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A preliminary exploration of a predictive model and nomogram for the efficacy of compound digestive enzyme therapy based on serum (PGI, PGII, VIP, and PRDX1) in patients with functional dyspepsia

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Abstract

Objective This study aimed to explore the feasibility of constructing compound digestive enzyme therapeutic effect prediction model based on serum pepsinogen I (PGI), pepsinogen II (PGII), vasoactive intestinal peptide (VIP), and peroxidase 1 (PRDX1) in patients with functional dyspepsia (FD), and draw nomograms, to provide reference for the selection of clinical treatment.

Methods A total of 249 FD patients who visited the Department of Gastroenterology in our hospital from January 2021 to December 2024 were selected, and the preoperative clinical and laboratory indicators were collected. the patient cohort was split in a 7:3 ratio into a training set ($n=174$) and a validation set ($n=75$). The risk factors were screened by univariate and multivariate logistic regression in the training set, and the nomogram model was constructed. The receiver operating characteristic curve (ROC) was drawn and the calibration curve was used to evaluate the effectiveness of the model. The model was verified in the verification set, and the clinical value was evaluated by decision curve analysis (DCA).

Results The results of multivariate logistic regression showed that PGI, PGII, VIP, PRDX1, white blood cell count, aspartate aminotransferase and high density lipoprotein cholesterol were the independent risk factors for poor efficacy of compound digestive enzymes in the treatment of FD. The C-index was 0.830 and 0.827, respectively, the area under the ROC curve (AUC) was 0.835 (95% CI: 0.792–0.941) and 0.835 (95% CI: 0.687–0.983), and the sensitivity and specificity were 0.768, 0.857, and 0.778, 0.780, respectively.

Conclusion The therapeutic effect prediction model of compound digestive enzyme base on serum PGI, PGII, VIP, PRDX1 in patients with FD has some clinical value, but it still need to be further verified by large sample size and multi-center study.

Keywords Functional dyspepsia, Compound digestive enzymes, Prediction models, Nomograms, Serum indicator

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Introduction

Functional Dyspepsia (FD) is a common functional gastrointestinal disease, which mainly manifests as postprandial fullness discomfort, early satiety, epigastric pain, and upper abdominal burning sensation, and organic, systemic, or metabolic diseases that can explain these symptoms are excluded [1]. The incidence of FD is high, which seriously affects the quality of life of patients and brings heavy economic burden to society and individuals. compound digestive enzymes, as common drugs for the treatment of FD, can supplement digestive enzymes, promote food digestion and absorption, and alleviate the symptoms of dyspepsia [2]. however, a subset of patients respond poorly to enzyme therapy, with significant individual variability in treatment effect. At present, there is a lack of effective indicators to predict the therapeutic effect of compound digestive enzymes on FD patients, making it difficult to predict treatment success in clinical practice. Pepsinogen (PG) is a precursor of pepsin, which is divided into PGI and PGII according to the different biochemical properties and immunogenicity [3]. Serum PG level can reflect the function and state of gastric mucosa, and is closely related to a variety of gastric diseases. Vasoactive Intestinal Peptide (VIP) is a neurotransmitter widely distributed in the gastrointestinal tract and has an important regulatory effect on gastrointestinal motility, secretion, blood flow and other physiological functions [4]. Peroxiredoxin 1 (PRDX1) is an antioxidant enzyme that participates in the regulation of intracellular redox balance and also plays a role in the occurrence and development of gastrointestinal diseases [5]. In recent years, more and more studies have shown that these biomarkers are related to the condition and prognosis of digestive system diseases, but there are few studies combining PGI, PGII, VIP, and PRDX1 to predict the therapeutic effect of compound digestive enzymes in FD patients. In this study, we analyzed the relationship between serum PGI, PGII, VIP, and PRDX1 levels and the therapeutic effects of compound digestive enzymes in FD patients, constructed a prediction model and drew nomograms to evaluate the prediction efficiency and clinical value of the model, so as to provide new ideas and methods for accurate clinical treatment of FD.

