



OPEN

## Bolus transit of upper esophageal sphincter on high-resolution impedance manometry study correlate with the laryngopharyngeal reflux symptoms

Jia-Feng Wu<sup>1</sup>, Wei-Chung Hsu<sup>2</sup>, I.-Jung Tsai<sup>1</sup>, Tzu-Wei Tong<sup>3</sup>, Yu-Cheng Lin<sup>3</sup>, Chia-Hsiang Yang<sup>3,4</sup> & Ping-Huei Tseng<sup>5</sup>✉

Laryngopharyngeal reflux symptom is a troublesome upper esophageal problem, and reflux symptom index (RSI) is commonly applied for the assessment of clinical severity. We investigated the relationship between the upper esophageal sphincter impedance integral (UESII) and RSI scores in this study. Totally 158 subjects with high-resolution esophageal impedance manometry (HRIM) with RSI questionnaire assessment were recruited. There are 57 (36.08%), 74 (46.84%), 21 (13.29%), and 6 (3.79%) patients were categorized as normal, ineffective esophageal motility disorder, absent contractility, and achalasia by HRIM examination, respectively. Subjects with RSI > 13 were noted to have lower UESII than others with RSI ≤ 13 (7363.14 ± 1085.58 vs. 11,833.75 ± 918.77 Ω s cm; P < 0.005). The ROC analysis yielded a UESII cutoff of < 2900 Ω s cm for the best prediction of subjects with RSI > 13 (P = 0.002). Both female gender and UESII cutoff of < 2900 Ω s cm were significant predictors of RSI > 13 in logistic regression analysis (OR = 3.84 and 2.83; P = 0.001 and 0.01; respectively). Lower UESII on HRIM study, indicating poor bolus transit of UES during saline swallows, is significantly associated with prominent laryngopharyngeal reflux symptoms scored by RSI score.

### Abbreviations

HRIM	High-resolution esophageal impedance manometry
LPRD	Laryngopharyngeal reflux disease
RSI	Reflux symptom index
UESII	Upper esophageal sphincter impedance integral
UESRI	Upper esophageal sphincter relaxation integral

Esophageal dysmotility is a troublesome problem in both adults and children, and the current diagnosis is based on high-resolution esophageal manometry (HRM)<sup>1,2</sup>. Laryngopharyngeal symptom is considered one of the most difficult-to-diagnose manifestations of laryngopharyngeal and/or upper esophageal problems and may associate the function of the upper esophageal sphincter (UES)<sup>3</sup>. The clinical symptoms of laryngopharyngeal reflux disease (LPRD) include voice problem, throat clearing, the sensation of excess throat mucus, dysphagia, cough, breathing difficulties, troublesome or annoying cough, or lump sensation in the throat<sup>4,5</sup>.

Reflux symptom index (RSI), a nine-item self-administered outcome questionnaire, was developed to assess the symptoms and severity of laryngopharyngeal reflux symptoms and validated in follow-up studies<sup>3-5</sup>. A total RSI score of more than 13 is considered positive as far as diagnosis of LPRD<sup>4,5</sup>. However the diagnosis of LPRD

<sup>1</sup>Departments of Pediatrics, National Taiwan University Hospital, Taipei, Taiwan, ROC. <sup>2</sup>Departments of Otolaryngology, National Taiwan University Hospital, Taipei, Taiwan, ROC. <sup>3</sup>Graduate Institute of Electronics Engineering, National Taiwan University, Taipei, Taiwan, ROC. <sup>4</sup>Department of Electrical Engineering, National Taiwan University, Taipei, Taiwan, ROC. <sup>5</sup>Department of Internal Medicine, National Taiwan University Hospital, Chung-Shan S. Rd, No. 7, Taipei, Taiwan, ROC. ✉email: pinghuei@ntu.edu.tw

remains difficult and the pathophysiology of the clinical symptoms of LPRD, especially the associated UES function, remains unknown in large<sup>3–5</sup>.

HRM and automatically calculated parameters, including the distal contractile integral (DCI), distal latency, and 4 s integrated relaxation pressure (IRP4s) to quantify the pressure changes in the esophagus, have been well developed to assist the differential diagnosis of various esophageal motility disorders<sup>6,7</sup>. The concomitant assessment of the esophageal intraluminal impedance signal is regarded as an effective modality for the assessment of bolus transit patterns in esophageal high-resolution impedance manometry (HRIM) study<sup>8,9</sup>. However, the current HRM study mainly assessed the function of the lower esophageal sphincter and esophageal body. The HRIM interpretation systems for assessing the bolus transit depend on the visual interpretation of impedance signals by clinical physicians<sup>6–13</sup>. A generalized automated analysis system to assess the UES motor function and bolus clearance remain needed. Assessing the UES pressure change and bolus transit by HRIM study may offer evidence of the pathophysiology of LPR symptoms.

In this study, we aimed to analyze the relationship between Novo parameters of UES (pressure and bolus clearance function) and the presence and severity of LPR symptoms in terms of RSI scores, and their possible roles for the automatic diagnosis of LPRD in the HRIM study.

