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Multichannel impedance monitoring for distinguishing nonerosive reflux esophagitis with minor changes on endoscopy in children

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Abstract

Objectives: There are reports describing the relationship between baseline impedance level and esophageal mucosal integrity at endoscopy, such as erosive and nonerosive reflux esophagitis. However, many children with symptoms of gastroesophageal reflux disease have normal findings or minor changes on esophagogastroduodenoscopy. We aimed to examine whether modest changes at esophagogastroduodenoscopy can be evaluated and correlated with esophageal multichannel intraluminal impedance monitoring.

Methods: Patients (ages 0–17 years) with upper gastrointestinal symptoms who underwent combined esophagogastroduodenoscopy and multichannel intraluminal impedance monitoring at the Women's and Children's Hospital, Adelaide, Australia, between 2014 and 2016 were retrospectively studied and the following data were collected and used for analysis: demographics, multichannel intraluminal impedance data, included baseline impedance. Endoscopic findings were classified by modified Los Angeles grading, Los Angeles *N* as normal, Los Angeles M as with minimal change such as the erythema, pale mucosa, or friability of the mucosa following biopsy. Patients on proton pump inhibitor were excluded.

Results: Seventy patients (43 boys; 61%) were enrolled with a mean age of 7.9 years (range 10 months to 17 years). Fifty-one patients (72.9%) were allocated to Los Angeles *N*, while Los Angeles *M* was evident in 19 patients (27.1%). Statistically significant differences were observed in the following parameters: frequency of acid and nonacid reflux and baseline impedance in channels 5 and 6. The median values of the data were 18.3 episodes, 16.0 episodes, 2461.0 Ω, 2446.0 Ω in Los Angeles *N*, 36.0 episodes, 31.0 episodes, 2033.0 Ω, 2009.0 Ω in Los Angeles *M*, respectively.

Conclusion: Lower baseline impedance is helpful in predicting minimal endoscopic changes in the lower esophagus. A higher frequency of acid and nonacid reflux episodes was also predictive of minimal endoscopic change in the lower esophagus.

Keywords: children, minimal change, nonerosive esophagitis, reflux esophagitis

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Introduction

Esophageal multichannel intraluminal impedance (MII) is one of the useful diagnostic methods for assessing gastroesophageal reflux (GER). In 2011, Farre and colleagues[1] described an additional MII parameter, esophageal baseline impedance (BI) that the authors proposed might be useful to examine esophageal mucosal integrity. Since the introduction of this impedance parameter, several papers examining its relevance in pediatric patients have emerged.[2–7] BI has been demonstrated to be influenced by proton pump therapy, acid reflux, prolonged acid reflux events, and mucosal integrity. BI values were thought to

