Correlation of Dry Eye Disease and Laryngopharyngeal Reflux Based on Improved Symptoms With Combined Therapy

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Summary: Objective. To investigate the correlation between dry eye disease (DED) and laryngopharyngeal reflux (LPR) from the perspective of treatment response.

Study Design. Cross-sectional studies.

Setting. Analysis of data from patients with DED-related symptoms and LPR-related symptoms from May 2022 to January 2023 at AIER Eye Hospital (Hainan).

Methods. The Ocular Surface Symptom Index (OSDI) scales and The Reflux Symptom Score (RSS) were investigated in patients attending China Aier Eye Hospital (Hainan) from May 2022 to January 2023, and OSDI scores >12 were categorized as DED, and RSS scores >13 were categorized as suspected laryngopharyngeal reflux (suspected LPR). Patients with DED and suspected LPR were randomly divided into three groups (group A: 0.3% sodium vitreous acid drops and 1% cyclosporine A drops only; group B: 0.3% sodium vitreous acid drops, 1% cyclosporine A drops, and Gastroftal tablets containing magnesium alginate and cimicifuga oil and esomeprazole; and group C: Gastroftal tablets and esomeprazole only orally) and were reviewed after 3 months for the RSS- and DED-related examinations.

Result. Two hundred and nineteen patients were enrolled. One hundred and ninety-one DED-positive and 28 DED-negative patients, 84 suspected LPR-positive and 135 LPR-negative patients, and the OSDI scores of LPR patients were significantly higher than those of LPR-negative patients ($P < 0.001$). Parameters related to DED and LPR were significantly lower in patients in group B than in groups A and C after treatment ($P < 0.001$).

Conclusions. LPR and DED are closely related. For patients with both LPR and DED, treating LPR and DED at the same time may be a better option.

Key Words: Laryngopharyngeal reflux–Dry eye diseases–Therapeutic–Correlation–Validation.

INTRODUCTION

Dry eye disease (DED) is defined as a multifactorial disease affecting both the ocular surface and the tear film leading to tear film instability and damage to the ocular surface, which results in symptoms of discomfort, irritation, visual disturbances, and photophobia.[1] Laryngopharyngeal reflux (LPR) is an inflammatory condition of the upper aerodigestive tract tissues related to the direct and indirect effect of gastric or duodenal content reflux, which induces morphological changes in the upper aerodigestive tract.[2] In a study conducted by Mazzacane et al, it was observed that a significant proportion (34%) of individuals diagnosed with ocular surface inflammation exhibited the presence of LPR.[3] In their study, Bonini et al conducted an investigation utilizing the Reflux Symptom Index (RSI) scale, Symptom Assessment in Dry Eye (SANDE) scale, and Ocular Surface Symptom Index (OSDI) scale. The results demonstrated that patients diagnosed with laryngopharyngeal reflux disease (LPRD) exhibited significantly higher scores in the SANDE (both frequency and severity) and OSDI scales compared to individuals without LPRD.[4] Furthermore, Iannella et al documented the presence of pepsin in the tear fluid of 20% of youngsters, indicating a potential link between gastric reflux events and ocular surface damage.[5] The Reflux Symptom Score (RSS) scale was recently created and validated by Lechien et al.[6] Moreover, recent research has demonstrated that the RSS scale possesses the potential to serve as a more efficient and streamlined method for the detection of LPRD.[7] The aforementioned literature serves as a foundation for conducting a comprehensive examination of the correlation between LPR and DED. There is a lack of comparative research investigating the prevalence of DED in people who have both DED and LPR, both before and after undergoing LPR treatment. Consequently, we employed various assessment tools, such as the RSS scale, OSDI scale, Schirmer I test, conjunctival fluorescein staining (CFS), tear film break-up time (BUT), and Gastroftal treatment, to investigate the association between DED and LPR in terms of treatment response. Our objective was to propose a novel therapeutic strategy for individuals suffering from LPR-related DED.

MATERIALS AND METHODS

Study participants

This research study recruited 191 patients diagnosed with DED and 28 DED-negative patients between May 2022

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Table 1.
Comparison of LPR-Positive and LPR-Negative Patients in DED-Related Parameters

	LPR+ (84)	LPR- (135)	Z/X2	*P*
Height (cm)	163.56 ± 9.11	164.93 ± 8.28	−0.903	0.367
Weight (kg)	59.82 ± 12.49	60.65 ± 14.57	−0.101	0.92
BMI	22.2 ± 3.23	22.25 ± 4.97	−0.677	0.499
Age	49.5 ± 15.53	43.46 ± 14.82	−2.864	0.004
Sex (male/female)	50/34	84/51	0.159	0.69
Smoking	28/56	21/114	9.423	0.002
Alcohol consumption	31/53	30/105	5.555	0.018
Carbonated beverages	36/48	73/62	2.606	0.106
Caffeine or tea	50/34	75/60	0.039	0.067
OSDI scores	40.81 ± 19.43	29.25 ± 16.92	−4.258	0.001
BUT test	7.52 ± 4.64	8.55 ± 5.41	−1.374	0.169
Schirmer test (mm/5 min)	6.74 ± 17.37	6.6 ± 2.72	−5.041	0.001
Corneal fluorescein staining scores	3.4 ± 1.82	1.19 ± 1.86	−8.807	0.001
RSS scores	95.65 ± 78.18	2.05 ± 3.4	0.001	0.001
QoL scores	24.27 ± 19.28	1.36 ± 2.98	−11.909	0.001