## Materials and methods

**Study participants.** We enrolled 158 subjects into this cohort for analysis between 2014 and 2020. There are 101 consecutive patients with various esophageal symptoms such as reflux, dysphagia, and globus sensation (53.40 ± 15.85 years; 38 males and 63 females) and another 57 adult asymptomatic health control subjects (age 41.54 ± 11.75 years; 32 males and 25 females) receiving the HRIM study and RSI questionnaire at the same day in the gastrointestinal motility laboratory of National Taiwan University Hospital into this analysis. The interpretation of the manometric parameters of HRM was based on the Chicago Classification version 3.0 criteria<sup>6</sup>. The anthropometric data including the body height and weight of the study subjects were also collected. The study protocol was approved by the Institutional Review Board of National Taiwan University Hospital. The written informed consent was obtained from all patients for the HRIM examination and RSI questionnaire assessment in this study. The study was conducted following the principles of the Declaration of Helsinki and the International Conference on Harmonization for Good Clinical Practice.

**HRIM study and data interpretation.** In this study cohort, all subjects were instructed to maintain a nil per os status for at least 8 h before the HRIM examination. The HRIM examination in this study was performed using a 4.2-mm-diameter silicone catheter with 22 closely spaced water-perfused pressure sensors and 12 impedance channels (PART#CE4-1083; Dentsleeve International Ltd., Ontario, Canada) as described in our previous study<sup>13</sup>. The side holes of the HRIM catheter were perfused with distilled water at a rate of 0.15 mL per min using a pneumatic perfusion pump throughout the manometric study, and the pressure/impedance data was recorded using external pressure transducers (Solar GI HRIM water-perfused system, Medical Measurement Systems, Enschede, Netherlands).

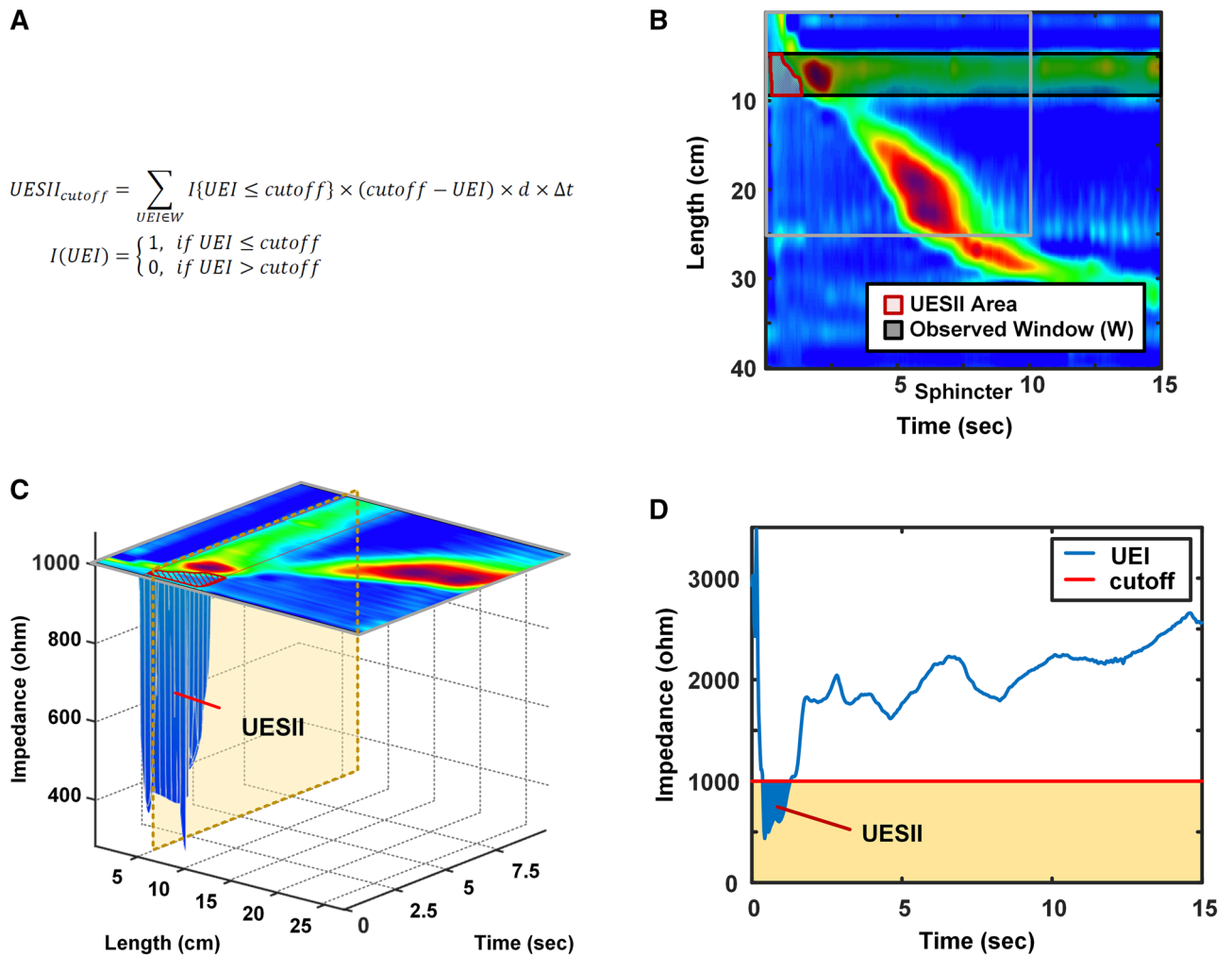
All subjects were instructed to take 10 liquid swallows of 5 mL saline at 30 secs intervals after the successful HRIM catheter insertion. The HRIM pressure and impedance signals were recorded at a frequency of 20 Hz and stored on a personal computer. The MMS HRIM software converts recorded signals into digital data, which are displayed as color plots on the Solar GI HRM Compact Pole system (version 9.5, MMS, Solar GI HRIM water-perfused system, Medical Measurement Systems, Enschede, Netherlands).