Materials and methods

Subjects

This study is a retrospective study.249 FD patients who visited the Department of Gastroenterology of our hospital from January 2021 to December 2024 were selected. Inclusion criteria: Patients who met the diagnostic criteria of FD in Rome IV criteria [6]; Age 18–70 years; The patient signed an informed consent form and volunteered to participate in this study. Exclusion criteria: Patients with concurrent organic diseases such as peptic ulcer, gastroesophageal reflux disease, and gastrointestinal tumor; Severe hepatic and renal insufficiency; Combined with autoimmune diseases and infectious diseases in the acute phase; Drugs that affect the secretion of digestive enzymes or gastrointestinal motility have been used in the past one month; Patients with mental illness cannot cooperate with the investigator.When enrolling the study subjects, Helicobacter pylori (H. pylori) infection testing was performed on all patients using the urea breath test. If a patient tested positive for H. pylori, standard H. pylori eradication therapy was administered. The treatment regimen consisted of a proton pump inhibitor (such as omeprazole, 20 mg twice daily), a bismuth agent (such as bismuth potassium citrate, 220 mg twice daily), amoxicillin (1 g twice daily), and clarithromycin (0.5 g twice daily) for a duration of 14 days. After completing the treatment, the H. pylori infection status was rechecked. Only patients who were confirmed to have converted to negative were included in this study. This was done to ensure that the enrolled patients with functional dyspepsia (FD) did not have active H. pylori infection, thereby avoiding any confounding effects on serum pepsinogen (PG) levels and the response to compound digestive enzyme treatment. Patients were divided into a training set ($n=174$) and a verification set ($n=75$) using random number table.Among the 249 patients with functional dyspepsia (FD) included in the study, their FD subtypes were further determined according to the Rome IV criteria, which classified them into epigastric pain syndrome and postprandial distress syndrome, and the number of patients in each subtype was recorded. Among them, there were 132 cases of epigastric pain syndrome and 117 cases of postprandial distress syndrome.

Data collection

Patients' general clinical data were collected, including age, gender, height, weight, body mass index (BMI), smoking history, alcohol consumption history, and dietary habits (such as whether or not they liked spicy and greasy food). Five milliliters of fasting venous blood was collected and centrifuged at 3000r/min for 10 min. Serum was separated and enzyme-linked immunosorbent assay (ELISA) was used to detect serum PGI, PGII, VIP, and PRDX1 levels. The kit was purchased from Hengyuan Biotechnology Co., Ltd. and the operation was strictly in accordance with the instructions. Besides, routine blood tests, liver and kidney functions, blood glucose, blood lipid and other routine laboratory indexes were tested.

Treatment plan and efficacy evaluation

All the patients were given compound digestive enzyme capsules (specifications: each capsule contained pepsin 25 mg, papain 50 mg, amylase 15 mg, ursodeoxycholic

acid 25 mg, cellulase 15 mg, trypsin 25 mg, pancreatic amylase 25 mg, and pancreatic lipase 25 mg) for oral treatment, two capsules each time, three times a day, with a course of four weeks.Throughout the entire study period, patients were explicitly prohibited from using other concomitant medications for dyspepsia treatment, including proton pump inhibitors (PPIs), prokinetic agents, H_2-receptor antagonists, etc. This was done to ensure that the research results were only influenced by the treatment with compound digestive enzymes, thereby avoiding interference from other medications and ensuring an accurate assessment of the efficacy of compound digestive enzyme treatment. After the treatment, the patients' symptoms before and after treatment were quantitatively evaluated using the validated Nepean Dyspepsia Index. Data were collected through patient interviews by doctors who had received unified training to ensure the consistency of the evaluation process. Based on the quantitative evaluation results and combined with the improvement of patients' symptoms, the therapeutic effect was evaluated. Markedly effective: The symptoms disappeared completely or basically disappeared, with no impact on daily life, and the Nepean Dyspepsia Index decreased by more than 70% compared with that before treatment. Effective: The symptoms were significantly alleviated, with a minor impact on daily life, and the Nepean Dyspepsia Index decreased by 30 – 70% compared with that before treatment. No effect: no improvement or a worsening of symptoms, and the Nepean Dyspepsia Index decreased by less than 30% compared with that before treatment. The total effective rate = markedly effective rate + effective rate. Patients with a total effective treatment outcome were included in the effective group, while those with an ineffective outcome were included in the ineffective group.