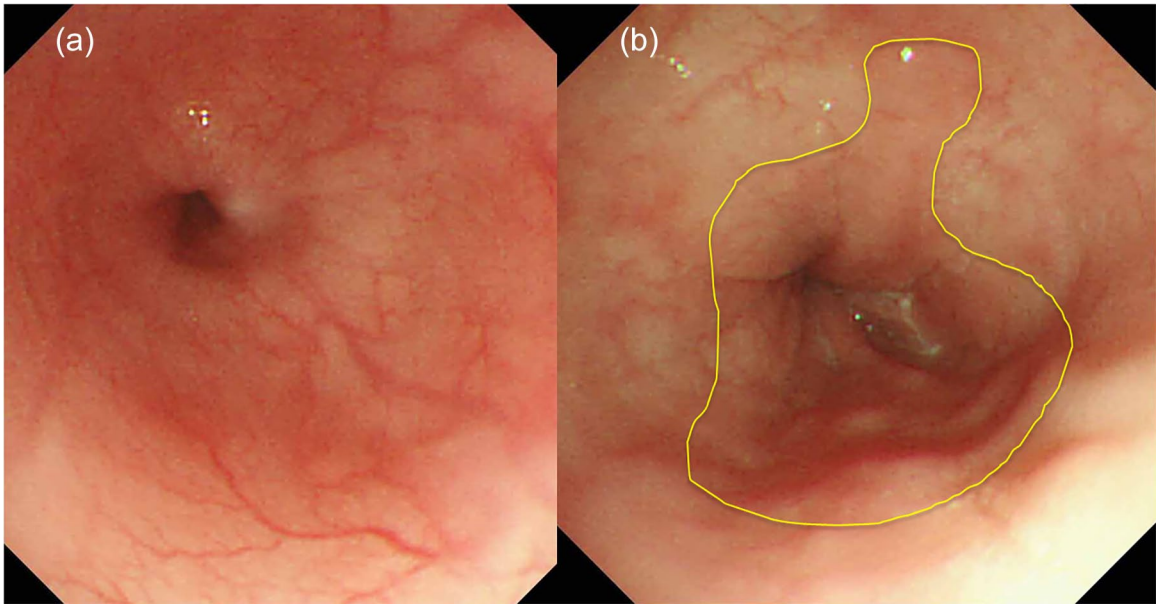

Figure 1. (a) A still endoscopic image of Los Angeles *N* (LA-N). (b) A still image of Los Angeles M (LA-M) as minimal changes (yellow line shows edematous and erythematous mucosa.

reflect the status of the mucosa. However, the calculation may not be easy without the utilization of adjunctive software.

Esophagogastroduodenoscopy (EGD) and esophageal biopsy may detect esophagitis; however, these procedures have variable sensitivity and specificity in detecting pH-positive gastroesophageal reflux disease (GERD). Comparative reliability of endoscopic findings can be improved using standardized parameters but still remains a subjective assessment of mucosal integrity using a grading system such as the Los Angeles Classification.[8,9] Using this classification, patients can be distinguished by the endoscopic description of their esophageal mucosa into nonerosive reflux disease (NERD) or erosive esophagitis reflux disease (ERD). ERD is distinguished by visible mucosal breaks and is reliably associated with GERD.[10] However, pediatric patients infrequently demonstrate this level of reflux esophagitis.[11,12] Most pediatric patients with GERD demonstrate NERD at endoscopy. Some authors have defined the importance of minimal change (LA-M) (Figure 1), while others have downplayed its significance as they could not obtain interobserver agreement.[13,14]

With the development of advanced endoscopic imaging techniques, such as magnified narrow-band imaging, the ability to detect minimal esophageal injury[15,16] has improved. Minute changes of intrapapillary capillary loops such as a dilation and elongation with regular intervals may be suggestive of inflammatory changes in the esophagus of NERD patients. Although these findings gained interobserver agreement, these studies did not define the exact length and intervals that should be considered as defining minimal change. Therefore, further advances in technology may bring us magnified clear high-definition views and improved differentiation between normal and minimal findings; however, these findings remain subjective.

The hypothesis of this study was that objective identification of minimal esophageal mucosal changes at endoscopy can still be identified with the help of objective measures such as impedance baseline. Thus, the primary objective of this study is to determine whether patients defined as LA-M have altered BI compared with those with Los Angeles *N* (LA-N). Moreover, we explored whether other parameters in MII data demonstrate significant differences in these two groups and whether minor changes in EGD can be further characterized by MII monitoring.

Material and methods

Patients (ages 0–17 years) with symptoms related to GER who underwent EGD and MII monitoring at the Women's and Children's Hospital, Adelaide, Australia, between 2014 and 2016 were

retrospectively studied, and the following data were collected: demographics (age, gender), MII parameters, histological findings, and endoscopic findings. Patients' major symptoms were classified as respiratory including cough, throat pain, and sneeze, gastrointestinal feeling of regurgitation, burp, epigastric pain, and others, such as irritation. Patients on proton pump inhibitors (PPIs) were excluded. Other exclusions were the presence of esophageal anatomical anomaly, eosinophilic esophagitis, and previous antireflux surgery. All patient data were de-identified and stored for analysis. The study was approved by the WCH Human Research Ethics Committee (916A/March/2020).

MII recording

For MII study, participants were intubated with ambulatory pH-impedance catheters (ComforTec®, Diversatek, Inc., United States) and all data were recorded with ZepHr® (Diversatek). The catheter chosen was dependent on the patient's height or age (either ZIN-BS-45 or ZPN-BS-46). Data were stored on a single portable digital recorder. The MII probe was positioned in the lower esophagus at two and a half vertebrae above the diaphragm, with the position adjusted according to a lateral chest X-ray. The distal channel 6 is located at 1 cm lower than the esophageal pH-monitoring probe.

