ORIGINAL ARTICLE

Predictors of duodenal eosinophil counts among subjects undergoing diagnostic endoscopy

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ABSTRACT

Introduction: Duodenal eosinophilia has been implicated in the pathophysiology of functional dyspepsia. In a retrospective observational study, we previously reported that duodenal eosinophilia (as defined by a mucosal count of greater than 15 eosinophils per 5 high power fields), was associated with symptomatic erosive gastroesophageal reflux disease (GERD), concomitant co-morbidities and Chinese ethnicity but not functional dyspepsia among 289 multiracial subjects undergoing diagnostic endoscopy in 2019 before the COVID-19 pandemic. We tested the reproducibility of those findings on a larger sample that included the original cohort and another 221 subjects who underwent endoscopy in 2022 after the easing of pandemic restrictions.

Materials and Methods: Archived duodenal histology slides were assessed by a pathologist blind to demographic and clinical data gleamed retrospectively from clinical chart review. Logistic regression analysis was used to explore associations between duodenal eosinophilia and the variables age, gender, ethnicity, year of sampling (2019 vs 2022), concomitant co-morbidities, functional dyspepsia, symptomatic erosive GERD (Los Angeles Grades A to D), endoscopic oesophagitis, gallstone disease, Helicobacter pylori infection, irritable bowel syndrome and NSAID consumption. Three different thresholds for defining duodenal eosinophilia (>15, >22 and >30 eosinophils per 5 high power fields) were tested.

Results: Year of sampling (2019, pre-pandemic) strongly predicted duodenal eosinophilia across all thresholds (OR 11.76, 13.11 and 21.41 respectively; p = 0.000). The presence of concomitant co-morbidities was a modest predictor across all thresholds whereas Chinese ethnicity only predicted at the lowest threshold. Absolute duodenal eosinophil counts predicted symptomatic erosive GERD (OR 1.03; p = 0.015) but not functional dyspepsia (OR 1.00; p = 0.896) after adjusting for age, gender, ethnicity, concomitant comorbidities and year of endoscopy. None of the subjects reached the threshold for the diagnosis of eosinophilic duodenitis.

Conclusion: The cumulative impact of environmental exposures on duodenal eosinophil counts may be much greater than of putative factors linked to functional dyspepsia. A signal linking duodenal eosinophil counts and symptomatic erosive GERD was detected.

KEYWORDS:
Duodenal eosinophilia, GERD, functional dyspepsia

INTRODUCTION

There has been much interest recently in duodenal mucosal eosinophil counts; an interest that has been driven by two main considerations. Firstly, the postulation that duodenal microinflammation is a key factor in the pathogenesis of functional dyspepsia and secondly that eosinophilic gastrointestinal disorders as a cause of abdominal symptoms may be underdiagnosed.[1-4] Furthermore, duodenal eosinophil counts are relatively easily determined in most histopathology laboratories and is a potentially attractive biomarker of duodenal microinflammation. In a previously published study, we retrospectively audited the duodenal mucosal biopsies of 289 patients who underwent elective diagnostic oesphagogastroduodenoscopy (OGD) in a Malaysian tertiary hospital in the year 2019 with a view to identifying the relative strength of the associations between duodenal eosinophilia and several demographic variables and clinical conditions.[5] We found that the presence of symptomatic erosive gastroesophageal reflux disease (GERD), the presence of comorbidities and Chinese ethnicity were each independently associated with duodenal eosinophilia as defined by a duodenal mucosal eosinophil count of greater than 15 eosinophils per 5 high power field (eos/5hpf). However, we failed to detect an association between duodenal eosinophilia and undifferentiated functional dyspepsia.[5] In the current study, we aimed to assess the reproducibility of our previous findings by expanding the sample size to include a similar cohort of 221 patients who underwent elective diagnostic OGD in the year 2022. The analysis was conducted on a consolidated sample that consisted of both the 2019 and 2022 cohorts.