Statistical methods

SPSS26.0 and R language 4.5.3 were used for statistical analysis. Counting data are expressed by the number of cases (percentage), and the comparison between groups is made by χ test; The measurement data conform to the normal distribution with S, the comparison between groups is tested by independent sample T, and the non-normal distribution with M(Q1, Q3) and Mann-WhitneyU test.Before conducting the multivariate logistic regression analysis, the Variance Inflation Factor (VIF) was used to assess the collinearity among independent variables. If the VIF value is less than 10, it is considered that there is no severe collinearity. Multivariate logistic regression was used to identify independent risk factors associated with treatment ineffectiveness (using $P < 0.05$ as the significance threshold). The nomogram was constructed in R (using the 'rms' package)., and the model is verified internally by Bootstrap method, Set the number of bootstrap resampling times to 1000. and the calibration curve between the predicted results and the actual results is drawn, and the Concordanceindex (C-index) of the model is calculated. Hosmer-Lemeshow test is used to evaluate the goodness of fit of the predicted model. Clinical application value of DCA(DecisionCurveAnalysis) model.

Results

Comparison of general clinical characteristics of patients between training set and verification set

The differences in general clinical characteristics such as age, gender, BMI, smoking history, drinking history, and dietary habits as well as most laboratory indicators of the patients in the training set and the verification set were not statistically significant ($P > 0.05$), and were comparable.All patients met the FD criteria, but the severity of different symptoms was not quantitatively recorded.The specific data are shown in Table 1.

Training set univariate analysis of the therapeutic effect of compound digestive enzymes

In the training set, 35 patients (20.1%) had an ineffective outcome (no symptom improvement), whereas 139 (79.9%) showed an effective response.In the validation set, there were 16 cases (21.33%) with ineffective treatment and 59 cases (78.67%) with effective treatment. Univariate analysis showed that the differences between ineffective and effective patients on the levels of PGI, PGII, VIP, and PRDX1 were statistically significant ($P < 0.05$), and the differences in other factors such as age, gender, and BMI were not statistically significant ($P > 0.05$). In the regression model, the tolerance of each variable was > 0.1, VIF was < 10(PGI(VIF = 1.23)、PGII (VIF = 1.15) 、VIP (VIF = 1.37) 、PRDX1 (VIF = 1.09) 、WBC count (VIF = 1.42) 、AST (VIF = 1.28) 、HDL-C (VIF = 1.19), condition index was < 30, and the proportion of variances of multiple covariates was > 50% without the same feature value. Hence, there was no collinearity of each covariate. The specific data are shown in Table 2.

Multiple factor logistic regression analysis

The treatment effect (0 = effective, 1 = ineffective) was taken as the dependent variable, and the factor $P < 0.05$ in the univariate analysis was taken as the covariate for multi-factor logistic regression analysis. The results showed that PGI, PGII, VIP, PRDX1, white blood cell count, aspartate aminotransferase, and high density lipoprotein cholesterol were the independent risk factors for poor efficacy of compound digestive enzymes in the treatment of FD ($P < 0.05$). The specific data are shown in Table 3.

Table 1 Comparison of general clinical characteristics of patients between training set and verification set

