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Accuracy of the diagnosis of gastroesophageal reflux disease by a trial of potassium-competitive acid blocker treatment

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Abstract

Aim The aim of this study was to explore the accuracy of the diagnosis of gastro-esophageal reflux disease (GERD) through tegoprazan treatment trials, and to analyze factors that may influence test accuracy.

Methods This was a single-blind, single-arm 2 weeks tegoprazan treatment trials from March 2023 to April 2024. Patients with 'typical' reflux or heartburn as their most troublesome symptom who were considered likely to have GERD were recruited.: Patients were submitted to endoscopy and/or esophageal pH monitoring. After the recording patient used tegoprazan for 2 weeks. This was defined as positive for tegoprazan therapy if the scores for symptoms have decreased to 50%, 75% and 100% of the baseline after 1 and 2 weeks. Calculate different sensitivity, specificity and Youden index for each criterion.

Results This represents a mid-term report from the study, with 98 and 91 fully evaluable at one and two weeks. The Youden index indicated that a symptom relief of > 75% after one week offers greater diagnostic value with sensitivity and specificity of 77.5% and 51.9%. Multivariate regression analysis indicated that lower BMI, preference for coffee, endoscopic mucosal erosion, ineffective esophageal peristalsis and positive SAP are independent risk factors predicting the efficacy of P-CAB treatment.

Conclusions The P-CAB test (tegoprazan) presents a promising tool for the diagnosis of GERD. A one-week treatment with a criterion of 75% reduction in symptom scores from baseline may be the most cost-effective approach.

Trial registration chictr.org.cn registration number ChiCTR2200065994.

Keywords Tegoprazan, Gastroesophageal reflux disease, Treatment trial

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Introduction

Gastroesophageal reflux disease (GERD) is a chronic digestive disease in which gastric contents refluxing into the esophagus causing damage to the esophageal mucosa, with reflux and heartburn as the main symptoms [1]. GERD is a common clinical disease with a prevalence ranging from 10–20%. [2–3] Due to the recurrence of the disease, patients need to repeat medical consultations and take long-term medication, which can severely impact their quality of life and health [4].

In clinical practice, the golden standard diagnostic tests for patients with suspected GERD—endoscopy and 24-hour esophageal pH monitoring—are invasive and not universally accepted. However, non-invasive diagnostic methods are limited. Proton Pump Inhibitors (PPIs) are the main therapeutic method and often used for diagnostic treatment, but it is ineffective in ruling out other diseases due to their low specificity. Studies in Western countries have shown that the PPI test exhibits a sensitivity of 71% but a notably lower specificity of 44% [5]. Similarly, research in the Chinese population has indicated a low specificity of 44.4% [6]. PPIs are prodrugs that require to be activated in an acidic environment, so the initial dose does not achieve full effect and must be taken half an hour before meals [7, 8]. Moreover, the effects of different CYP2C19 genotypes on gastric pH can vary significantly among individuals. These above limitations may contribute to the low specificity [9].

Potassium-competitive acid blockers (P-CAB) have the characteristics of rapid onset, long duration of action and stability under acidic conditions [10]. And the acid-suppressive effect is not affected by food intake [11] and gene polymorphism [8]. Current guidelines suggest that P-CAB may be used as a diagnostic test for GERD, but there is a lack of supporting evidence [1].

As far as we know, there are no studies of P-CAB test for diagnosing GERD. To find a more appropriate and efficient non-invasive diagnostic method to alleviate patient suffering, our study aims are to investigate the diagnostic value of the P-CAB test for GERD and identify the clinical factors that affect its diagnostic accuracy.

Methods

Patients aged 18–75 years with 'typical' reflux or heartburn symptoms as their most troublesome symptom, who were considered likely to have GERD, were consecutively recruited. Patients had to have these symptoms for at least twice a week for the past 3 months or longer. Patients with atypical reflux symptoms, such as chest pain, coughing, abdominal pain, or throat discomfort as their most troublesome symptom were not eligible for the study.