**Quantification of the upper esophageal sphincter impedance integral (UESII).** We calculated the UESII below impedance thresholds of 1000Ω over an observed time window of 15 s to quantify the bolus transit signal of UES during the 5-mL saline liquid swallow test (Fig. 1A–D). In the formula (Fig. 1A), the “UEI” means upper esophageal impedance, “*d*” is the distance between two adjacent impedance channels for “UEI”, “ $\Delta t$ ” is the sampling interval of the sensors, “*W*” is the observed window, and “*I*” is the indicator function. The mean UESII of 10 liquid swallows in each subject was evaluated in the statistical analyses.

**Quantification of the upper esophageal sphincter relaxation integral (UESRI).** The UESRI below pressure thresholds of 10 mmHg over an observed time window of 15 s to quantify the motor function of UES relaxation during the 5-mL saline liquid swallow test was calculated (Fig. 2A–D). In the formula (Fig. 2A), “UEP” means upper esophageal pressure, “*d*” is the distance between two adjacent impedance channels for “UEP” or two adjacent pressure sensors for “UEP”, “ $\Delta t$ ” is the sampling interval of the sensors, “*W*” is the observed window, and “*I*” is the indicator function. The mean UESRI of 10 liquid swallows in each subject during HRIM examination was evaluated in the statistical analyses.

**Symptom questionnaires evaluation.** All study subjects were assessed for gastrointestinal symptoms by using validated RSI symptom questionnaires on the same day of HRIM study<sup>3</sup>. The RSI score > 13 is used for the clinical diagnosis of LPRD<sup>3</sup>. The total RSI score, and the 9 individual RSI sub-scores are included in the data analysis.

**Statistical analysis.** The MedCalc (version 20.09; MedCalc Software, Ostend, Belgium) and STATA (version 14.2; StataCorp LP, College Station, TX, USA) software were applied for the statistical analyses in this study. The MATLAB software (version 8.6 R2015b; MathWorks, Natick, MA, USA) was used to quantify the UESRI, and UESII in this study. Fisher’s exact test or the chi-squared test was used to determine differences in categorical



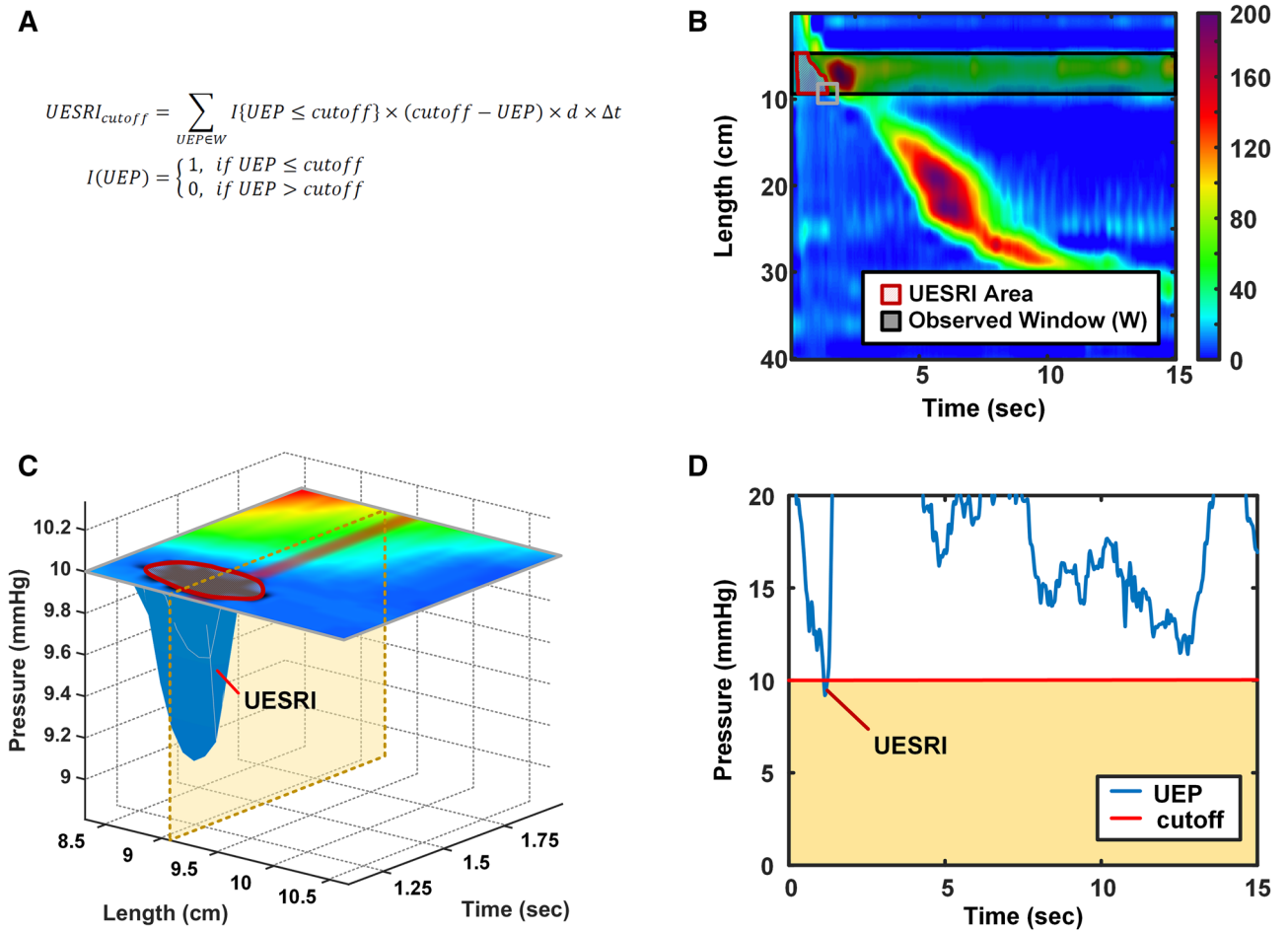
**Figure 1.** (A) In the formula of upper esophageal sphincter impedance integral (UESII), the “*UEI*” means upper esophageal impedance, “*d*” means the distance between two adjacent impedance channels, “ $\Delta t$ ” is the sampling interval, “*W*” is the observed window, and “*I*” is the indicator function. (B) The 2D plot of UESII of the wet swallow. (C) The 3D plot of UESII of the wet swallow was demonstrated. (D) Calculation of the UESII value at less than 1000  $\Omega$ .