Abbreviations: BMI, body mass index; QoL, quality of life.

and January 2023 at AIER Eye Hospital (Hainan), China. Suspected LPR-positive patients were 84 (50 males, 34 females; 19–81 years, mean age 49.98 ± 15.77 years) and LPR-negative 135 patients (84 males, 51 females; 21–81 years, mean age 46.37 ± 15.51 years) (Table 1). Inclusion criteria: (1) patients ≥18 years of age, male or non-pregnant female; (2) patients with symptoms related to DED. The exclusion criteria were (1) glaucoma diagnosis; (2) bacteria, viral, or fungal eye infection; (3) allergic conjunctivitis; (4) cancer; (5) ocular or nasal surgery in the 3 months before the trial; (6) prolonged use of sedative, anti-allergy, and cough suppressant medications; (7) current pregnancy or breastfeeding; (8) proton pump inhibitors or gastrointestinal motility drugs within 1 week. The detailed process of the research is shown in Figure 1. All patients gave their informed consent.

Clinical features evaluation

Examinations for DED

All patients had their right eyes examined in the following order: tear film BUT, CFS, and Schirmer I test.

OSDI

The OSDI is a 12-item questionnaire designed to investigate eye symptoms. In addition, its reliability and validity have been verified through validation studies.[8,9] The OSDI scoring was performed according to a four-point scale: normal (≤12), mild (13−22), moderate (23−32), and severe (≥33).

BUT

One drop of 0.25% chloramphenicol eye drop soaked with fluorescein test strip was placed in the inferior fornix and observed under cobalt blue light (×16) of a slit lamp within 30 seconds. The time between the opening of the eye after the last instant of vision and the appearance of the first dry spot on the tear film was recorded and averaged over three consecutive measurements. BUT < 10 seconds was considered abnormal.

CFS

Staining method same as BUT examination, corneal staining was observed under cobalt blue light of slit lamp.[10] The cornea was divided into 4 quadrants, with no staining scored as 0, less than 5 spots of staining scored as 1, the presence of massive staining or filaments scored as 3, and staining between scores of 1 and 3 scored as 2. The 4 quadrant scores were summed and scored on a scale of 0 to 12. A score of ≥3 is positive corneal fluorescein staining (+) and < 3 is negative corneal fluorescein staining (-).

Schirmer I test

Using a standard Schirmer I test strip placed at the junction of the inner and outer 1/3 of the conjunctival sac of the lower lid the subjects were instructed to gently close their eyes and the length of tear maceration was read after 5 minutes. Schirmer I test < 10 mm/5 minutes was considered abnormal.

RSS

Patients diagnosed with DED who also have symptoms related to LPR are screened based on the RSS developed and validated by Lechien et al.[6] For patients with visual disabilities, RSS evaluations are performed with the help of dictation from a professionally trained physician. The RSS includes 22 items (Table 1), and patients were assessed based on symptom severity (0 = not severe, 5 = very troublesome when it occurs) and frequency (0 = no occurrence, 1, 2, 3, and