Major exclusion criteria were: Alert (or 'alarm') features, such as unintentional weight loss in the previous 3 months, haematemesis, melena or rectal bleeding in the previous year, progressive dysphagia or any other symptoms suggestive of malignancy. Patients with esophageal cancer, esophageal varices, eosinophilic esophagitis, or esophageal hiatal hernia ≥ 3 cm. Patients with esophageal motility disorders such as esophageal obstructive lesions (including achalasia, mechanical obstruction) and severe esophageal motility disorders (like distal esophageal spasm, esophageal dysperistalsis). Previous anti-reflux surgery or surgery for peptic ulcer or other gastrointestinal resections; Daily aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) were excluded.

Informed written consent was obtained before the start of the study and the protocol was approved by the Medical Ethics Committee of the Third People's hospital of Chengdu.

Study protocol

On the first day, patients were required to complete a Likert scale, GERD-Q, Hospital Anxiety and Depression Scale (HADS), and Esophageal Hypervigilance and Anxiety Scale (EHAS) at baseline. After inclusion, patients underwent endoscopy and 24-hour esophageal pH monitoring. Subsequently, patient were prescribed 50 mg of tegoprazan daily for 2 weeks. During this period, patients were required to report daily on the adequacy of symptom suppression related to reflux or heartburn. Patients were followed up at week 1 and 2 after enrollment, either through hospital visits or by telephone. Follow-up practitioners were blinded to the results of the endoscopy and pH monitoring until the end of the study to ensure uniform follow-up for all patients. Patients were not allowed to take any other antisecretory or prokinetic drug.

Study investigations

Endoscopy

Endoscopy examination was performed by experienced endoscopists. The presence and severity of esophagitis were evaluated on the LA classification [15].

24-hour esophageal pH monitoring

24-hour esophageal pH monitoring was performed after discontinuation of PPIs / P-CAB ≥ 7 days, antacid ≥ 1 day, prokinetics and histamine H2 antagonists ≥ 3 days [13]. Prior to the 24-h pH recording patients underwent manometry using a high-resolution manometry system (Medtronic, Dublin, Ireland). After removal of the manometric catheter, a pH catheter (Versaflex Z, Given Imaging, Israel) was placed. Acid exposure time (AET), mean nocturnal baseline impedance (MNBI), total reflux events and symptom association probability (SAP) were calculated.

Investigation-based criteria for reference diagnosis of GERD

According to the Lyon consensus 2.0 [14] and ACG clinical guideline [15] for the diagnosis and management of GERD, for the primary predetermined analysis, GERD was diagnosed when at least one of the following protocol-defined criteria was present:

1. Reflux esophagitis (RE, LA grades B-D).
2. AET > 6%. If borderline high esophageal acid exposure (AET for 4–6%), positive of SAP, total reflux episodes > 80 / day, MNBI < 1500Ω were considered adjunctive or supportive evidence of GERD.

Symptom evaluation

The frequency and severity of the predominant symptom were assessed on a 5 point Likert scale (frequency: 0 (none), 1 (1 day/week), 2 (2–3 days/week), 3 (more than 3 days/week), and 4 (every day/week); severity: 0 (none), 1 (mild), 2 (moderate), 3 (severe), and 4 (very bothersome)). A composite symptom score was obtained by multiplying the frequency score by the severity score.

Acid inhibitory treatment test

This was defined as positive for GERD if the scores for reflux or heartburn symptoms score decreased to 50%, 75% and 100% of baseline levels after 1 and 2 weeks. Calculate different sensitivity, specificity and Youden index for each criterion.

Sample size calculation

This study is a diagnostic test. There is no study on P-CAB as a diagnostic test for GERD. According to the Lyon Consensus on GERD, the sensitivity and specificity of the PPI test for GERD are 71% and 44%, with an allowable error of 0.1, α of 0.05, and a confidence level of 1-β = 0.10. The sample size was calculated using PASS 15 software. Assuming a 10% non-response rate, according to relevant studies, the diagnosis ratio of typical heartburn reflux symptoms according to the golden standard for GERD ranged from 30 to 55%. Thus, this study requires at least 290 participants. This article is a midterm research report of the study.