Once the MII probe was in place, subjects could leave the hospital and return to their daily routine. During this time, a diary was kept of mealtimes, posture and symptoms of interest (e.g. chest pain, heartburn, regurgitation, and eating). Recording of the MII was performed with a Sleuth mobile impedance recorder. All patients were required to avoid acidic food and fluid. Regarding the MII data, an automatic (Autoscan Bioview Analysis Software) and a manual reading were performed by S.G., a medical technician. As for MII parameters, acid exposure time (%) and longest episode of acid exposure(sec) were collected.

Endoscopy

All endoscopies were performed by senior consultants in the Gastroenterology unit, Women's and Children's Hospital. The endoscopes used were GIF-HQ190 (Olympus, Australia), and all endoscopies were performed under general anesthesia. Endoscopic findings were described and subsequently classified according to the modified Los Angeles grading, LA-N as normal, LA-M with minimal change including findings such as erythematous, pale or friable mucosa[17–19] (Figure 1). All four endoscopists were blinded to the results of impedance data at the time of endoscopy.

BI

Impedance data included: the number of acid and nonacid reflux events, and BI (distal channels; 5,6 was objectively calculated using a previously described MATLAB-based algorithm (MathWorks, Natick, MA).[2,3]

Pathology

All patients had at least one biopsy in the lower esophageal mucosa, approximately 10–20 mm from the *Z* line. Senior pathologists at the Women's and Children's Hospital evaluated all specimens, and they were blinded to the results of MII study. Abnormal histologic findings include basal hyperplasia, papillary elongation, and intraepithelial inflammatory cells such as eosinophils, neutrophils, and mononuclear cell infiltration.[20] Basal cell hyperplasia was defined as follows: normal epithelial basal layer thickness less than 15%, mild basal hyperplasia 15–30%, while moderate-to-severe basal hyperplasia greater than 30% of epithelial thickness. Papillary elongation defined as follows: normal papillary length less than 50% of epithelial thickness, mild elongation 50–75% of moderate to severe greater than 75% of epithelial thickness. All criteria were assessed and biopsies allocated to three grades: normal, mild, and moderate esophagitis.

Statistical analysis

All statistical analyses were performed with SPSS® version 20 (IBM, Chicago, IL). All data, except evaluation of pathological findings, were analyzed by Mann–Whitney test. Pathological results were investigated by chi-square test, p value < 0.05 was defined as statistically significant. To evaluate cut-off values of BI, receiver operating characteristic (ROC) curves were generated.

Results

The total number of subjects available for analysis was 145, of these, 70 patients met the entry criteria, excluding patients with eosinophilic esophagitis, a history of esophageal atresia and previous fundoplication. The 70 patients (43 boys 61%)

Table 1. Age, pH parameters, and numbers of reflux episodes.

	Values = median		
	LA-N	**LA-M**	***p* (*<0.05)**
Age (month)	84	103	0.207
Acid exposure time (%)	1.3	2.5	0.580
Longest episode of acid exposure (min)	2.8	4.3	0.186
Number of acid reflux	18.3	36.0	0.007*
Number of nonacid reflux	16.0	31.0	0.004*

LA-M, Los Angeles *M*; LA-N, Los Angeles *N*.
*$p < 0.05$.

had a mean of age of 7.9 years (range: 0.8–17.0 years). Fifty-one patients (72.9%) were allocated to LA-N, while LA-M was evident in 19 patients (27.1%). PH and impedance data were compared between the two groups, LA-N and LA-M. There were no statistically significant differences in mean acid exposure time and mean of the longest episode of acid exposure (Table 1).

Major symptoms were not different in both groups; patients who complained of respiratory symptoms were 22 (43.1%) in LA-N and 10 (52.6%) in LA-M, and those with gastrointestinal symptoms were 24 (47.0%) in LA-N and 8 (42.1%) in LA-M.