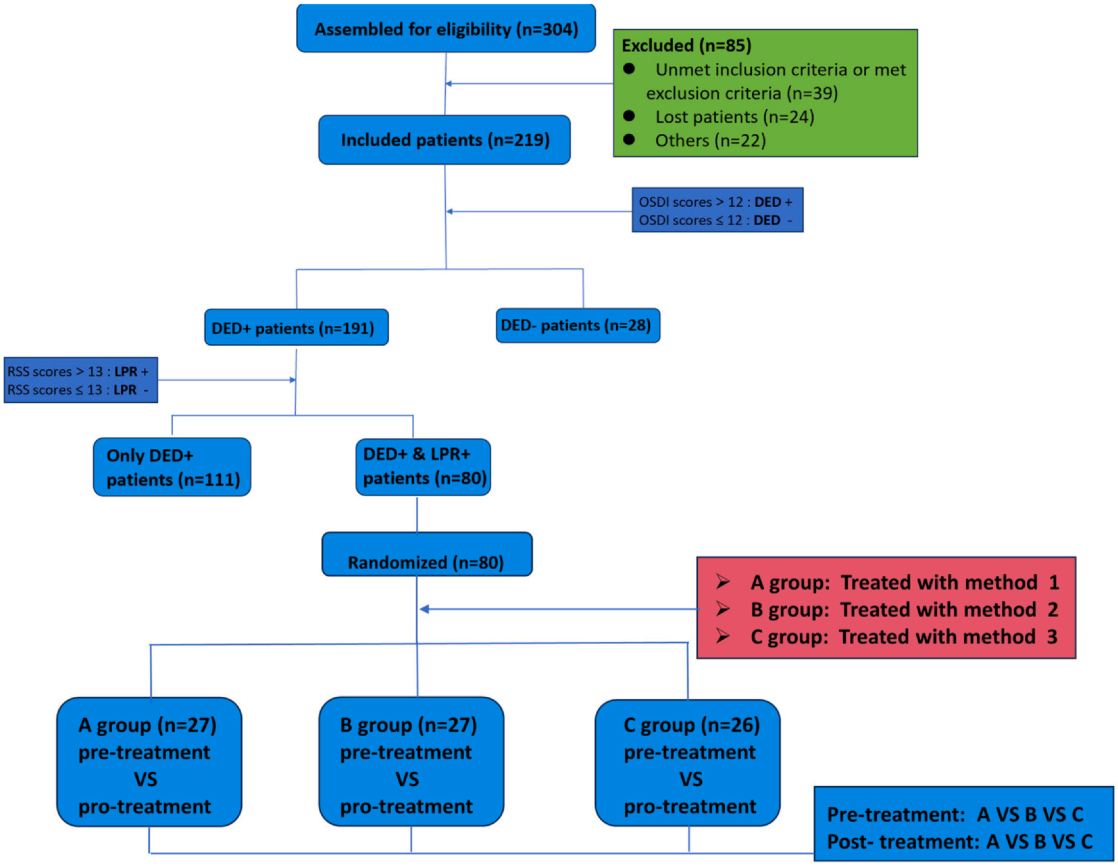

FIGURE 1. Schematic diagram of this study. DED+, patients with dry eye positive. DED-, patients with dry eye negative dry eye. LPR+, patients with laryngopharyngeal reflux positive. LPR-, patients with laryngopharyngeal reflux negative. DED and LPR, patients with both dry eye and laryngopharyngeal reflux. Method 1, patients treated with 0.3% sodium vitrate eye drops and 1% cyclosporine A drops. Method 2, patients treated with combination therapy (0.3% sodium vitrate drops and 1% cyclosporine A drops) and oral therapy (Gastroftal tablets containing magnesium alginate and simethicone, and esomeprazole). Method 3, patients treated with Gastroftal tablets and esomeprazole.

4 = occurred 1–2, 2–3, 3–4, 4–5 weekly over the past month respectively, 5 = occurs daily). Finally, the severity score is multiplied by the frequency score to obtain a symptom score ranging from 0 to 25, the sum of these symptom scores is calculated to obtain the RSS total score (ranging from 0 to 550), and a patient was considered to have suspected LPR when the RSS > 13. The quality of life (QoL) score of each item was added to obtain the QoL total score.

Treatment

Treatment of both dry eye and suspected LPR was performed in accordance with relevant guidelines and literature.[11,12] All patients are advised to reduce consumption of high-sugar, hard-to-digest foods while taking the medication and to avoid eating before bedtime. They should also pay attention to eye hygiene, reduce the use of electronic devices and use their eyes wisely. Selected patients were screened and if met inclusion and exclusion criteria were recruited and randomly (1:1) treated with 0. 3% sodium vitrate eye drops and 1% cyclosporine A drops (group A) or combination therapy (0.3% sodium vitrate drops and 1% cyclosporine A drops) and oral therapy (Gastroftal tablets containing magnesium alginate and simethicone and esomeprazole) (group B) or use of Gastroftal tablets and esomeprazole (group C). Patients in group A were treated with 1 drop of 0. 3% sodium vitrate eye drops, followed by 1 drop of 1% cyclosporine A eye drops 10 minutes later, 4 times/day; patients in group B were treated with 1 drop of 0.3% sodium vitrate eye drops, followed by 1 drop of 1% cyclosporine A eye drops 10 minutes later, 4 times/day and 2 Gastroftal tablets after lunch and dinner, Esomeprazole Magnesium Enteric-coated Tablets taken orally once daily 30 minutes before breakfast; patients in group C were treated with 2 Gastroftal tablets to be taken after lunch and dinner, Esomeprazole Magnesium Enteric-coated Tablets taken orally once daily 30 minutes before breakfast. Three months later the patient came to our outpatient clinic for a follow-up and the same examination as previously described. The primary outcome was the evaluation of OSDI change between groups. The secondary outcomes were the evaluation of change for RSS, CFS, and BUT scores.

Table 2.
Comparison of Patients With Different Severity of DED in DED-Related Screening Parameters and Each RSS Parameter