MATERIALS AND METHODS

The cohort of the year 2019 consisted of 289 subjects as previously described.[5] The 2022 cohort consisted of 221 consecutive subjects who underwent elective diagnostic OGD between January and August of 2022 for a variety of indications performed by a single gastroenterologist (SMR). As in our previously reported study, we excluded patients in whom the OGD was primarily therapeutic or undertaken in an emergency setting, as well as patients who had a bleeding diathesis or who were on anticoagulants and/or antiplatelet agents. Four patients who had undergone diagnostic OGD in

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both 2019 and 2022 were included in the 2019 cohort but were excluded from the 2022 sample. Helicobacter pylori infection was routinely determined by the rapid urease test on biopsies taken from both the gastric antrum and body. It was routine practice for at least a single mucosal biopsy to be taken from the second part of the duodenum in all subjects. The clinical and endoscopic data were gleamed from the clinical charts by the gastroenterologist (SMR) who was blind to the results of the histology review. The definitions of functional dyspepsia, irritable bowel syndrome (IBS), symptomatic GERD, gallstone disease and comorbidities were as previously described.[5] Reflux oesophagitis on endoscopy was defined as the presence of erosive changes (grade A to D) as described by the Los Angeles classification.[6]

The archived histology slides were examined and reported by the pathologist (SR) who was blind to the clinical data. The histology protocol was as previously reported.[5] The eosinophils were counted in 5 random high-power fields at X40 magnification and field diameter of 0.55 mm. The duodenal mucosal eosinophil counts were expressed as the number of eosinophils per 5 high power fields (eos/5 hpf).

Statistical Analysis and Definition of Duodenal Eosinophilia
Statistical analyses were performed with the Epi InfoTM version 7.2 statistical software package available from the Centres for Disease Control and Prevention (CDC) website. Logistic regression analysis was used to determine the independent association between multiple explanatory variables and a dichotomous response variable. Association was expressed in terms of odd ratios (OR) and 95% confidence intervals (CI). Differences in the rates of categorical variables between groups were tested using the Chi-square test while differences in numerical variables were tested with the non-parametric Kruskal-Wallis test.

Logistic regression analysis was undertaken using three different thresholds to define duodenal eosinophilia. In the first analysis, duodenal eosinophilia was defined as more than 15 eos/5 hpf as proposed by Chaudhari et al[7] and was the definition used in our previous publication.[5] The second threshold was >22 eos/5 hpf as suggested in previous studies exploring the association between functional dyspepsia and duodenal eosinophilia.[8,9] The third cut off was arbitrarily set at >30 eos/5 hpf, a level twice as high as the initial threshold. Logistic regression models were also constructed to determine if the absolute eosinophil count was independently predictive of functional dyspepsia and/or symptomatic erosive GERD after adjusting for age, gender, ethnicity, presence of comorbidities and year of endoscopy (2019 or 2022).

Ethical Approval
This retrospective observational study was approved by the hospital research and ethics committee (PHKL-EC-2023-0002) in accordance with the ethical standards laid down by the 1964 Helsinki Declaration.

RESULTS

Demographic and Clinical Data
The median age of the total sample was 50 years (14 to 90). There were 255 male subjects and an equal number of female subjects. In terms of ethnicity, 79 were Malay, 162 were Chinese, 193 were Indian and 76 were of other ethnicities. Compared to the 2019 cohort, the mean age was slightly higher, the proportion of Malay subjects was lower and the proportions of subjects of Indian and 'other ethnicity' were higher in the 2022 cohort (Table I). There were also significantly more subjects with comorbidities and symptomatic erosive GERD in the 2022 cohort (Table I).

Logistic Regression Analyses to Assess the Independent Association Between Duodenal Eosinophilia and Several Variables
As shown in Table II, duodenal eosinophilia as defined by more than 15 eos/hpf was independently associated with having undergone OGD in the year 2019 (as opposed to 2022), the presence of comorbidities and Chinese ethnicity (as opposed to Malay or Indian ethnicity). There was no statistically significant association between duodenal eosinophilia and either symptomatic erosive GERD, reflux oesophagitis (irrespective of symptoms), functional dyspepsia, gallstone disease IBS or the consumption of NSAIDs. Undergoing OGD in 2019 (as opposed to 2022) was the strongest predictor of duodenal eosinophilia (OR 11.76; 95% CI 7.24–19.12).

On repeating the analysis after redefining duodenal eosinophilia at a higher threshold (>22 eos/5hpf) the independent association between duodenal eosinophilia and undergoing OGD in 2019 (OR 13.11; 95% CI 6.61 26.04, p = 0.000) as well as the association between duodenal eosinophilia and the presence of comorbidities (OR 2.46; 95% CI 1.43 4.24, p = 0.001) were preserved. However, Chinese ethnicity was no longer associated with duodenal eosinophilia. None of the other variables significantly predicted duodenal eosinophilia.