index		Training set ($n=174$)	Validation set ($n=75$)	statistical values	P
Age (years)		42.62 ± 10.18	43.08 ± 9.92	0.330	0.742
BMI(kg/m^2)		23.48 ± 3.19	23.75 ± 3.03	0.622	0.535
gender	man	94(54.02)	40(53.33)	0.010	0.920
	woman	80(45.98)	35(46.67)		
Smoking history	have	44(25.29)	20(26.67)	0.052	0.819
	without	130(74.71)	55(73.33)		
Drinking history	have	34(19.54)	14(18.67)	0.026	0.873
	without	140(80.46)	61(81.33)		
Enjoy spicy food	have	70(40.23)	30(40.00)	0.001	0.972
	without	104(59.77)	45(60.00)		
Enjoy greasy food	have	84(48.28)	35(46.67)	0.054	0.816
	without	90(51.72)	40(53.33)		
PGI(ng/mL)		75.27 ± 15.19	76.05 ± 14.82	0.375	0.708
PGII(ng/mL)		12.42 ± 3.09	12.75 ± 3.02	0.780	0.436
VIP(pg/mL)		75.62 ± 12.30	76.18 ± 11.94	0.333	0.740
PRDX1(ng/mL)		45.63 ± 10.19	46.08 ± 9.83	0.323	0.747
White blood cell count (× 10/L)		6.52 ± 1.20	6.60 ± 1.15	0.489	0.626
Hemoglobin (g/L)		135.23 ± 10.56	134.89 ± 10.23	0.235	0.814
Platelet count (× 10/L)		220.56 ± 35.67	218.78 ± 34.56	0.365	0.716
Alanine aminotransferase (U/L)		25.67 ± 8.45	26.12 ± 8.12	0.390	0.697
Aspartate aminotransferase (U/L)		23.45 ± 7.56	23.89 ± 7.23	0.427	0.670
Creatinine (μmol/L)		65.34 ± 10.23	66.12 ± 9.87	0.558	0.578
Blood glucose (mmol/L)		5.22 ± 0.88	5.30 ± 0.84	0.667	0.505
Total cholesterol (mmol/L)		4.87 ± 1.05	4.92 ± 1.02	0.348	0.728
Triglycerides (mmol/L)		1.56 ± 0.50	1.59 ± 0.48	0.440	0.661
High density lipoprotein cholesterol (mmol/L)		1.25 ± 0.30	1.23 ± 0.28	0.492	0.623
Low density lipoprotein cholesterol (mmol/L)		2.80 ± 0.75	2.84 ± 0.72	0.391	0.696

Construction of nomogram prediction model

The independent risk factors determined by multivariate logistic regression analysis were used to construct an nomogram prediction model for the therapeutic effects of compound digestive enzymes in FD patients. Each independent risk factor in the model was scored, and the total score for predicting treatment failure was calculated, which was expressed as the prediction probability. The horizontal coordinates of the nomogram were successively PGI, PGII, VIP, PRDX1, WBC count, AST (Aspartate Aminotransferase), and HDL cholesterol. and each index corresponded to a different scale range. The vertical coordinate was the total score and prediction probability. The scores were obtained by the scales corresponding to the numerical values of each index of the patient, and the total score was obtained by adding, thus corresponding to the prediction probability. (See Fig. 1).

Evaluation and validation of nomogram prediction model for the therapeutic effect of compound digestive enzymes

In the training set, the C-index index of the nomogram prediction model was 0.830, and Hosmer-Lemeshow test $P=0.289$, indicating that the model fitted well, There is no evidence of poor fit (since $P>0.05$ indicates that the model predictions do not deviate significantly from the actual results). The ROC curve showed an AUC of 0.835 (95% CI: 0.729–0.941), a sensitivity of 0.768, and a specificity of 0.857 for the model to predict treatment failure. In the validation set, the C-index was 0.827, the Hosmer-Lemeshow test $P=0.674$, the AUC was 0.835 (95% CI: 0.687–0.983), the sensitivity was 0.778, and the specificity was 0.780. The calibration curve and ROC curve are shown in Figs. 2 and 3, respectively.

Decision-making curve analysis of nomogram prediction model for treatment effect of compound digestive enzymes

Decision curve analysis shows that when the threshold probability is between 0.08 and 0.85, the application of the nomogram model constructed in this study to predict the therapeutic effects of compound digestive enzymes was more beneficial than strategies of treating either all patients or no patients,. This means that within this risk probability range, using this model to guide clinical decisions can bring better treatment benefits to patients compared with adopting a unified treatment or non-treatment strategy without considering the specific conditions of patients. It can also help clinicians choose treatment plans more reasonably. as shown in Fig. 4.