	DED-	DED Mild	DED Moderate	DED Heavy	H/X2	*P*
OSDI scores	8.36 ± 2.94	18.35 ± 2.48	27.43 ± 2.92	50.07 ± 16.14	191.561	0.001
T-BUT scores	13.7 ± 6.49	8.82 ± 5.57	7.81 ± 4.32	6.49 ± 3.81	31.149	0.001
Corneal fluorescein staining scores	3 ± 2.98	1.39 ± 1.83	1.18 ± 1.7	1.7 ± 1.96	12.643	0.005
Schirmer scores	10.96 ± 3.68	7 ± 1	5.94 ± 2.47	4.33 ± 2.03	78.787	0.001
Hoarseness or a voice problem	0 ± 0	0.7 ± 1.84	1.46 ± 3.78	3.17 ± 5.2	27.445	0.001
Throat pain	0 ± 0	0.61 ± 1.7	0.83 ± 2.12	2.95 ± 4.28	32.558	0.001
Pain during swallowing time	0 ± 0	0.35 ± 0.78	1.1 ± 3.8	1.72 ± 3.63	24.632	0.001
Difficulty swallowing (pills, liquids, or solid foods)	0 ± 0	0 ± 0	0.38 ± 1.77	0.76 ± 1.9	18.655	0.001
Clearing your throat	1.29 ± 3.21	0.7 ± 1.72	1.17 ± 2.85	4.29 ± 6.79	16.092	0.001
Sensation of something sticking in the throat	1.43 ± 3.17	0.65 ± 1.5	1.99 ± 4.33	3.92 ± 5.97	11.114	0.011
Excess mucous in the throat or postnasal drip sensation	0.14 ± 0.36	1.13 ± 3.36	1.56 ± 4.48	3.23 ± 5.43	13.265	0.004
Ear pressure/pain (daytime or nigh-time)	0 ± 0	0 ± 0	0.51 ± 2.57	1.39 ± 3.53	25.449	0.001
Tongue burning	0 ± 0	0.09 ± 0.42	0.31 ± 1.12	1.33 ± 3.19	16.035	0.001
Other symptoms	0 ± 0	0.35 ± 1.67	0.1 ± 0.53	0.1 ± 0.83	1.250	0.741
Ear nose and throat disorders	2.86 ± 6.33	4.57 ± 9.54	9.39 ± 20.63	22.85 ± 33.51	16.930	0.001
Heartburn, stomach acid coming up	0 ± 0	0.78 ± 2.75	0.89 ± 2.8	4.69 ± 6.88	35.045	0.001
Regurgitations of liquids, solid foods, or burps	0 ± 0	1 ± 2.04	1.15 ± 3.07	5.01 ± 6.67	33.423	0.001
Abdominal pain	0 ± 0	1.17 ± 3.47	0.74 ± 2.5	2.05 ± 3.83	30.135	0.001
Diarrheas	0 ± 0	1.26 ± 3.7	1.25 ± 3.39	3.06 ± 5.51	23.844	0.001
Constipation	0 ± 0	2 ± 5.63	0.35 ± 1.06	1 ± 3.14	8.909	0.031
Indigestion	0 ± 0	1.35 ± 3.1	1.07 ± 2.83	4.97 ± 7.2	36.228	0.001
Abdominal distension and/or flatus	0 ± 0	0.96 ± 2.67	1.85 ± 4.33	5.23 ± 7.18	34.257	0.001
Halitosis	0 ± 0	1.48 ± 5.22	1.11 ± 3.17	3.98 ± 6.61	24.518	0.001
Nausea	0 ± 0	2.04 ± 4.23	0.99 ± 3.22	3.42 ± 5.82	18.119	0.001
Other symptoms	0 ± 0	0 ± 0	0.08 ± 0.71	0.29 ± 2.57	1.065	0.785
Abdominal disorders	0 ± 0	12.04 ± 17.85	9.47 ± 20.62	33.7 ± 43.79	37.154	0.001
Cough after eating or lying down	0 ± 0	0.7 ± 2.2	0.86 ± 2.37	3.32 ± 5.3	30.372	0.001
Cough daytime	0 ± 0	0.78 ± 2.11	0.76 ± 2.27	3.56 ± 5.65	29.012	0.001
Breathing difficulties, breathlessness, or wheezing	0 ± 0	0.13 ± 0.46	0.42 ± 1.89	1.24 ± 2.57	20.054	0.001
Chest pain	0 ± 0	0 ± 0	0.35 ± 1.33	0.55 ± 1.38	12.674	0.001
Other symptoms	0 ± 0	0 ± 0	0.06 ± 0.47	0.18 ± 1.29	1.919	0.589
Chest/respiratory disorders	0 ± 0	1.61 ± 4.61	2.44 ± 6.77	8.85 ± 13.49	30.042	0.001
QoL scores	0.43 ± 1.07	6.04 ± 9.76	6.01 ± 10.51	17.06 ± 20.63	31.055	0.001
RSS scores	2.86 ± 6.33	18.22 ± 26.85	21.31 ± 42.91	65.41 ± 84.55	25.142	0.001
Prevelance	28.00	23.00	72.00	96.00		
Prevelance of LPR	0.14	0.35	0.31	0.52	15.556	0.001

Abbreviations: T-BUT, tear break-up time.

Statistical analysis

Statistical Package for the Social Sciences for Windows (SPSS version 23.0; IBM, Armonk, NY) was used for the statistical analysis. Normally distributed data are shown as mean ± standard deviation. The chi-square test was used to compare the differences between groups. Parametric data differences were compared using a *t* test. The Mann-Whitney *U* test was used to compare differences between two groups of nonparametric data. The Kruskal-Wallis test is used to compare differences between multiple sets of nonparametric data. Symptom assessment parameters before and after treatment in the same group of patients were analyzed, and the results were expressed with the *P* value. A level of significance of $P < 0.05$ was used.

RESULT

Patients information

The study sample consisted of 219 individuals, comprising 134 males and 85 females. The participants had a mean age of 45.78 ± 15.35 years and a BMI of 22.23 ± 4.38 kg/m^2. There were a total of 84 patients who tested suspected positive for LPR, while 135 patients tested negative for LPR. There were a total of 191 individuals who tested

positive for DED, while 28 patients tested negative for DED. Among the DED-negative patients, 23 had mild DED, 72 had moderate DED, and 96 had severe DED. The prevalence of smoking history ($P < 0.01$) and alcohol use ($P < 0.05$) was found to be substantially greater among suspected LPR-positive patients compared to LPR-negative patients. However, no statistically significant differences were observed in the remaining general information, as indicated in Table 1.

Comparison of suspected LPR-positive and LPR-negative patients in DED-related parameters

The OSDI scores ($P < 0.001$), BUT test scores ($P < 0.001$), Schirmer test scores ($P < 0.001$), CFS scores ($P < 0.001$), RSS scores ($P < 0.001$), and QoL scores ($P < 0.001$) exhibited a statistically significant increase in suspected LPR patients compared to LPR-negative patients, as indicated in Table 1.