Significant differences were observed in four parameters: Frequency of acid and nonacid reflux, and BI in channel 5, 6. The median values (range) of BI in channel 5, and 6 were 2461.0 Ω (1782–3739), and 2446.0 Ω (1182–3695), in LA-N, 2033.0 Ω (1163–3523) and 2009.0 Ω (1193–2805) in LA-M, respectively, ($p = 0.014$ and 0.007, respectively). The median frequencies of acid and nonacid reflux were 18.3 and 16.00 in LA-N, 36.0 and 31.0 for LA-M ($p = 0.007$ and $p = 0.004$, respectively). There was no significant difference noted in BI in all remaining impedance sensors between the two study groups (Figure 2).

For pathological results, normal findings were observed in the LA-N group in 38 of 51 patients (74.5%), while 5 of 19 patients (26.3%) in LA-M had normal histopathological findings ($p = 0.001$). Mild inflammatory changes were observed in 12 patients (23.5%) in LA-N, and 12 patients (63.2%) in LA-M. Moderate changes were seen in 1 patient (2%) in LA-N and 2 patients (10.5%) in LA-M. The data are presented in Table 2. The distribution of patients varies between the groups; 75% of patients in LA-N were classified in the histologically normal category while only 26% of patients in LA-M demonstrate normal findings pathological grade and BI values did not indicate any correlation in each group.

ROC curves of four parameters such as the BI of Ch5 and Ch6 are shown in Figure 3, while the number of acid and nonacid reflux events is indicated in Figure 4. Each area under the curve (AUC) was 0.66 in Ch5 and 0.67 in Ch6, while 0.71 and 0.72, respectively, in the number of reflux. Therefore, the number of acid and nonacid reflux maintained more than 0.7 which shows moderate accuracy of prediction ability. The cut-off values of the number of acid and nonacid reflux with use of Youden index are 27.0 and 26.5 and the sensitivity of those are 0.68 and 0.63, while the specificity were 0.71 and 0.75, respectively.

Discussion

There is a report that compares BI values in ERD and NERD in children.[7]

Generally, many pediatric patients reveal NERD, even though they show GERD symptoms. Thus, we tested the hypothesis that BI may assist in the assessment of differences in the mucosal integrity between patients with LA-N and LA-M at endoscopy. As a result, this distinction might help to tell apart patients in LA-M who need medication from patients in LA-N by only using MII. This study has shown that BI values in the lower esophageal impedance channels 5 and 6 were

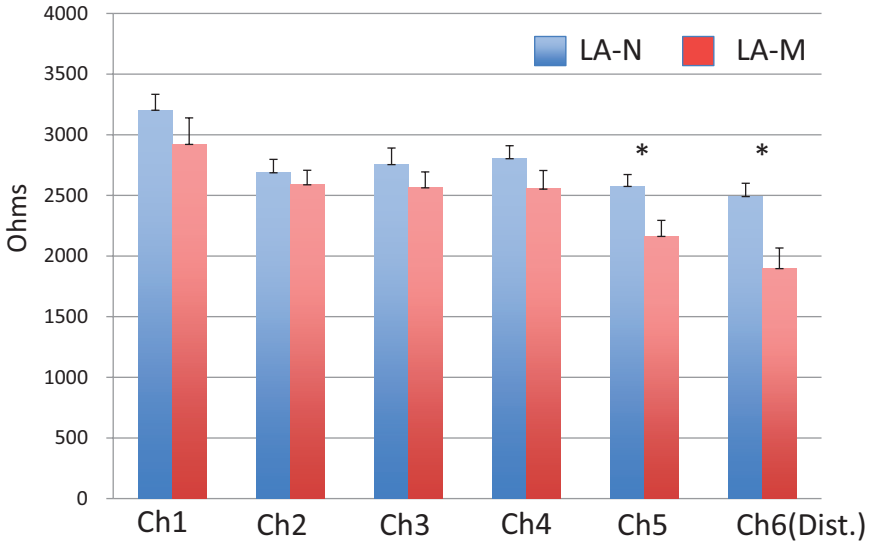

Figure 2. Baseline impedance in all channels.
*$p < 0.05$.

Table 2. Comparison of the pathologic findings of the two groups.