variables between the groups. Student’s t-test with unequal variance was applied to assess differences in the mean, standard error (SE), and 95% confidence interval (CI) values of the continuous variables between groups. Correlation analysis between RSI score and UES metrics was analyzed. Univariate and multivariate logistic regression analyses were also performed. Receiver operating characteristic (ROC) analysis was performed to determine cutoff values for predicting RSI > 13 and their respective area under the curve (AUC) values. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of each diagnostic parameter were also analyzed. A P value < 0.05 was regarded as indicative of statistical significance.

## Results

**General characteristics.** Among these 101 consecutive patients with various esophageal symptoms, 74 (73.27%), 21 (20.79%), and 6 (5.94%) patients were categorized as ineffective esophageal motility disorder, absent contractility, and achalasia (2 type I, 3 type II, and 1 type III achalasia patients) according to the Chicago Classification version 3.0 criteria, respectively. All healthy control (n = 57) had normal esophageal manometry data. There are 48 (30.38%) subjects with self-reporting RSI score > 13 on the same day of HRIM study in this study cohort (Table 1).

The RSI score is significantly higher in subjects with esophageal motility disorders (ineffective esophageal motility disorders, absent contractility, and achalasia) than others with normal esophageal manometry data ( $13.90 \pm 1.08$  vs.  $0.53 \pm 0.17$ ; 95% CI 11.76–16.05 vs. 0.19–0.85;  $P < 0.0001$ ). The percentage of female subjects in the RSI score > 13 group (n = 48) is significantly higher than that in the RSI score  $\leq 13$  group (n = 110) in this cohort (79.16% vs. 46.45%;  $P < 0.001$ ). Subjects with RSI score > 13 (n = 48) were also noted to have lower UESII than others with RSI score  $\leq 13$  (n = 110) ( $7363.14 \pm 1085.58$  vs.  $11,833.75 \pm 918.77 \Omega \text{ s cm}$ ; 95% CI, 5179.24–9547.05 vs. 10,012.78–13,654.71  $\Omega \text{ s cm}$ ;  $P < 0.005$ ). In this cohort, RSI > 13 was found in 47.30% (35/74)



**Figure 2.** (A) In the formula of upper esophageal sphincter relaxation integral (UESRI), the “UEP” means upper esophageal impedance, “d” means the distance between two adjacent pressure sensors, “Δt” is the sampling interval, “W” is the observed window, and “I” is the indicator function. (B) The 2 D plot of UESRI of the wet swallow. (C) The 3D plot of UESRI of the wet swallow. (D) Calculation of the UESRI value at less than 10 mmHg.

	Study cohort (n=158)
Male gender, n (%)	70 (44.30%)
Age, mean ± SE (years)	49.13 ± 1.24
Body weight, mean ± SE (Kg)	61.28 ± 1.20
Height, mean ± SE (m)	1.63 ± 0.01
Body mass index, mean ± SE (kg/m2)	22.94 ± 0.33
Waist, mean ± SE (cm)	80.30 ± 0.94
<b>High resolution esophageal manometry finding</b>	
Normal, n (%)	57 (36.08%)
Ineffective esophageal motility disorder, n (%)	74 (46.84%)
Absent contractility, n (%)	21 (13.29%)
Achalasia, n (%)	6 (3.79%)
<b>Reflux symptom index (RSI)</b>	
RSI score > 13, n (%)	48 (30.38%)
RSI score ≤ 13, n (%)	110 (69.62%)
Upper esophageal sphincter relaxation integral (UESRI), mmHg s cm	2175.69 ± 311.24
Upper esophageal sphincter impedance integral (UESII), Ω s cm	10,475.59 ± 736.28

**Table 1.** General characteristics of the study cohort.

	UESII		UESRI	
	Correlation coefficient	P value	Correlation coefficient	P value
Total RSI score	- 0.22	0.005	- 0.09	0.27
<b>RSI sub-score</b>				
Hoarseness or a problem with your voice	- 0.26	0.001	- 0.01	0.93
Clearing your throat	- 0.16	0.04	- 0.09	0.28
Excess throat mucus or postnasal drip	- 0.10	0.23	- 0.10	0.20
Difficulty swallowing food, liquids, pills	- 0.23	0.004	0.01	0.86
Coughing after you ate or after lying down	- 0.10	0.19	- 0.09	0.26
Breathing difficulties or choking episode	- 0.19	0.02	- 0.01	0.87
Troublesome or annoying cough	- 0.10	0.23	- 0.09	0.25
Sensation of something sticking in your throat or a lump in your throat	- 0.21	0.007	- 0.10	0.19
Heartburn, chest pain, indigestion, or stomach acid coming up	- 0.18	0.02	- 0.06	0.46

**Table 2.** Correlation between upper esophageal sphincter impedance integral (UESII), and upper esophageal sphincter relaxation integral (UESRI) with reflux symptom index (RSI).