Statistical analysis

All statistical analyses were conducted by SPSS 25 (IBM, Armonk, NY, USA). We used mean(standard) deviation for continuous variables with normal distribution, median (interquartile range) for those without normal distribution. Categorical variables were presented as percentages. The sensitivity, specificity and predictive values were calculated using a 2 × 2 contingency table. A receiver operating characteristic (ROC) curves analysis was performed by plotting sensitivity on the y-axis against the 1-specificity, to determine optimal diagnostic cut-off values and duration of P-CAB test. Univariate analyses were performed using parametric (Student's t-test and one-way ANOVA) or non-parametric methods (Mann–Whitney U test and Kruskal-Wallis tests) for continuous variables, and chi-square test for categorical variables. The p-values were considered significant when < 0.05.

Results

Of the 113 patients formally screened, thirteen (13.3%) left the study prematurely. Thus, 100 patients were enrolled. Two patients developed rashes 3 days and 1 week after taking the medicine, and disappeared after stopping, which was considered possibly drug-related. No serious adverse events occurred in the remaining patients. At the second week 6 patients withdrew due to personal reasons or poor drug efficacy. Finally, 98 (98%) and 91(91%) were fully evaluable at one week and two weeks' follow-ups (Fig. 1).

72 patients were diagnosed GERD with a median age of 55 years. Patients with erosive esophagitis had a higher proportion of male (61.1%) and a higher BMI (26.5) compared to that with non-erosive. More than 80% of the patients suffer from anxiety and depression (Table 1).

Because esophageal pH monitoring is an invasive procedure, in order to clarify the diagnosis of GERD, it was required in patients with an unclear diagnosis of GERD (no esophageal mucosal erosion or LA-A esophagitis), and patients with grade B/C/D esophagitis can choose to do it. Finally, a total of 62 patients underwent this examination. 24 h pH monitoring was abnormal in 58.1% of patients. In the group with abnormal PH monitoring, MNBI was lower, SAP positivity was higher ($p < 0.01$) (online appendix 1).

The P-CAB test was positive under these assumptions in 19 patients with NERD, 52 with RE in the first week. 92.4% had a reduction greater than 50% by the end of the 2-week period. Symptomatic relief in the RE group was better than in the NERD group at week 2 (Table 2). Table 3 shows sensitivity, specificity, positive and negative predictive values using three different cut-off values and two time intervals for P-CAB test. The corresponding ROC curves are presented in Fig. 2. The Youden index for these six diagnostic criteria indicated that symptom relief > 75% after 1 week had the highest diagnostic value for the P-CAB test.

The patients were divided into two groups based on the effectiveness of treatment. In the effective treatment group, there were more endoscopic mucosal erosion (69.1%), higher AET, total reflux times (70%) and more positive SAP under pH monitoring. Lower LES resting pressure and more ineffective were observed during high-resolution manometry (online appendix 2, 3).