	Pathology			Total (*n*)
	Normal	**Mild**	**Moderate**	***p < 0.05**
LA-N	38 (74.5%)	12 (23.5%)	1 (2.0%)	0.51 *
LA-M	5 (26.3%)	12 (63.2%)	2 (10.5%)	0.19 *
n	43	24	3	0.70

LA-M, Los Angeles *M*; LA-N, Los Angeles *N*.
*$p < 0.05$.

significantly lower in the LA-M group compared with LA-N group. The more proximal channels located in the mid and upper esophagus did not show any statistical differences in BI between the LA-M and LA-N groups. These results could be explained by the refluxate predominantly reaching the lower esophagus in patients with LA-M and not the mucosa in the mid and upper esophagus. However, we do not have biopsy changes from the mid and upper esophagus to compare to the BI from the upper impedance sensors.

Other parameters of MII examined in this study were acid exposure, longest episode of acid exposure, and frequency of acid and nonacid reflux. These parameters have been widely assessed in studies comparing different grades of LA endoscopic classification. Our results revealed that the frequency of acid and nonacid reflux, but not acid exposure time nor the longest acid exposure time, were significantly different between the two groups. Furthermore, minimal change in NERD could not be distinguished by the reflux index, instead influenced by the frequency of acidic and nonacidic reflux events. This result is in contrast to the results of Savarino and colleagues[21] who found that the frequency of nonacid reflux in adult patients was not associated with nonerosive or indeed ERD. In our study, the number of acid and nonacid reflux episodes may vary widely in the two groups (LA-M and LA-N); however, esophageal acid exposure did not have any significant influence in children without ERD.

With regard to pathologic findings, statistical differences were observed in LA-N and LA-M groups. It is well documented that normal findings at EGD may not always support normal histological findings of the esophagus.[22] Normal endoscopic appearance of the esophageal mucosa