Comparison of patients with different severity of DED in DED-related screening parameters and each RSS parameter

Significant differences were observed in OSDI scores, CFS scores, RSS scores (excluding other symptoms in ear nose and throat (ENT) disorders, abdominal disorders, and chest/respiratory disorders), and QoL scores among the DED mild group, DED moderate group, DED heavy group, and DED-negative patients. The prevalence of LPR was found to be considerably greater in the groups with mild, moderate, and heavy DED compared to the patients without DED, as indicated in Table 2.

Correlation between DED-related inspection parameters and RSS items

A notable association was seen between the scores obtained from the RSS and the OSDI, CFS, and Schirmer test results ($P < 0.01$). A notable association was observed between the scores of chest/respiratory disorders and OSDI, with statistical significance ($P < 0.05$). Additionally, a substantial correlation was found between the scores of chest/respiratory disorders and the Schirmer test ($P < 0.01$). There was a strong correlation seen between scores of abdominal disorders and OSDI scores, as well as CFS and the Schirmer test ($P < 0.01$). There was a strong correlation seen between scores on the OSDI and the Schirmer test with scores on the OSDI and the Schirmer test ($P < 0.01$). The QoL scores exhibited a strong correlation with the OSDI scores, as indicated by a P value of less than 0.05. Additionally, CFS and the Schirmer test demonstrated a substantial correlation with the QoL scores, with a P value of less than 0.01 (Figure 2).

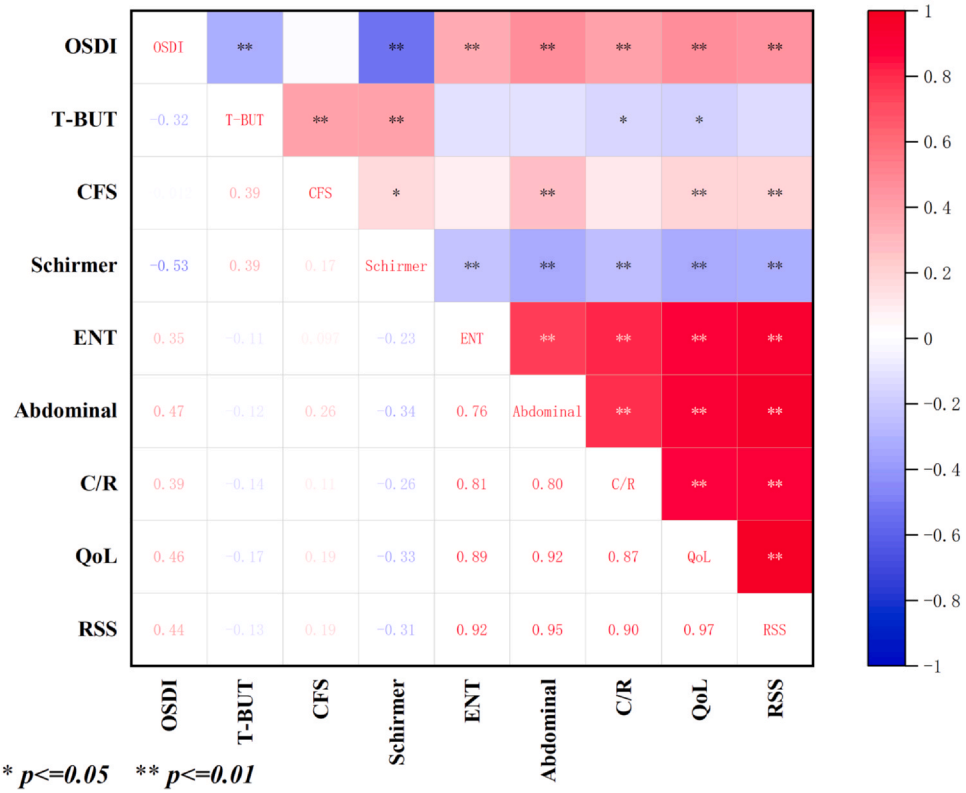

FIGURE 2. Correlation between DED-related inspection parameters and RSS items. C/R, chest/respiratory disorders scores on patient-completed RSS forms; ENT, ear nose and throat disorders scores on patient-completed RSS forms; Abdominal distension and/or flatus, abdominal distension and/or flatus scores on patient-completed RSS forms.