IEM patients, 16.67% (1/6) achalasia patients, and 57.14% (12/21) patients with absent contractility, and 0% (0/57) subjects with normal esophageal manometry ( $P < 0.001$ ).

There is no significant difference in UESRI between subjects with RSI score  $> 13$  and  $\leq 13$  ( $1680.35 \pm 274.75$  vs.  $2391.81 \pm 429.88$  mmHg s cm; 95% CI, 1127.62–2233.07 vs. 1539.796–3243.82 mmHg s cm;  $P = 0.29$ ).

**The UES metrics in subjects with normal HRIM.** The mean UESII, indicating the bolus transit of UES, in subjects with normal esophageal manometry is  $14,095.36 \Omega$  s cm (95% CI, 11,889.32–16,301.41  $\Omega$  s cm). The mean UESRI, indicating the pressure change of UES during 5 mL liquid swallow, is  $1490.95$  mmHg s cm (95% CI, 1128.69–1853.21 mmHg s cm) in subjects with normal esophageal manometry.

**Relationship between RSI and UES metrics.** The UES bolus transit metric, UESII, was demonstrated to negatively correlate with the total RSI score in this study cohort ( $P = 0.005$ , Table 2). The UESII was further demonstrated to correlate negatively with 6 of the 9 RSI sub-score items (including hoarseness or a problem with your voice, clearing your throat, difficulty swallowing food/liquids/pills, breathing difficulties or choking episode, the sensation of something sticking in your throat or a lump in your throat, and heartburn/chest pain/indigestion/stomach acid coming up) in the study cohort ( $P < 0.05$ , Table 2). There is no significant statistical difference between UESRI and RSI total/sub-score items in this study (Table 2).

**Predictors of RSI score  $> 13$  in this study population.** The ROC analysis revealed that a UESII cutoff of  $2900 \Omega$  s cm had the best ability to differentiate subjects with RSI score  $> 13$  from others with RSI score  $\leq 13$  (AUC 64.8%,  $P = 0.002$ , Fig. 3A). The PPV, NPV and diagnostic accuracy for this cutoff (UESII  $< 2900 \Omega$  s cm) to predict RSI score  $> 13$  are 52.63%, 76.67%, and 70.89%, respectively.

There were 35.14% (26/74) of ineffective esophageal motility disorder patients, 66.67% (4/6) of achalasia patients, 28.57% (6/21) of absent contractility patients, and 3.51% (2/57) of normal manometry subjects with UESII  $< 2900 \Omega$  s cm ( $P < 0.001$ ).

In the univariate logistic regression analysis models, both female gender and UESII  $< 2900 \Omega$  s cm were significant predictors for the prediction of RSI score  $> 13$  in this study cohort (OR = 4.56 and 3.65;  $P < 0.001$  and = 0.001, respectively, Table 3).

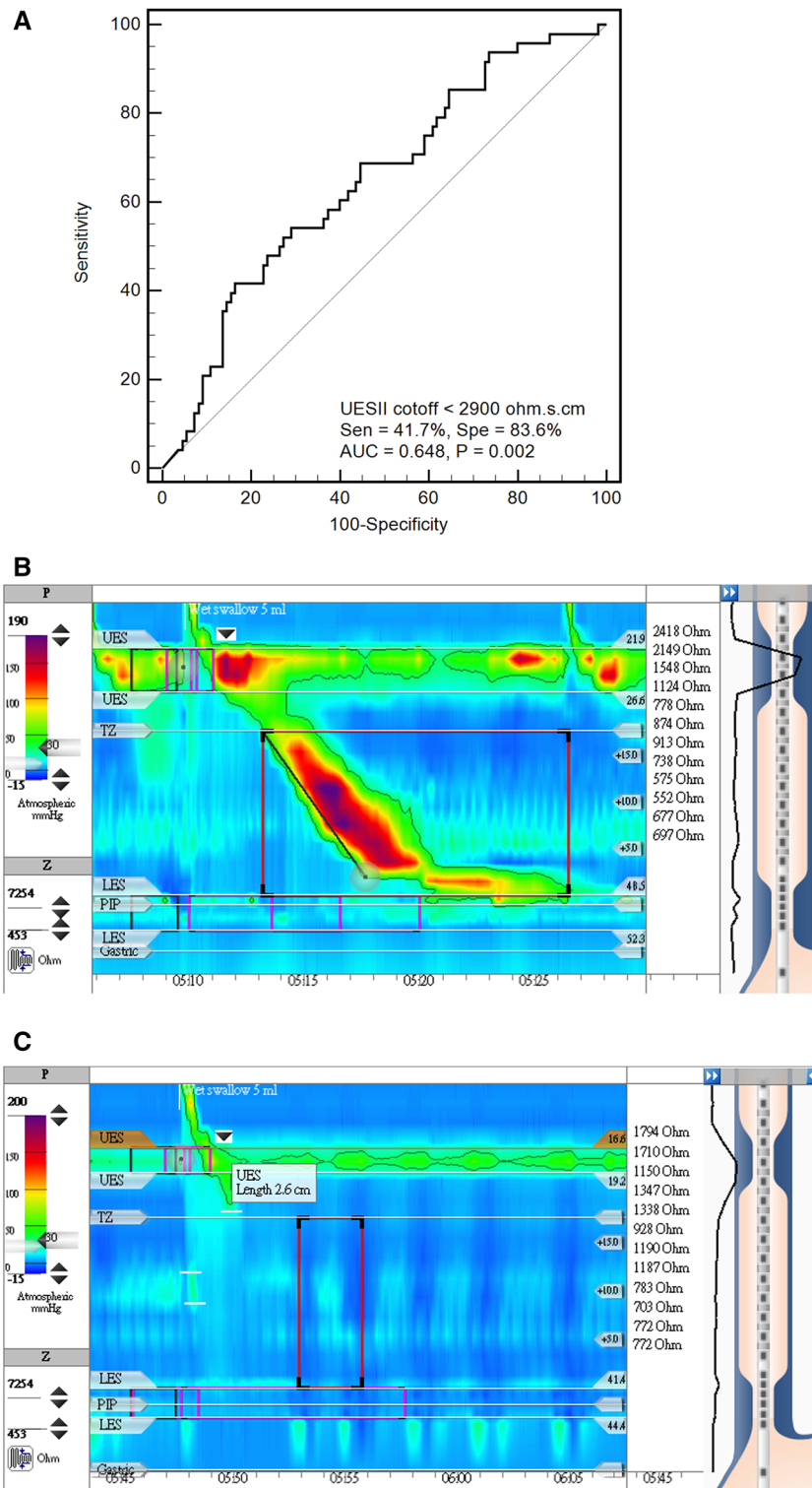
The UESII  $< 2900 \Omega$  s cm remained a significant predictor of RSI score  $> 13$  after the adjustment of gender in the multivariate logistic regression model (OR = 2.83; 95% CI = 1.27–6.30;  $P = 0.01$ ; Table 3).