At an even higher cut off (>30 eos/5hpf), undergoing OGD in 2019 (OR 21.41; 95% CI 6.41 71.43, p = 0.000) and the presence of comorbidities (OR 2.28; 95% CI 1.13 4.58, p = 0.021) remained statistically significant predictors of duodenal eosinophilia. At this highest cut off, male gender was associated with duodenal eosinophilia (OR 1.95; 95% CI 1.03 3.70, p = 0.041). In addition, an association between functional dyspepsia and duodenal eosinophilia that approached statistical significance was also detected (OR 2.20; 95% CI 0.95-5.12, p = 0.067). None of the other variables significantly predicted duodenal eosinophilia.

Logistic Regression Analysis to test if Absolute Duodenal Eosinophil Counts were Independently Predictive of Functional Dyspepsia or Symptomatic Erosive GERD
After adjusting for age, gender, ethnicity, year of endoscopy and the presence of comorbidities, the absolute duodenal eosinophil count was independently predictive of symptomatic erosive GERD (OR 1.03; 95% CI 1.01 1.05, p = 0.015) but not functional dyspepsia (OR 1.00; 95% CI 0.98 1.02, p = 0.896).

Comparison of Duodenal Eosinophil Counts Between the 2019 and 2022 Cohorts
The duodenal eosinophil counts per hpf in the 2019 cohort was significantly higher than in the 2022 cohort (median 18 [range 1 85] vs median 7 [range 1 35]; p = 0.000]. The duodenal eosinophil count was greater than 30 eos/5hpf in

Table I: Comparison of demographic and clinical variables between the 2019 and 2022 cohorts

	2019 cohort (n = 289)	2022 cohort (n = 221)	p-value
Median age (range) at time of OGD in years	48 (15 88)	53 (14 90)	0.002[a]
Number of males: females	137:152	118:103	0.211
Ethnicity: Number (% of total in the cohort)			
Malay	56 (19.3)	23 (10.4)	
Chinese	93 (32.2)	69 (31.2)	0.029 [a]
Indian	102 (35.3)	91 (41.2)	
Others	38 (13.2)	38 ((17.2)	
Number of subjects (%) with:			
Co-morbidities	105 (36.3)	115 (52.0)	0.000 [a]
Helicobacter pylori infection	27 (9.3)	19 (8.6)	0.892
Functional dyspepsia	45 (15.6)	36 (16.3)	0.922
Irritable bowel syndrome[b]	53 (18.3)	35 (15.8)	0.533
Gallstone disease	17 (5.9)	11(5.0)	0.804
Symptomatic erosive GERD	29 (10.0)	44(19.9)	0.002 [a]
Endoscopic evidence of oesophagitisc	81 (28.0)	76(34.4)	0.148
Recent consumption of NSAIDs	16 (5.5)	9(4.1)	0.581

[a]Statistically significant difference ($p < 0.05$). [b]Denotes all subjects with irritable bowel syndrome symptoms including those with other coexisting or overlapping conditions. In our original publication5 the denoted number was of subjects in whom irritable bowel syndrome was the predominant cause of symptoms. [c]Includes subjects with visible oesophageal erosive changes on endoscopy irrespective of symptoms

Table II: Logistic regression model of predictors of duodenal eosinophilia defined as >15 cells per 5 high power fields

	Odds ratio (95% confidence interval)	p-value
Age	0.99 (0.98 - 1.01)	0.383
Female gender	1.15 (0.75 - 1.76)	0.525
Year of endoscopy (2019 compared to 2022)	11.76 (7.24 – 19.12)	0.000[b]
Ethnicity: Chinese compared to Malay	2.03 (1.06 – 3.90)	0.033[b]
Chinese compared to Indian	1.71 (1.03 – 2.85)	0.038[b]
Chinese compared to Other	1.30 (0.67 – 2.52)	0.442
Presence of co-morbidities	1.76 (1.09 – 2.86)	0.021[b]
Helicobacter pylori infection	0.76 (0.36 – 1.60)	0.471
Functional dyspepsia	0.79 (0.43 – 1.43)	0.433
Irritable bowel syndrome	0.86 (0.49 -1.50)	0.590
Gall stone disease	1.00 (0.39 – 2.53)	0.998
Symptomatic erosive GERD	1.86 (0.86 – 4.01)	0.115
Endoscopic evidence of reflux oesophagitis[a]	0.87 (0.49 – 1.52)	0.615
Recent consumption of NSAIDs	2.23 (0.86 – 5.82)	0.100

[a]Includes subjects with visible oesophageal erosive changes on endoscopy irrespective of symptoms. [b]Statistically significant difference ($p<0.05$)