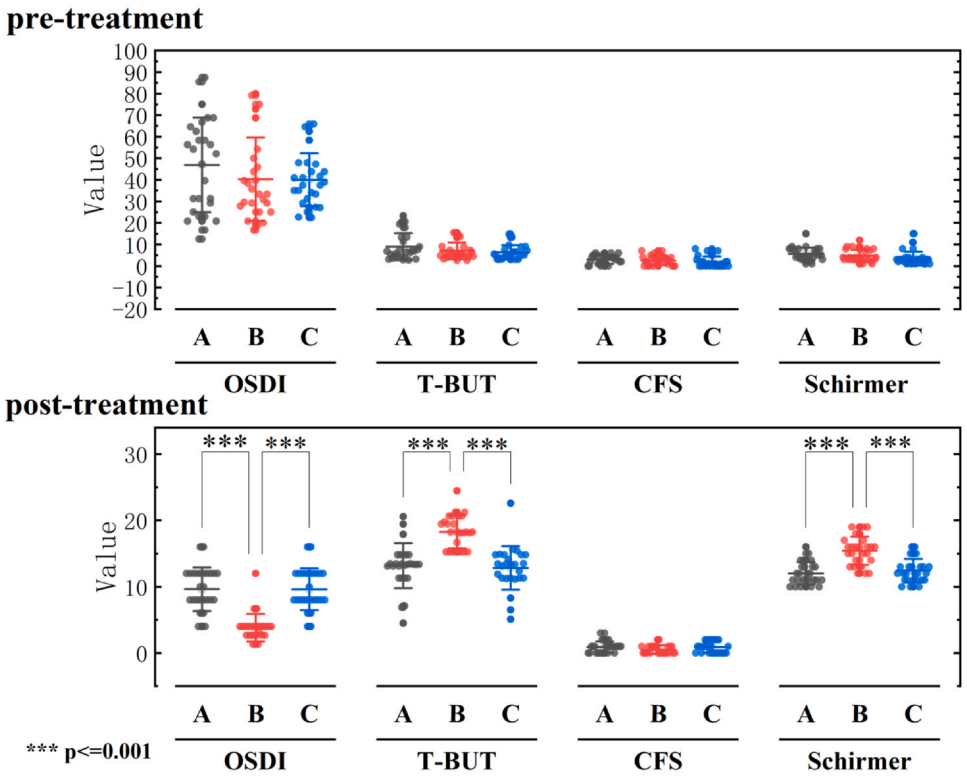

FIGURE 3. Comparison of between-group parameters in the three groups of DED and LPR patients before and after treatment. DED and LPR patients, patients with both dry eye and laryngopharyngeal reflux. A, patients in group A were treated with 1 drop of 0.3% sodium vitrate eye drops, followed by 1 drop of 1% cyclosporine A eye drops 10 minutes later, 4 times/day. B, patients in group B were treated with 1 drop of 0.3% sodium vitrate eye drops, followed by 1 drop of 1% cyclosporine A eye drops 10 minutes later, 4 times/day and 2 Gastroftal tablets after lunch and dinner. C, patients in group C were treated with 2 Gastroftal tablets to be taken after lunch and dinner.

Comparison of between-group parameters in the three groups of DED and LPR patients before and after treatment

Before therapy, there were no statistically significant disparities observed in the OSDI, CFS, and Schirmer's parameters across patients in groups A, B, and C ($P > 0.05$). Following the intervention, the OSDI scores exhibited a statistically significant decrease in group B compared to groups A and C ($P < 0.001$). Additionally, both BUT and Schirmer test results showed a statistically significant increase in group B compared to groups A and C ($P < 0.001$) (Figure 3).

Comparison of within-group parameters between the three groups of DED and LPR patients before and after treatment

The patients in group A exhibited significantly lower scores on the OSDI scale, with a statistical significance of $P < 0.01$. Additionally, the scores on the CFS scale were significantly lower in group A patients before therapy compared to after treatment, with a statistical significance of $P < 0.001$. The pretreatment Schirmer scores of group A patients were significantly lower compared to their post-treatment scores ($P < 0.001$). The OSDI scores and CFS exhibited a statistically significant increase in patients belonging to group B before therapy compared to after treatment ($P < 0.001$). Conversely, the BUT and Schirmer measurements showed a statistically significant decrease in group B patients before treatment in comparison to after treatment ($P < 0.001$). The OSDI scores exhibited a statistically significant increase in patients belonging to group C before therapy compared to after treatment ($P < 0.001$). Additionally, both BUT and Schirmer measurements demonstrated a statistically significant decrease in group C patients before treatment compared to after treatment ($P < 0.001$) (Figure 4).

DISCUSSION

DED is a complex and debilitating inflammatory condition of the ocular surface. Common symptoms of DED include ocular dryness, foreign body sensation, burning sensation, eye itching, pain, redness, visual fatigue, blurred vision, and fluctuating visual acuity.[13,14] Epidemiological studies conducted globally have reported the estimated prevalence of DED to be roughly 8.1%.[15] The range of individuals affected by DED varies from approximately 400 million to 3.7 billion,[16] signifying a substantial societal burden. The precise processes and therapeutic impacts of dry eye remain uncertain. In contrast, Iannella et al and Plateroti et al have

