterologists should consider a diagnosis of EoE in IBD patients with esophageal symptoms before attributing it as a symptom of IBD.

Our study also noted six times higher odds of having EoE in patients with CD. Previous studies on this topic have found conflicting results, with different associations in the pediatric and adult population [8, 10]. Gluten exposure may cause esophageal eosinophilia in patients with CD or may be caused directly by the disease [42]. A study on the pediatric population in Australia noted a higher prevalence of EoE (8.2%) in children with CD [45]. This was limited by the fact that not all children underwent esophageal biopsies. A study on 1000 randomly selected adults from the general population failed to establish an association between EoE and CD [10]. Although a systematic review showed that a gluten-free diet leads to histological resolution of EoE, it still couldn't establish an association between the two entities [46].

In addition to microbiome alterations that may similarly contribute to the development of both EoE and MASLD, other contributors may exist to explain the association between EoE and MASLD. A meta-analysis investigated various genetic risk loci associated with EoE. The patatin-like phospholipase domain containing (PNPLA3) protein gene is a notable regulator of lipid droplets in hepatocytes and hepatic stellate cells. It has been greatly associated with the development of MAFLD. Its overexpression has been linked to the overexpression of downstream inflammatory pathways. This leads to the overproduction of pro-inflammatory

compounds such as IL-1β and IL-6, which can attenuate the process of NASH with fibrosis [47]. Of note, PNPLA3 was found in a meta-analysis to be genetic loci associated with EoE, with an odds ratio of 1.343 [48]. Despite the significance of PNPLA3, the precise underlying mechanism of this gene remains unclear. In addition to genetics, both EoE and MAFLD involve a complex interplay of pathways that involve cytokine overexpression.

The study's major strength is that the data is obtained from a large database representative of the US population. The study is limited by its retrospective and observational nature, limiting the ability to evaluate for causality. Due to the study being an inpatient analysis, limitations also include a lack of data regarding esophageal biopsies and the method of diagnosis of EoE. In addition, we could not assess specific diagnostic methods to diagnose MASLD nor determine the stage of hepatic fibrosis and steatosis. Our study relies on ICD-10 codes, so coding errors cannot be ruled out. In addition, the inclusion of only the inpatient population can affect the generalizability of the results as only sick patients are included in the analysis. Despite these limitations, our study reports a novel association between MASLD and EoE and confirms the associations previously reported in the literature. Further prospective studies to confirm this association are warranted.

CONCLUSIONS

Using a large population database, our study reports that patients with MASLD have a twice higher risk of EoE. Other factors noted to have a higher association with EoE included young age, Caucasian race, IBS, GERD, IBD, and CD. Future prospective studies must confirm and understand the relationship between the two conditions and the impact of one condition's treatment on another.

Conflicts of interest: None to declare.

Authors' contribution: A.S., J.P.., I.K., and M.R. reviewed the literature, interpreted the data, drafted the manuscript, revised it for important intellectual content, and were involved in the final approval of the version to be published. All authors agree to be accountable for all aspects of the work.

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