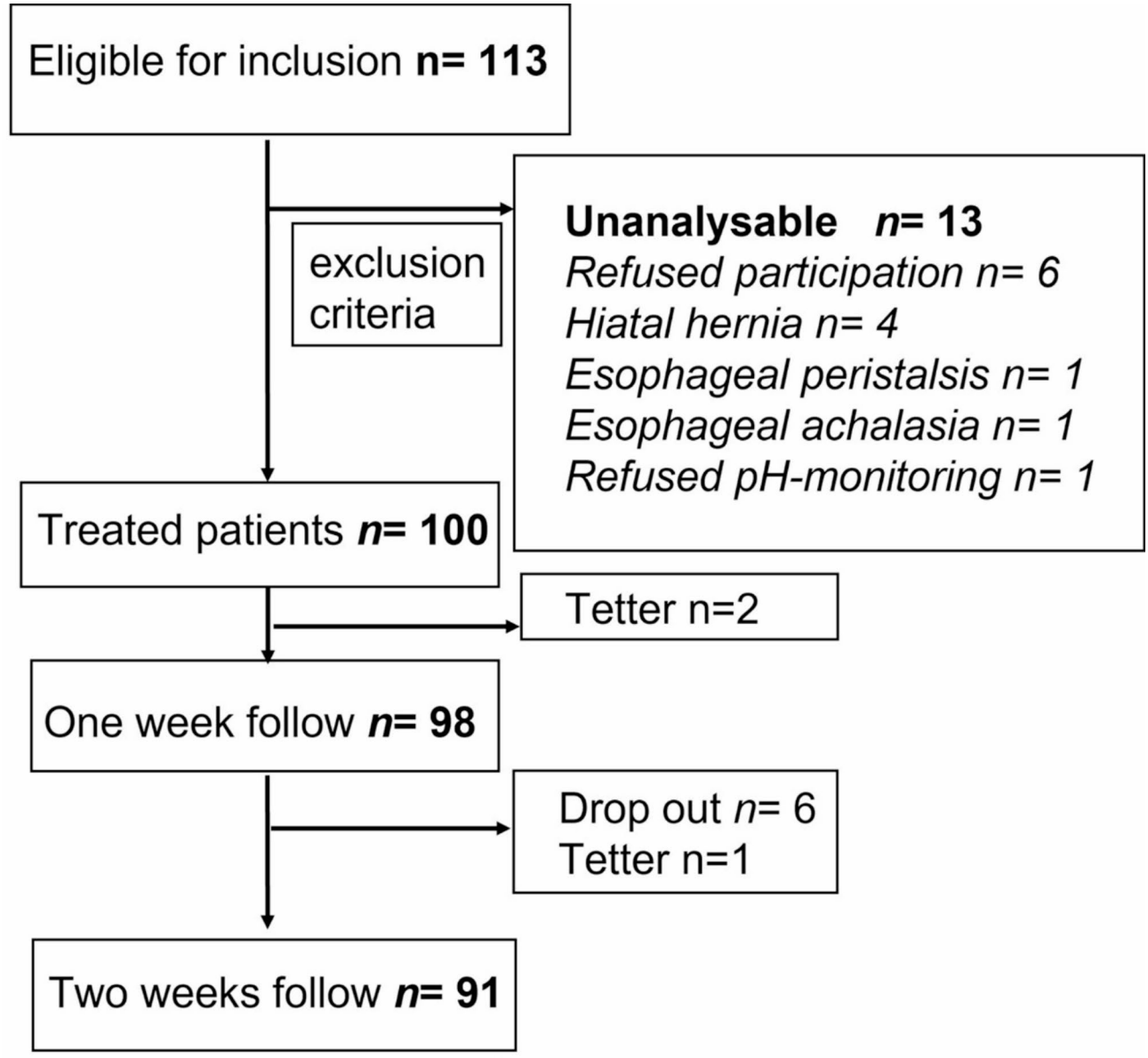

Fig. 1 Flowchart showing the number of patients

All factors were included in the univariate analyses, which identified lower BMI, preference for coffee, endoscopic mucosal erosion, ineffective swallowing times, and positive SAP as independent risk factors predicting the efficacy of P-CAB treatment (online appendix 4).

Discussion

GERD is a common chronic digestive disease. Risk factors include age, smoking, alcohol consumption, obesity, social factors, and psychosomatic conditions [1, 16]. This study supports these associations, noting a higher prevalence of males and elevated BMI in the esophageal erosion group. Anxiety and depression were present in all groups, probably due to persistence and recurrence of symptoms. Our previous studies had also confirmed that there is a significant link between mental symptoms (especially anxiety and depression) and GERD [17]. The higher EHAS scores in patients with NERD and negative pH monitoring were considered to be possibly related to esophageal mucosal hypersensitivity [18].The mean MNBI was lower and the SAP positive rate was higher in the group with abnormal pH monitoring, which is in accordance with the Lyon Consensus [14, 19, 20].

The diagnosis of GERD is mainly based on typical symptoms, esophageal pH monitoring, endoscopy and diagnostic PPI tests, but each of them have limitations. For example, pH monitoring was once called the "golden standard" for diagnosing, but it has been reported to be

Table 1 Main clinical and demographic characteristics for the first-week therapy patients