TableIII: Proportion of duodenal eosinophilia in various subsets of subjects

Subject subset	Proportion of subjects with duodenal eosinophilia as defined by an eosinophil count of:		
	>15/HPF	>22/HPF	>30/HPF
Co-morbidities	92/220 (41.8%)	54/220 (24.5%)	27/220 (12.3%)
Helicobacter pylori infection	17/46 (37.0%)	8/46 (17.4%)	5/46 (10.9%)
Functional dyspepsia	28/81 (34.6%)	19/81 (23.5%)	11/81 (13.6%)
Irritable bowel syndrome	34/88 (38.6%)	18/88 (20.5%)	7/88 (8.0%)
Gallstone disease	12/28 (42.9%)	9/28 (32.1%)	5/28 (17.9%)
Symptomatic erosive GERD	30/73 (41.1%)	15/73 (20.5%)	8/73 (11.0%)
Endoscopic evidence of oesophagitis	64/157 (40.8%)	38/157 (24.2%)	19/157(12.1%)
Recent consumption of NSAIDs	15/25 (60.0%)	6/25 (24.0%)	4/25 (16.0%)

HPF:– High power fields

53 (18.3%) of the subjects in the 2019 cohort and in only three (1.4%) of the 2022 cohort. Counts of greater than 22 eos/5hpf were found in 101(35.0%) and 11(5.0%) of the 2019 and 2022 cohorts, respectively. Counts of greater than 15 eos/5 hpf were found in 177(61.3%) and 32(14.5%) of the 2019 and 2022 cohorts respectively.

Proportion of Duodenal Eosinophilia in Subsets of the Subjects

For the sake of perspective, the proportions of duodenal eosinophilia using the three different thresholds in subsets of subjects with functional dyspepsia, symptomatic GERD, endoscopic evidence of reflux oesophagitis, IBS, gall stone disease, Helicobacter pylori infection and comorbidities respectively are shown in Table III. It should be noted that there would be obvious reasons for there to be overlap between the subsets as many subjects fall into more than one subset.

DISCUSSION

The key finding in our study is that among patients undergoing elective diagnostic OGD, duodenal mucosal eosinophilia was independently associated with having the OGD done in 2019 (as opposed to 2022) and the presence of co-morbidities. These associations were observed irrespective of whether duodenal eosinophilia was defined as greater than 15, 22 or 30 eos/5hpf. The association with having the OGD done in 2019 as opposed to 2022, was particularly strong with odds ratios of 11.76, 13.11 and 21.41 at thresholds of >15, >22 and >30 eos/5hpf, respectively. The association with co-morbidities was modest but consistent with odds ratios in the range of 1.76 2.38 at the three different thresholds. There was a weaker association between Chinese ethnicity and duodenal eosinophilia that was detected only at the lowest threshold of >15 eos/hpf.

The striking observation that the year of sampling (2019 as opposed to 2022) was the strongest predictor of duodenal eosinophilia is intriguing and any explanation for this would admittedly be speculative. It could be more than a coincidence that 2019 was the year before the onset of the COVID-19 pandemic while 2022 was when the world was starting to emerge from the worst of the pandemic. The years 2020 and 2021 in Malaysia were characterised by strictly enforced public health measures to prevent transmission of the virus that included social distancing and restrictions on travelling. There was a significant easing of these restrictions from 2022 onwards. It is conceivable that the public health measures designed to prevent viral transmission caused a significant reduction of environmental exposure to a myriad of agents including microbes and dietary constituents resulting in a reduced state of immune activation in the duodenal mucosa.

The modest but statistically significant association between duodenal eosinophilia and the presence of co-morbidities was consistent with our previous findings and is compatible with the notion that systemic disease is associated with intestinal inflammation and increased intestinal permeability.[10] It is acknowledged however that the co-morbidities represented a heterogenous group of conditions and it is quite possible that some conditions influence duodenal eosinophil counts more than others.

There are limitations to the conclusions that can be made in our study with respect to the possible association between duodenal eosinophilia and specific clinical entities such as functional dyspepsia and symptomatic erosive GERD predominantly because of the absence of truly healthy controls in our sample. In addition, the diagnosis of these clinical entities was based on practice based clinical impressions rather than validated questionnaires and therefore carries risks of subjectivity and bias. There were also gaps in information that are almost inevitable in retrospective observational studies such as ours. For instance, data on history of allergies was not complete enough to be included and it was not possible to subtype cases of functional dyspepsia based on the information in the case records. Finally, almost all subjects only had single biopsies from the second part of the duodenum. This could have resulted in some degree of under-detection as eosinophilic infiltration may have been patchy. A retrospective heterogenous sample such as in our study raises the possibility of confounding variables. We have mitigated this limitation by using logistic regression to adjust for confounding variables.