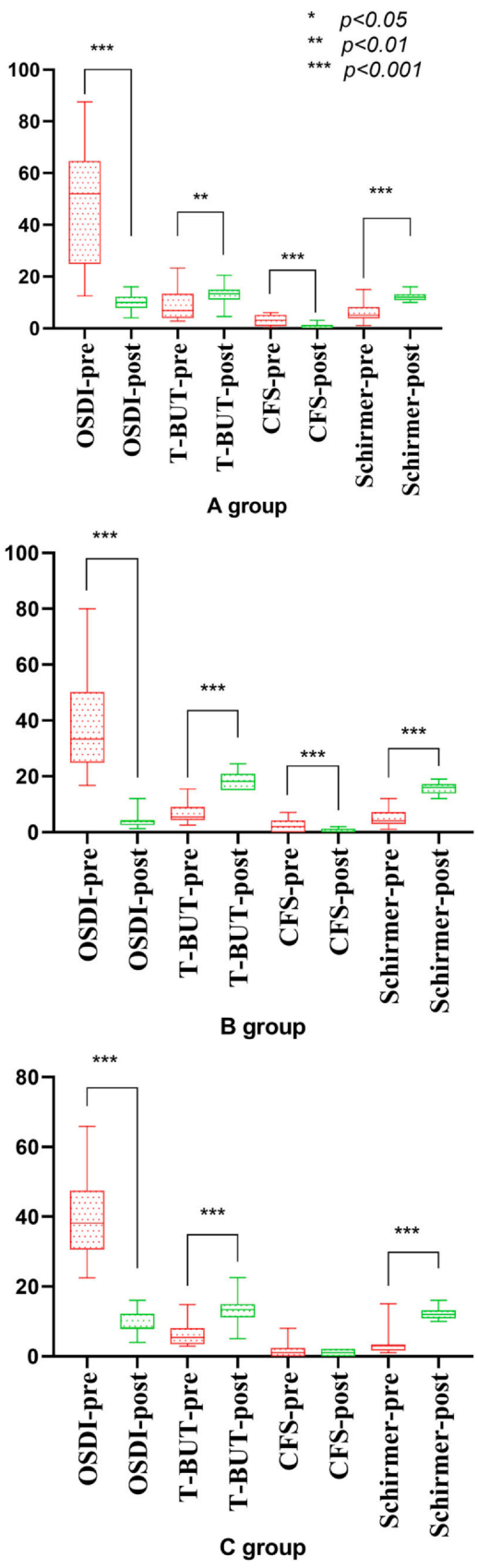

FIGURE 4. Comparison of within-group parameters between the three groups of DED and LPR patients before and after treatment. DED and LPR patients, patients with both dry eye and laryngopharyngeal reflux. OSDI-pre, OSDI scores for pretreatment assessment of patients. OSDI-post, OSDI scores for post-treatment assessment of patients. T-BUT-pre, T-BUT scores for pretreatment assessment of patients. T-BUT-post, T-BUT scores for post-treatment assessment of patients. CFS-pre, CFS scores for pretreatment assessment of patients. CFS-post, CFS scores for post-treatment assessment of patients. Schirmer-pre, Schirmer test for pretreatment assessment of patients. Schirmer-post, Schirmer test for post-treatment assessment of patients. T-BUT, tear break-up time.

shown the presence of salivary pepsin in the tear fluid of individuals diagnosed with LPR.[5,17] This empirical observation provides substantiated support for the potential association between LPR and ocular surface illness. The collective body of research indicates that there is a correlation between LPR and the occurrence, development, or worsening of dry eye symptoms. In a recent study conducted by Zhang et al, it was determined that the RSS scale, which was originally developed and validated by Lechien et al, had superior diagnostic capabilities for LPR compared to the RSI scale.[7] At now, there is a lack of comparative analyses pertaining to screening measures for DED before and after therapy within the same group of patients. Additionally, there is a dearth of research investigating the association between LPR and DED utilizing the recently developed RSS scale. Hence, we employed the RSS scale, OSDI scale, tear break-up time (T-BUT), CFS, and Schirmer test to administer three distinct treatments to individuals presenting with both DED and LPR. These patients were systematically grouped in a controlled manner to examine the association between DED and LPR, as well as to furnish empirical evidence and novel insights for managing patients afflicted with DED accompanied by LPR symptoms.

A study by Bonini et al showed that patients screened as LPR-positive had significantly higher OSDI values compared to those who tested negative for LPR. These findings align with our study results, which demonstrated a statistically significant elevation in OSDI scores among individuals who tested positive for RSS compared to those who tested negative for RSS. This observation implies that episodes of LPR could potentially have a role in the manifestation of dry eye symptoms. This could be attributed to the transportation of gastric contents and pepsin through the nasopharynx, nasolacrimal duct, and eventually reaching the tear film.[18] While the functionality of pepsinogen in conditions with low acidity has been confirmed, Samuels and Johnston have documented that pepsin induces inflammation in epithelial tissues even in non-acidic environments.[19] The conventional perspective

posits that the protein digestion function of pepsin on ocular surface mucosal cells has the potential to harm the ocular surface. However, a recent study by Plateroti et al has indicated that pepsin might disrupt various molecular chaperones that play a role in maintaining ocular surface homeostasis. Furthermore, it has been suggested that pepsin can act as a disruptive factor even under high pH conditions.[20] Furthermore, Galli et al observed a notable increase in the concentrations of total pepsin and bile acids in saliva specimens obtained from both individuals diagnosed with laryngeal cancer and healthy participants. This observation was made through a comparative analysis of pH levels, bile acid concentrations, total pepsin levels, and pepsin activity in saliva samples collected from patients with laryngeal cancer.[21] This observation implies that it is important to acknowledge the detrimental impact of bile acids on mucosal cells. While there is a lack of research investigating the specific impact of gastric contents on ocular surface mucosal cells across various pH environments, it is plausible to hypothesize that pepsin could potentially harm ocular surface mucosal cells in high pH environments. This could potentially serve as a catalyst for the onset of ocular surface inflammation. The inflammation of the mucosa on the ocular surface leads to a reduction in pH in the vicinity of the inflammation. This decrease in pH is accompanied by an increase in LPR events. Consequently, the pepsin atoms that reflux into the ocular surface following inflammation become more prone to activation in the acidic environment of the ocular surface. This cyclic process exacerbates the inflammation of the ocular surface. In contrast, Perez et al also documented that a majority of patients diagnosed with DED had intermittent episodes of vertigo.[22] Vomiting and gastroesophageal reflux with a high (gastrointestinal) reflux are prevalent symptoms observed in individuals with vertigo. The potential interdependence between these two conditions implies a potentially robust correlation between LPR and DED.