	First week evaluable *n* = 98			
Demography	Non-GERD *n* = 26	RE *n* = 52	NERD *n* = 20	P
Mean age, years (SD)	57 (9)	55(13)	55(12)	0.68
Gender M/F	7/19	35/17	9/11	<0.01[a]
Mean BMI, kg/m2 (SD)	22.4(3.2)	26.5(5.2)	22.6(3.4)	<0.01[b]
Smoking, n(%)	3(11.5)	15(28.8)	6(30)	0.2
Alcohol, n(%)	3(11.5)	18(34.6)	5(25)	0.1
Strong tea, n(%)	2(7.7)	10(19.2)	2(10)	0.33
coffee, n(%)	3(11.5)	6(11.5)	1(5)	0.69
Weight loss, n(%)	7(26.9)	7(13.5)	6(30)	0.19
H pylori positive, n(%)	4(15.4)	18(34.6)	8(25)	0.13
LA classification A, n	4	9	0	
LA classification B, n	0	35	0	
LA classification C, n	0	8	0	
LA classification D, n	0	0	0	
HADS Anxiety, n (%), (mean ± SD)	22(84.6),11.5 ± 3.5	47(90.4), 12.4 ± 3.6	18(90),12.6 ± 3.2	0.49
HADS Depression, n (%),(mean ± SD) (mean ± SD)	24(92.3),9.5 ± 2.6	43(82.7),9.1 ± 3.1	17(85),10.6 ± 6.0	0.31
EHAS Score	23.5(10.3,33.8)	15.5(8,25.8)	22.5(11,31.5)	0.23

BMI, body mass index; F, female; M, male; LA, Los Angeles; [b]RE vs. non-GERD&REvsNERD, [a]RE vs. NERD

Table 2 Percentages of patients showing response to P-CAB test according to durations of the test and cut-off values for symptoms response

1 week 2 weeks	**GERD (%) *n* = 71 *n* = 66**	**RE (%) *n* = 52 *n* = 49**	**NERD (%) *n* = 19 *n* = 17**	***p****
Cut-off 50%/1 week	78.9	84.6	63.2	0.05
Cut-off 50%/2 weeks	92.4	100	70.6	<0.01
Cut-off 75%/1 week	77.5	82.7	63.2	0.08
Cut-off 75%/2 weeks	87.9	98.0	58.8	<0.01
Cut-off 100%/1 week	69.0	75	52.6	0.07
Cut-off 100%/2 weeks	78.8	87.8	52.9	0.02

* Comparison of RE vs. NERD patients

normal in up to 25% of patients with erosive esophagitis and in 50% of those with NERD [21]. Similarly in this study pH monitoring was only available in 58.1% of patients with typical symptoms. Endoscopy has a high specificity (90–95%) [22], but the sensitivity in patients with typical symptoms is only around 50% [23].

PPI is the main treatment for GERD, but its diagnostic value is limited due to its low specificity. In the PPI test, 35% of patients with normal endoscopy and negative pH monitoring experienced symptomatic relief [7]. About 20 to 40% of GERD patients do not respond to short-term PPI therapy [24]. A real-world study showed that 54.6% of patients were unable to take their medication strictly before meals [25]. In addition, individual CYP2C19 genotypes differences also influence [9]. The above reasons may affect the results of diagnostic tests. The mechanism of P-CAB is different from PPI. Previous RCT studies have shown that in patients with RE, the 4-week endoscopic healing rate was 91.3% and the 8-week healing rate was 98.9% for Tegoprazan, which were non-inferior to esomeprazole [26].

There are no studies related to the use of P-CAB in the diagnostic treatment of GERD, leaving no established criteria for assessing therapeutic effectiveness and duration [27–28]. Most existing studies on PPI tests use the degree of relief symptoms to 50%, 75%, and 100% of baseline levels as the criterion for treatment effectiveness, with trial durations ranging from 1 to 8 weeks. Previous studies [23, 27, 29] found that setting the duration of the PPI test

Table 3 Values of sensitivity, specificity, predictive values and Youden's index using three different cut-off values and two-time intervals

	Sensitivity (%)	**Specificity (%)**	**Positive predictive value (%)**	**Negative predictive value (%)**	**Youden's index**	**Kappa**
Cut-off 50%/1 week	78.9	40.7	77.8	42.3	0.196	0.198
Cut-off 50%/2 weeks	92.4	26.1	78.2	54.5	0.185	0.223
Cut-off 75%/1 week	77.5	51.9	80.9	46.7	0.294	0.283
Cut-off 75%/2 weeks	87.9	26.1	77.3	42.9	0.14	0.16
Cut-off 100%/1 week	69.0	55.6	80.3	40.5	0.246	0.22
Cut-off 100%/2 weeks	78.8	39.1	78.8	39.1	0.179	0.179