Despite these limitations and the absence of direct clinical implications, the results do provide some insight into the determinants of duodenal eosinophil counts. Our previous observation of an association between symptomatic GERD and duodenal eosinophilia (defined as >15 eos/5hpf) was not reproducible on this larger sample. Nor was there any association between duodenal eosinophilia and the presence of endoscopically visible reflux oesophagitis regardless of symptoms. However, it is notable that the absolute duodenal eosinophil count did independently predict symptomatic erosive GERD, providing a signal that duodenal eosinophilia may well be linked to symptomatic erosive GERD. This is concordant with the observations of a large population-based study in which the presence of eosinophilia in the second part of the duodenum among subjects with functional dyspepsia predicted the onset of GERD 10 years later, suggesting that functional dyspepsia and GERD may be part of a spectrum of which duodenal eosinophilia is a link.[11] Our findings lend credence to that hypothesis. It is conceivable that in our study there was an intrinsic bias to label dyspeptic patients with endoscopic signs of oesophagitis as having GERD rather than functional dyspepsia. This could have been amplified by the fact that we accepted Los Angeles grade A oesophagitis as a criteria of reflux oesophagitis. Hence, subjects with overlapping GERD and functional dyspepsia may have been more likely to be labelled as GERD, perhaps explaining why duodenal eosinophil counts significantly predicted symptomatic GERD but not functional dyspepsia. It is also tempting to postulate that many subjects with functional dyspepsia and duodenal eosinophilia in previous studies may in fact have had GERD as the primary problem. The proposed hypothesis of duodenal microinflammation causing functional dyspepsia is based on the premise that duodenal stimulation plays an important role in controlling gastric motility and visceral hypersensitivity.[1] It is conceivable that this applies equally to GERD if indeed subsets of functional dyspepsia and GERD are part of the same spectrum.[1,11]

The limitations notwithstanding, our data would be compatible with a hypothesis that the cumulative impact of the various environmental exposures on duodenal eosinophil

counts is much larger than that of putative factors linked to individual clinical entities such as functional dyspepsia. The effect of these putative factors on the eosinophil density may be even further diluted by the influence of other factors such as the presence of co-morbidities and even ethnicity or gender. This could well explain the discordant findings of case control studies designed to detect an association between duodenal eosinophilia and functional dyspepsia. A recent meta-analysis and systematic review concluded that the evidence for a link between microinflammation and functional dyspepsia was of very low quality due to unexplained heterogeneity and possible publication bias.[12] It is possible of course that duodenal eosinophil count is a poorer marker of duodenal microinflammation than degranulated eosinophils as has been suggested by a number of studies.[12] Our results also expose the challenges and pitfalls in attempting to define normal duodenal eosinophil counts given the potential for marked variation in relation to time frames alone.

It is also noteworthy that none of the subjects in the sample had eosinophil counts that approached the levels compatible with the diagnosis of eosinophilic duodenitis. The widely accepted criterion for eosinophilic duodenitis is 30 eosinophils per high powered field.[4,13] The highest eosinophil count among our subjects was 85 eos/5 hpf that crudely translates to only 17 eos/hpf. Indeed, it is lower than even the 20 eos/hpf that has been suggested as the upper end of normal in a US population.[14] This is in sharp contrast to the findings of a recent multisite study in the US that found duodenal eosinophil counts of greater than 30 eos/hpf in 45% of subjects with unexplained moderate to severe abdominal symptoms.[4] Although the subjects in our study are unlikely to be comparable to that of the US study and the number of biopsies taken in our study may not have been enough to have detected patchy eosinophilia, it is nonetheless significant that not even a single subject in our sample reached the threshold for the diagnosis of eosinophilic duodenitis.

CONCLUSION

Among the variables investigated, sampling in the year 2019 (before the COVID-19 pandemic) was the strongest predictor of duodenal eosinophilia while the presence of comorbidities was a modest but statistically significant predictor. These results suggest that the cumulative impact of multiple exposures on duodenal eosinophil counts is much greater than that of putative factors linked to individual clinical entities such as functional dyspepsia. A signal suggesting a link between symptomatic GERD and duodenal eosinophil counts was detected.

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