Subjects with a high RSI score also had a lower impedance value above UES immediately after liquid swallow than others with a low RSI score (Fig. 3B,C). The evidence suggested that subjects with higher RSI scores may have the problem of UES bolus transit during liquid swallows, causing fluid retention above UES after the closure of UES.

## Discussion

The exact pathophysiology of LPRD remains unclear in large to date, and the proposed mechanism includes high gastroesophageal reflux, the impairment of the subjective and objective voice quality evaluations, and even psychological problems<sup>14–20</sup>. Belafsky et al. developed a nine-item questionnaire (RSI) for the assessment of symptoms in LPRD patients, and subjects with a total RSI score of more than 13 is considered diagnostic of LPRD<sup>3–5</sup>. There remains no gold standard for the diagnosis of LPRD to date<sup>6,7</sup>.

However, only a few LPRD patients were confirmed to have high gastroesophageal reflux assessed by multi-channel intraluminal esophageal impedance-pH monitoring previously<sup>5</sup>. Recent studies proposed the application of multichannel intraluminal esophageal impedance-pH monitoring, pepsin, and bile salt detection to assist the diagnosis of LPRD, but the diagnostic performance of these tools remains unclear<sup>5,18</sup>. All of these diagnostic



**Figure 3.** (A) The ROC analysis indicated that a upper esophageal sphincter impedance integral (UESII) cutoff of 2900  $\Omega$  s cm achieved the best differentiation between subjects with reflux symptom index (RSI) score > 13 and others with RSI score  $\leq$  13. (B) A subject with RSI score = 0 had the impedance value of 2418  $\Omega$  above upper esophageal sphincter immediate after 5 mL saline liquid swallow. (C) A subject with RSI score = 42 had the impedance value of 1794  $\Omega$  above upper esophageal sphincter immediate after 5 mL saline liquid swallow.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Female vs. Male (n = 88 vs. 70)	4.56	2.07–10.06	< 0.001	3.84	1.71–8.63	0.001
UESII < 2900 vs. $\geq$ 2900 $\Omega$ s cm (n = 38 vs. 120)	3.65	1.70–7.84	0.001	2.83	1.27–6.30	0.01

**Table 3.** Predictors of reflux symptom index (RSI) > 13 in this study cohort analyzed by univariate and multivariate logistic regression model.

modalities focus on high gastroesophageal reflux-related laryngopharyngeal reflux symptoms<sup>5,18</sup>. Other than RSI clinical symptom score, there is no validated diagnostic test to confirm LPRD to date<sup>5,18,19</sup>.

Current treatment options for LPRD include dietary measures, proton pump inhibitors, alginate, and magaldrate<sup>18</sup>. But the efficacy of anti-reflux and acid-suppression agents to relieve laryngopharyngeal reflux symptoms remains controversial<sup>18,21–23</sup>. The reported success rate of conventional therapy ranged from 17 to 87%, and the treatment outcomes varied substantially between studies<sup>20,21</sup>. Psychological problems are usually considered in LPRD patients with sub-optimal clinical responses to conventional therapeutic agents<sup>14,16</sup>. The low treatment success rate of conventional therapy is highly possible to associate with the diversity of LPRD, and the non-reflux mechanism of laryngopharyngeal reflux symptoms may play roles in part of these patients.