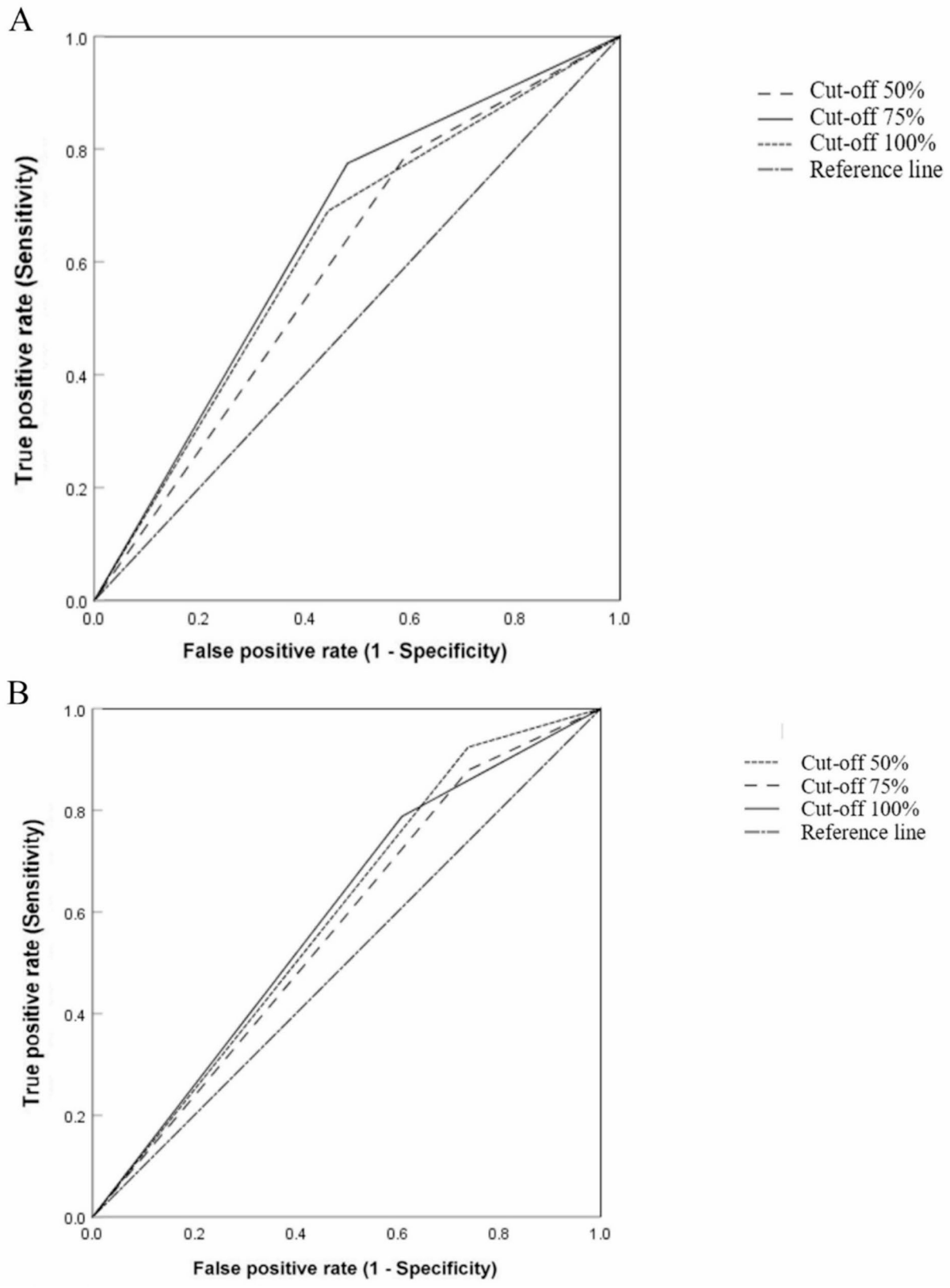

Fig. 2 ROC curves for different thresholds and duration of P-CAB test in 1 week(**A**)and 2 weeks(**B**)

to 1–2 weeks and the is sufficient for diagnosis and can save costs.