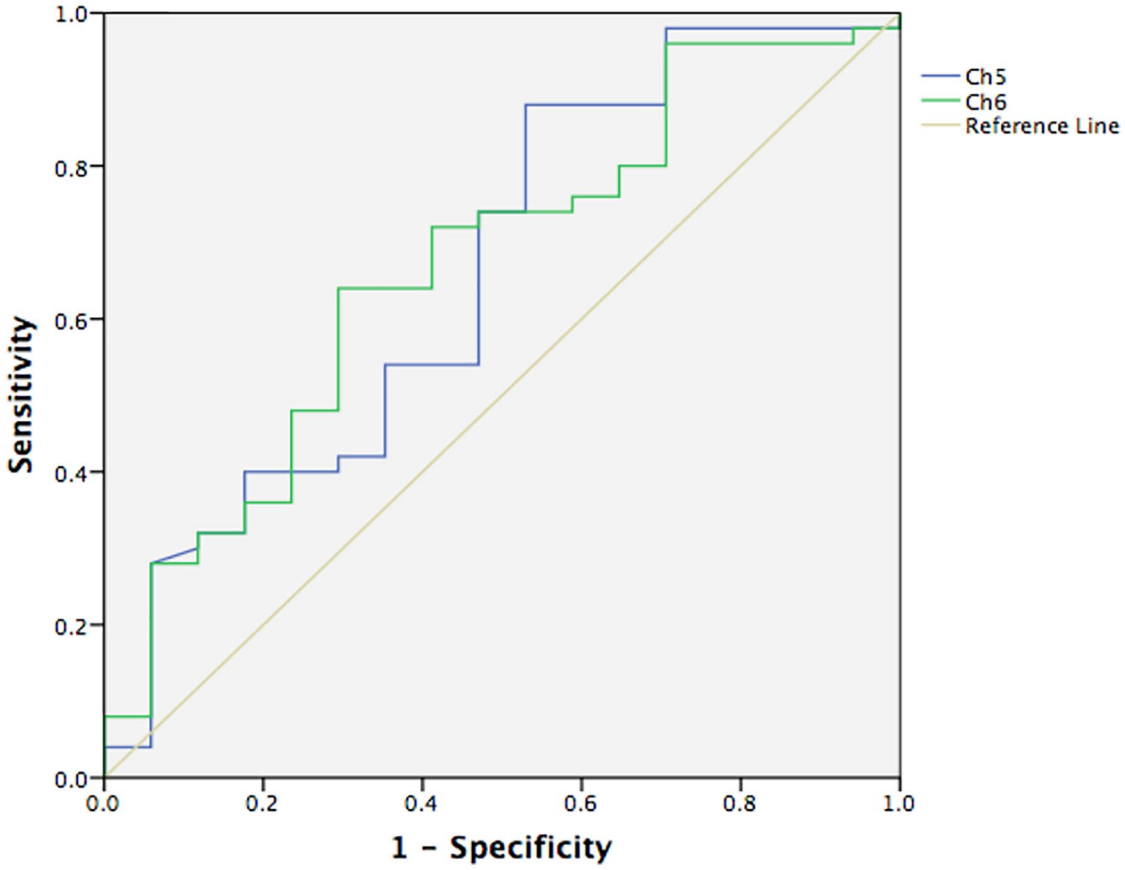

Figure 3. ROC curves of numbers of BI. Area under the curves are 0.66 in channel 5 and 0.67 in channel 6.

in pediatric patients does not exclude histologic evidence of reflux esophagitis. In this study, one patient (2%) in LA-N demonstrated moderate inflammatory changes in the mucosa and mild changes in 12 patients (23.5%) while normal findings were observed in 38 patients (74.5%). Each pathological group in LA-N did not reveal statistical differences in BI values, the number of acid and nonacid reflux, acid exposure time and other MII values. The patient in LA-N with moderate inflammatory changes in the mucosa was a 9-year-old boy who has bronchial asthma and autism. His BI values in channels 5 and 6 are 2590Ω and 2259Ω, respectively. In contrast, only 5 patients (26.3%) in LA-M revealed normal esophageal mucosa biopsy findings. Their MII parameters including BI, did not differ from patients classified into mild and moderate groups. With these results, the distribution of pathological changes between LA-N and LA-M was remarkably different; however, histological changes do not indicate differences of each parameter in this study. Parameters such as lowered BI may indicate the presence of dilated intercellular spaces on electron microscopy.[23,24]

It is not uncommon for interpretation of endoscopic findings to differ among endoscopists, especially between normal and minimal change; thus, the reliability is questionable.[13,14] For this reason, an objective measure is required for minimal change. ERD can reliably be distinguished from normal findings by almost all endoscopists.[14] Miwa and colleagues observed that senior/experienced endoscopists can discriminate slight changes reproducibly and video recordings can be helpful in supporting agreement.[14] All endoscopists in our study were senior consultants in a single pediatric gastroenterology unit who have at least 10 years' experience, competent in detecting minimal change in esophageal mucosa: pallor, whitish, reddish, and/or edematous changes. Although we did not blind and compare endoscopic scores between consultants in this study, it has been shown that experienced endoscopists from different institutions can score mucosal changes reliably.[25]