Certain academics propose that DED is sustained by a relentless cycle involving ocular surface inflammation, instability of the tear film, and hyperosmolarity.[22] The ocular surface epithelium and tear film of a normal eye consist of various immune cells, such as dendritic cells, macrophages, mast cells, lymphocytes, as well as fibroblasts, cytokines, and other immunological mediators. These components collectively contribute to the defense against pathogens and other potential environmental hazards. The development of DED can occur when there is a disruption in the homeostasis caused by aqueous tear shortage, hyperosmolarity of the tear film, and inflammation of the ocular surface microenvironment.[23] Additional aspects that could potentially contribute to DED encompass the immunological response and the neurogenic hypothesis.[24–27] The findings of our study revealed three distinct patient groups who underwent different treatment regimens, and their OSDI scores were assessed. The findings indicate that all three interventions demonstrate efficacy in alleviating ocular surface symptoms among individuals diagnosed with both LPR and DED. This phenomenon could perhaps be attributed to the regulatory role of hyaluronic acid (HA) in modulating the inflammatory response, cellular proliferation, and extracellular matrix remodeling.[28] Cyclosporin A (CsA) is an immunosuppressive agent that potentially functions by impeding the process of programmed cell death in conjunctival cup cells and lacrimal vesicle cells through the regulation of mucin synthesis and secretion.[29] Furthermore, Bian et al discovered that the presence of CsA on the ocular surface predominantly suppressed the activity of calmodulin phosphatase and impeded the functioning of the P38 mitogen-activated protein kinase and c-Jun N-terminal kinase pathways.[30] Furthermore, Daull et al found that CsA formulations showed efficacy in the modulation of toll-like receptors 1 (TLR1), reactive oxygen species (ROS), and interleukin 6 (IL6) pathways, as well as in the reduction of corneal epithelial lesions.[31] According to a recent study, the administration of CsA has shown efficacy in reducing corneal fluorescence staining scores and increasing tear volume in mice with DED. This effect was achieved through the inhibition of the HMGB1/TLR4/NF-κB-related pathway. The aforementioned research provides various degrees of support for the efficacy of CSA in treating DED.[32] However, in the case of individuals suffering from LPR, the effectiveness of dietary and lifestyle modifications, acid-suppressing medications, and alginate therapy has been well shown and is regarded as the preferred therapeutic option.[2,33,34] Nevertheless, a recent investigation conducted by Li et al involved the implementation of 24-hour multichannel intraluminal impedance-pH monitoring in a cohort of 344 patients. The study findings revealed that a substantial majority (74.1%) of LPR incidents observed in individuals with LPR were classified as non-acidic reflux. Alginate medications are of specific relevance in those with non-acidic or mixed reflux, as well as those experiencing postacid reflux.[35,36] Both the administration of proton pump inhibitors (PPIs) alone or in combination with HA and cyclosporine, as well as the use of HA and cyclosporine alone, result in notable improvements in the symptoms and examination parameters of patients with DED.

Our study also demonstrated that among patients diagnosed with DED who also presented with LPR, there was no statistically significant disparity in pretreatment RSS scores across the three groups. Following treatment, the combined administration of alginate and acid suppressants resulted in considerably lower RSS scores and OSDI scores compared to the other two treatment groups. This outcome implies that a treatment plan involving both alginate and acid suppression medications is the most optimal approach for relieving symptoms in DED patients who also experience pharyngeal reflux. These results align with the conclusions made by Balestrazzi. Simultaneously, our findings partially corroborate the perspective put forth by Gelardi et al.[37] The findings of our study indicate that the utilization of Gastroftal, HA, and cyclosporine in combination exhibits the

highest level of efficacy among the three therapy options. The observed improvement in the patient's symptoms can be attributed to the cessation of the triggering impact of pepsin, as well as the inhibitory actions of HA and cyclosporine on the inflammatory process occurring on the ocular surface. The combined administration of these medicines resulted in the most significant amelioration of the patient's condition. The utilization of weakly alkaline medications for the purpose of directly neutralizing the acidic conditions of the ocular surface has emerged as a potential therapeutic approach. However, additional research is required to investigate the specific consequences of this treatment strategy.

The experiment conducted in this study is subject to certain limitations. The present investigation did not encompass individuals with surgery-related DED, medication-related DED, contact lens usage, or DED resulting from systemic disease. Consequently, it remains uncertain if the findings of this study can be extrapolated to these specific patient populations. Furthermore, the patient cohort typically consists of individuals with a diverse range of conditions, such as dry eye in people with dry syndrome, non-drying dry eye, and varied degrees of evaporative dry eye. This variation in conditions unavoidably results in varying evaluations of the effectiveness of different treatment approaches. We did not have a relevant objective test to determine whether the patient had allergic conjunctivitis. Furthermore, the utilization of gold-standard testing, such as 24 hours multichannel intraluminal impedance (MII)-pH monitoring, was not employed in the diagnostic process of individuals with LPR.

CONCLUSION

In conclusion, we first proved a possible positive association between DED and LPR by analyzing DED-related examination parameters and RSS parameters in patients with DED and LPR. In patients with both LPR and DED, significant results were observed even with Gastroftal medication alone. This further validates that DED-related symptoms in these patients may be caused by LPR. For patients with both LPR and DED, treating LPR and DED at the same time may be a better option.

Credit authorship contribution statement

Xiaoyu Wang: Data curation; methodology; formal analysis; writing-original draft. **Tingting Wu, Zhi Liu:** Data curation; methodology; formal analysis; revision. **Ying Wang:** Data curation; conceptualization; methodology; project administration; writing-review and editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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