A recent study demonstrated abnormal findings on HRM identified in 43.3% of patients with LPR symptoms, but there remain 56.7% of subjects with LPR symptoms without obvious abnormal findings based on current HRIM interpretation criteria<sup>23</sup>. The data implying the important role of routine HRM study in patients with LPR symptoms to evaluate the possibility of an esophageal motility disorder<sup>23</sup>. However, there are no HRIM criteria established to assist the confirmation of laryngopharyngeal symptoms in subjects with normal manometry data graded by current guidelines<sup>6,7,13</sup>.

Since the majority of laryngopharyngeal symptoms scored by RSI questionnaire are located above UES<sup>3</sup>. We firstly demonstrated that the UES motility function may associate with the laryngopharyngeal reflux symptoms, and thus quantify the UES metrics (UES pressure change by UESRI, and UES bolus transit by UESII) in this study. Poor bolus transit of UES, indicating by lower UESII, is associated with a higher RSI total score and the majority of RSI sub-scores (66.7%) in our study.

Our data showed further subjects with a high RSI score had a lower impedance value above UES immediately after liquid swallow than others with a low RSI score. The evidence indicating subjects with high RSI scores have the problem of fluid retention above UES after the contraction of UES. These non-swallow foods or liquid above UES after swallow can induce laryngopharyngeal reflux symptoms such as hoarseness, clearing throat, difficulty in swallowing food/liquids/pills, choking episode, and lump sensation of the throat. Hence, gastroesophageal reflux maybe not be the sole etiology for laryngopharyngeal reflux symptoms. UES bolus transit failure may be responsible for part of the mechanism of laryngopharyngeal reflux symptoms. The therapeutic management to improve UES bolus transit may help to relieve laryngopharyngeal reflux symptoms, especially for those with inadequate response to conventional anti-reflux therapeutic agents.

There are possible limitations of our study. Our cohort is recruited between 2014 and 2020, and all HRIM data were analyzed according to version 3.0 of Chicago Classification at the time of HRIM study. We re-assessed our HRIM data according to version 4.0 of Chicago Classification, which is published in 2021, and only the number of the diagnosis of IEM has changed (from 74 in version 3.0 to 44 in version 4.0 of Chicago Classification) while the diagnosis of other esophageal motility disorders remains unchanged. There is no statistic difference between IEM subjects fulfill both version 3.0 and 4.0 Chicago Classification (n = 44) and IEM subjects only fulfill version 3.0 Chicago Classification (n = 30) in total RSI score ( $13.48 \pm 1.47$  vs.  $15.03 \pm 2.16$ ,  $P = 0.54$ ) and UESII value ( $8118.16 \pm 1354.73$  vs.  $9442.67 \pm 1784.51$   $\Omega$  s cm,  $P = 0.58$ ). Since our study only assessed the pressure and bolus change of UES, version of the Chicago Classification will not alter the results and conclusions of the current study. Our study demonstrated the bolus transit of UES (UESII) is associated with RSI score, but not the pressure changes of UES (UESRI) during 5 mL saline liquid swallow of the HRIM study. Further larger-scale studies, with larger statistical power, are still needed in the future to confirm this phenomenon. Different HRIM catheters may result in different measurements, and further studies applying other design HRIM catheters remain needed. Water-perfused manometry system used in the present study has been validated for the assessment of UES and esophageal bolus transit function in previous studies<sup>13,24–26</sup>. The side holes of the HRIM catheter were perfused with distilled water at a rate of 0.15 mL per min throughout the manometric study in our institute. Since distilled water perfused from the catheter is electrolyte-free, we believe it had a minimal impact of the impedance measurement on our subjects.

In conclusion, our findings suggest that the novel parameter UESII, which indicates the bolus transit of UES of liquid swallow, is correlated well with RSI symptom scores. This novel parameter may have a role in explaining the physiology and its clinical consequences in clinical symptoms of laryngopharyngeal reflux. It may also serve as an adjunct parameter of UES in HRIM study, and possibly help the clinicians to make stratified therapeutic decisions in the future.

### Data availability

Data maybe available after the approval of IRB of NTUH.