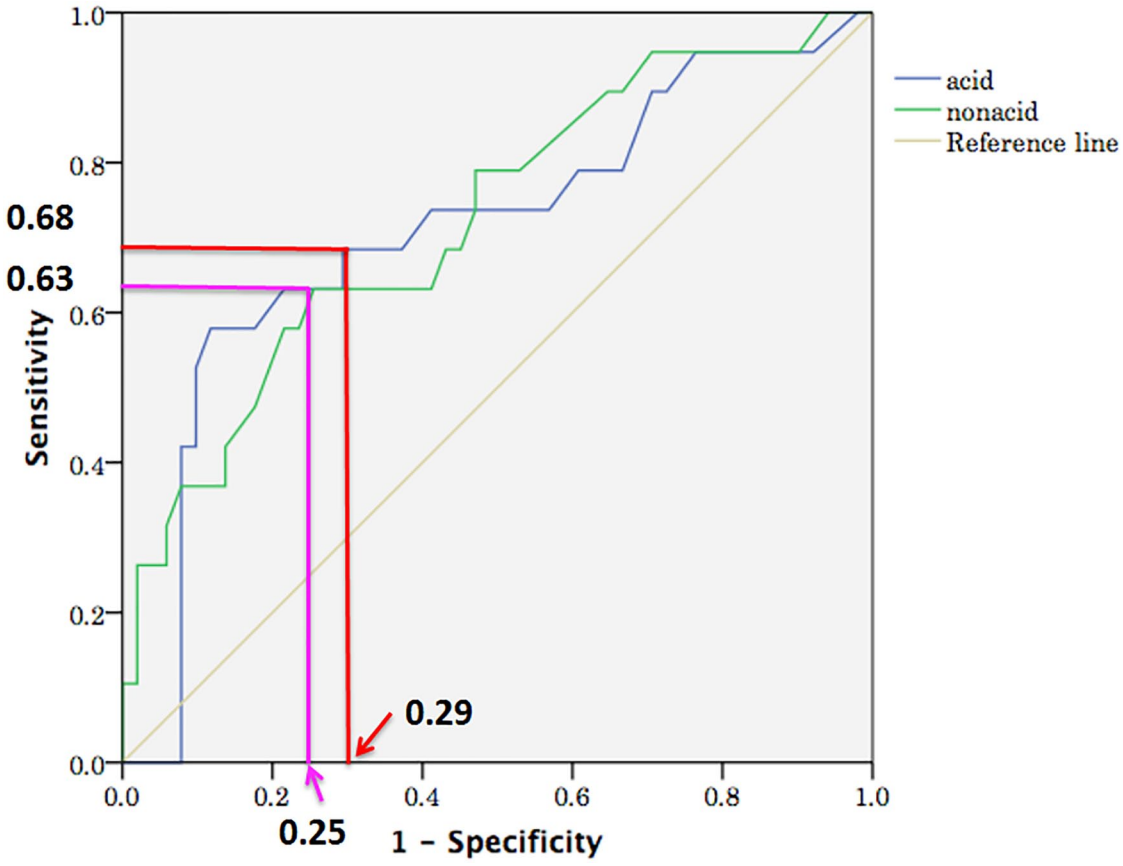

Figure 4. ROC curves of the numbers of acid reflux and nonacid reflux. Each area under the curve is 0.71 in acid and 0.72 in nonacid reflux.

The weakness of this study is that all patients who had taken PPIs prior to endoscopy were excluded, potentially excluding patients with more severe disease from the study. It is possible that patients with more severe symptoms such as hematemesis are more likely to have ERD and be prescribed empirical trial of PPI. With regard to pediatric patients, as they often require general anesthesia when they undergo EGD, pediatric gastroenterologists may prescribe PPIs for children and adolescents who have relatively severe symptoms for symptom relief while an endoscopy is pending.[26,27] Patients who are resistant to empirical PPI treatment may need to be examined by EGD, although usually an empiric trial of PPI is not recommended.[22] All patients with ERD were excluded in this study. It is widely believed that PPIs have a significant influence on the esophageal mucosa, improving mucosal integrity.[2] Salvatore and colleagues[5] revealed that BI values vary with age category >BI values are lower in infants (and lowest in the first months of life) compared to older children. In this study, the youngest patient was 10 months old girl while the remainder were more than 20 months old; therefore, age would not be expected to have a significant influence on BI in our study. As AUC for BI was 0.66 in Ch5 and 0.67 in Ch6, these parameters may be relatively weak to distinguish between LA-N and LA-M. We speculate that cut-off values of Ch5 and Ch6 in each group revealed statistical differences. This result suggests that BI values may not have been ready-to-use for practical diagnostic precision yet; however, it is possible to use it as a reference tool. On the contrary, as for the frequency of reflux, both acid and nonacid reflux showed a moderate predictive accuracy. There were 27.0 episodes of acid reflux and 26.5 of nonacid reflux in cut-off values. These would be a supportive indicator for the determination of LA-M esophagitis, even though patients complain of similar symptoms to those with LA-N.

Conclusion

To detect endoscopic minimal change, lower esophageal BIs were helpful. Furthermore, the frequency of acid and nonacid reflux episodes

was associated with minimal change in distal esophagus and not the level of esophageal acid exposure.

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Author contributions

Concept and design: F.J. and D.M. Collecting data: F.J., R.A-.A., P.H., R.C., D.M., and G.S. Analysis and interpretation: F.J., G.S., D.M., and T.O. Drafting and editing of the manuscript: F.J., D.M., and T.O.

Ethical approval

This study has been approved by the research ethics committee at Women's and Children's Hospital of Adelaide (916A/March/2020).

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Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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