Although this article is an interim report of this study, we are pleased to find that the results of the study are as expected, and the specificity is numerically higher than the previous PPI test data. The most useful threshold for defining a positive response to the P-CAB test is symptom relief of ≥ 75%, while the optimal duration is 1 week. With a sensitivity of 77.5% and a specificity of 51.9%, the optimal duration of 1 week significantly shortens the test period, making it more cost-effective.

The results of multivariate regression analysis showed that lower BMI and preference for coffee were related to the efficacy of P-CAB treatment. A cohort study found that weight loss can significantly reduce the symptoms of GERD patients. The efficacy is related to the degree of BMI reduction [30]. There is still controversy about the relationship between coffee and GERD [39], but coffee can promote gastric acid secretion as we know, and the effectiveness of acid suppression therapy is related to it. Previous studies have shown [32, 33] that esophageal motility disorders, EGJ morphology, and negative SI are independent risk factors for PPI therapy. This study also found that decreased esophageal clearance and positive SAP are independent risk factors for P-CAB therapy.

We encountered the following two problems in our study that need to be noted in future trial: First, three patients developed rashes, which resolved after stop medicine for 1–3 days. The risk of rash should be mentioned when enrolling patients; Second, there were more grade B esophagitis patients in this study, and more cases in the RE group than in the NERD group. A multicenter retrospective study found that 45.5%, 30.3%, 15.9%, and 8.3% of patients were diagnosed with grade A, B, C, and D esophagitis at the first time of endoscopic examination [34]. It may be because grade A is non-specific and is found in 5-7.5% of asymptomatic people, presenting as physiological acid reflux. Therefore, the Lyon consensus [14] proposes that reflux monitoring must be performed to indicate the presence of pathological reflux for diagnosis in grade A esophagitis. However, pH monitoring is an invasive procedure, and grade A esophagitis and patients with possible NERD who cannot undergo this examination were excluded. In John Dent's study [5], the most excluded people were those who could not undergo reflux monitoring. Therefore, he believed that the outcome may not be representative of the actual target patient. Subsequent studies on the diagnostic efficacy of P-CAB in real-world settings may avoid this selection bias.

This study also had several limitations. Firstly, six patients withdrew after 1 week of treatment due to ineffective results, which may have increased the effective rate observed in the second week. Subsequent studies should analyze this group by including in week 2 as treatment ineffective and by direct exclusion, respectively; Secondly, there was no placebo group because previous PPI studies have shown no difference in placebo response between GERD and non-GERD group [5]; Thirdly, no comparative study with PPI was conducted, and the difference was only numerically represented. Subsequent research will be designed for non-inferiority research. Fourthly, in the Lyon diagnostic criteria, grade A esophagitis is not conclusive evidence but inconclusive (borderline) evidence. However, since four grade A patients in this study were included in the non-GERD group due to the results of reflux monitoring (AET, MNBI, total reflux events), if they were excluded and recalculated the diagnostic specificity would be improved (52.2%). In subsequent studies, such cases need to be separately calculated for inclusion and exclusion results.

This study confirms that the Tegoprazan test has high diagnostic value for GERD. If the diagnostic test course is 7 days, using 75% relief of symptom score as the judgment criterion may be more in line with the principle of economic cost-effectiveness.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-03981-1.

Supplementary Material 1

Author contributions

PD and QW conducted the research and were responsible for project administration, funding acquisition and analysis formal. PD and LL analyzed the data and wrote the paper; KS and FT were responsible for data curation and supporting resources; QL, XZ, FL, XY, ZY connected patients for symptom investigation and follow-up data collection. LL completed the esophageal high-resolution manometry and 24-hour esophageal pH monitoring; JL, LJ, PZ and XS completed the endoscopy and collected endoscopic data.

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Data availability

The data that support the findings of this study are not openly available due to reasons of patient privacy and data sensitivity and are available from the corresponding author upon reasonable request. All data are in the controlled access data storage of the Digestive Disease Database of Chengdu Third People's Hospital.

Declarations

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics approval
Informed written consent was obtained before the start of the study and the protocol was approved by the Medical Ethics Committee of the Third People's hospital of Chengdu[2022]S-No.71.

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