Received: 26 June 2021; Accepted: 1 October 2021

Published online: 14 October 2021

## References

- Carlson, D. A. *et al.* High-resolution impedance manometry parameters enhance the esophageal motility evaluation in non-obstructive dysphagia patients without a major Chicago Classification motility disorder. *Neurogastroenterol. Motil.* **29**, e12941 (2017).
- Singendonk, M. M. J. *et al.* Novel pressure-impedance parameters for evaluating esophageal function in pediatric achalasia. *J. Pediatr. Gastroenterol. Nutr.* **66**, 37–42 (2018).
- Belafsky, P. C., Postma, G. N. & Koufman, J. A. Validity and reliability of the reflux symptom index (RSI). *J. Voice* **16**, 274–277 (2002).
- Nacci, A. *et al.* Reflux Symptom Index (RSI) and Singing Voice Handicap Index (SVHI) in singing students: A pilot study. *J. Voice* **S0892–1997**(20), 30171–30175 (2020).
- Tseng, W. H. *et al.* Double-blind, placebo-controlled study with alginate suspension for laryngopharyngeal reflux disease. *Laryngoscope* **128**, 2252–2260 (2018).
- Kahrilas, P. J. *et al.* The Chicago Classification of esophageal motility disorders, v3.0. *Neurogastroenterol. Motil.* **27**, 160–174 (2015).
- Yadlapati, R. *et al.* Esophageal motility disorders on high-resolution manometry: Chicago classification version 4.0. *Neurogastroenterol. Motil.* **33**, e14058 (2021).
- Tutuian, R. & Castell, D. O. Clarification of the esophageal function defect in patients with manometric ineffective esophageal motility: Studies using combined impedance-manometry. *Clin. Gastroenterol. Hepatol.* **2**, 230–236 (2004).
- Tseng, R. *et al.* Normative values and factors affecting water-perfused esophageal high-resolution impedance manometry for a Chinese population. *Neurogastroenterol. Motil.* **30**, e13265 (2018).
- Blonski, W., Hila, A., Vela, M. F. & Castell, D. O. An analysis of distal esophageal impedance in individuals with and without esophageal motility abnormalities. *J. Clin. Gastroenterol.* **42**, 776–781 (2008).
- Carlson, D. A. *et al.* Improved assessment of bolus clearance in patients with achalasia using high-resolution impedance manometry. *Clin. Gastroenterol. Hepatol.* **16**, 672–680 (2018).
- Lin, Z. *et al.* Parameters for quantifying bolus retention with high-resolution impedance manometry. *Neurogastroenterol. Motil.* **26**, 929–936 (2014).
- Wu, J. F. *et al.* Pressure-impedance analysis: Assist the diagnosis and classification of ineffective esophageal motility disorder. *J. Gastroenterol. Hepatol.* **35**, 1317–1324 (2020).
- Hill, C. *et al.* Psychoemotional factors and their influence on the quality of life in patients with GERD. *Surg. Endosc.* <https://doi.org/10.1007/s00464-020-08145-8> (2020).
- Altıntaş, A., Soylu, A., Yegin, Y., Çelik, M. & Kaya, K. H. Impact of Laryngopharyngeal reflux on the levels of depression and anxiety in patients with obstructive sleep apnea syndrome. *J. Craniofac. Surg.* **28**(2), e121–e124 (2017).
- Joo, Y. H., Song, Y. S. & Pae, C. U. Relationship between depression and laryngopharyngeal reflux. *Psychiatry Investig.* **14**(2), 226–229 (2017).
- Lechien, J. R., Saussez, S., Harmegnies, B., Finck, C. & Burns, J. A. Laryngopharyngeal reflux and voice disorders: A multifactorial model of etiology and pathophysiology. *J. Voice* **31**, 733–752 (2017).
- Lechien, J. R. *et al.* Review of management of laryngopharyngeal reflux disease. *Eur. Ann. Otorhinolaryngol. Head Neck Dis.* **S1879–7296**(20), 30271–30274 (2020).
- Campagnolo, A. M., Priston, J., Thoen, R. H., Medeiros, T. & Assunção, A. R. Laryngopharyngeal reflux: Diagnosis, treatment, and latest research. *Int. Arch. Otorhinolaryngol.* **18**(2), 184–191 (2014).
- Lechien, J. R. *et al.* Changes of laryngeal and extralaryngeal symptoms and findings in laryngopharyngeal reflux patients. *Laryngoscope* **131**, 1332–1342 (2021).
- Lechien, J. R. *et al.* Evaluation and management of laryngopharyngeal reflux disease: State of the art review. *Otolaryngol. Head Neck Surg.* **160**(5), 762–782 (2019).
- Lechien, J. R. *et al.* The management of suspected or confirmed laryngopharyngeal reflux patients with recalcitrant symptoms: A contemporary review. *Clin. Otolaryngol.* **44**, 784–800 (2019).
- Sikavi, D. R., Cai, J. X., Carroll, T. L. & Chan, W. W. Prevalence and clinical significance of esophageal motility disorders in patients with laryngopharyngeal reflux symptoms. *J. Gastroenterol. Hepatol.* **36**(8), 2076–2082 (2021).
- Van Houtte, E., Van Lierde, K., D'haeseleer, E., Van Imschoot, B. & Claeys, S. UES pressure during phonation using high-resolution manometry and 24-h dual-probe pH-metry in patients with muscle tension dysphonia. *Dysphagia* **27**(2), 198–209 (2012).
- Hung, J. S. *et al.* Evaluation of baseline impedance during water-perfused high resolution impedance manometry in patients with symptomatic GERD. *J. Clin. Gastroenterol.* **53**(5), 350–354 (2019).
- Wu, J. F. *et al.* Distal contractile to impedance integral ratio assist the diagnosis of pediatric ineffective esophageal motility disorder. *Pediatr. Res.* **84**(6), 849–853 (2018).

## Acknowledgements

This work is supported by the Intelligent & Sustainable Medical Electronics Research Fund in National Taiwan University, and a grant from National Taiwan University Hospital (NTUH.108-P07). The author thanks Ms. Hui-Chuan Lee, from the Gastrointestinal Motility Center of National Taiwan University Children's Hospital, for the technical support for this study.

## Author contributions

J.F.W., the first author of the study, is responsible for the study design, data management and manuscript writing. W.C.H. and P.H.T. are responsible for long term patients follow, recruitment, and critical review of the manuscript. I.J.T., T.W.T., Y.C.L. and C.H.Y. are responsible for data analysis and critical review of the manuscript. P.H.T., the corresponding author, was responsible for patient recruitment, study design, critical review of the article, and is the principal investigator of this study.

## Funding

This work is supported by the Intelligent & Sustainable Medical Electronics Research Fund in National Taiwan University, and a grant from National Taiwan University Hospital (NTUH.108-P07).

## Competing interests

The authors declare no competing interests.



### Additional information

**Correspondence** and requests for materials should be addressed to P.-H.T.

**Reprints and permissions information** is available at [www.nature.com/reprints](http://www.nature.com/reprints).

**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2021