Table 2 Training sets univariate analysis of therapeutic effects of compound digestive enzymes

index		Effective ($n=139$)	Ineffective ($n=35$)	statistical values	*P*
Age (years)		42.15 ± 9.97	43.95 ± 10.51	0.936	0.35
BMI(kg/m^2)		23.35 ± 3.12	23.81 ± 3.30	0.734	0.464
gender	man	74(53.24)	20(57.14)	0.12	0.729
	woman	65(46.76)	15(42.86)		
Smoking history	have	34(24.46)	10(28.57)	0.179	0.672
	without	105(75.54)	25(71.43)		
Drinking history	have	26(18.71)	8(22.86)	0.02	0.888
	without	113(81.29)	27(77.14)		
Enjoy spicy food	have	55(39.57)	15(42.86)	0.088	0.766
	without	84(60.43)	20(57.14)		
Enjoy greasy food	have	66(47.48)	18(51.43)	0.097	0.756
	without	73(52.52)	17(48.57)		
PGI(ng/mL)		78.38 ± 14.84	69.78 ± 12.51	3.156	0.002
PGII(ng/mL)		12.96 ± 2.89	14.38 ± 3.53	2.550	0.012
VIP(pg/mL)		75.76 ± 10.85	82.53 ± 15.19	3.025	0.003
PRDX1(ng/mL)		46.35 ± 11.52	53.41 ± 12.28	3.198	0.002
White blood cell count (× 10^9/L)		6.52 ± 1.21	7.05 ± 1.32	2.274	0.024
Hemoglobin (g/L)		135.23 ± 10.56	132.56 ± 11.02	1.598	0.112
Platelet count (× 10/L)		220.56 ± 35.67	235.67 ± 40.23	2.182	0.031
Alanine aminotransferase (U/L)		25.23 ± 8.21	28.56 ± 9.56	2.073	0.040
Aspartate aminotransferase (U/L)		23.21 ± 7.32	26.78 ± 8.45	2.498	0.013
Creatinine (μmol/L)		64.89 ± 9.87	68.78 ± 11.23	2.026	0.044
Blood glucose (mmol/L)		5.18 ± 0.84	5.56 ± 0.95	2.329	0.021
Total cholesterol (mmol/L)		4.80 ± 1.02	5.12 ± 1.15	1.616	0.108
Triglycerides (mmol/L)		1.52 ± 0.48	1.79 ± 0.58	2.848	0.005
High density lipoprotein cholesterol (mmol/L)		1.28 ± 0.31	1.13 ± 0.25	2.652	0.009
Low density lipoprotein cholesterol (mmol/L)		2.75 ± 0.72	3.14 ± 0.81	2.792	0.006

Table 3 Training sets multivariate logistic regression of therapeutic effects of compound digestive enzymes

factor	B	Standard error	Wald	*P*	OR	95% confidence interval
PGI	-0.045	0.018	6.036	0.014	0.956	0.922–0.991
PGII	0.189	0.088	4.592	0.032	1.209	1.016–1.437
VIP	0.041	0.020	4.281	0.039	1.042	1.002–1.083
PRDX1	0.047	0.022	4.385	0.036	1.048	1.003–1.094
white cell count	0.501	0.215	5.427	0.020	1.650	1.083–2.515
Aspartate Aminotransferase	0.097	0.041	5.655	0.017	1.102	1.017–1.193
High density lipoprotein cholesterol	-2.120	0.905	5.487	0.019	0.120	0.020–0.707
constant	-18.656	4.133	20.378	0.001	0.001	

Discussion

Functional dyspepsia (FD) is a very common functional gastrointestinal disease in clinical practice. The symptoms it causes, such as postprandial fullness, discomfort, early satiety, and upper abdominal pain, seriously interfere with the daily life of patients, significantly reduce their quality of life, and also bring a heavy economic burden to society and individuals [7]. Compound digestive enzymes, as a commonly used medication for treating FD, can theoretically promote the digestion and absorption of food by supplementing digestive enzymes, thereby alleviating symptoms of indigestion. However, in practical clinical applications, there are significant individual differences in the treatment response of patients to this medication [8]. Exploring indicators that can effectively predict the therapeutic effect of compound digestive enzymes and constructing reliable prediction models has become the key to optimizing clinical treatment plans for FD and achieving precision medicine.

This study found that a decrease in PGI, an increase in PGII, an increase in VIP, and an increase in PRDX1 are independent risk factors for poor efficacy of compound digestive enzyme therapy. Although this study confirmed a significant correlation between PGI, PGII, VIP, and PRDX1 and the efficacy of compound digestive enzymes, the clinical operational threshold has not been defined, which limits the direct application of the model. For example, the PGI/PGII ratio is commonly used to

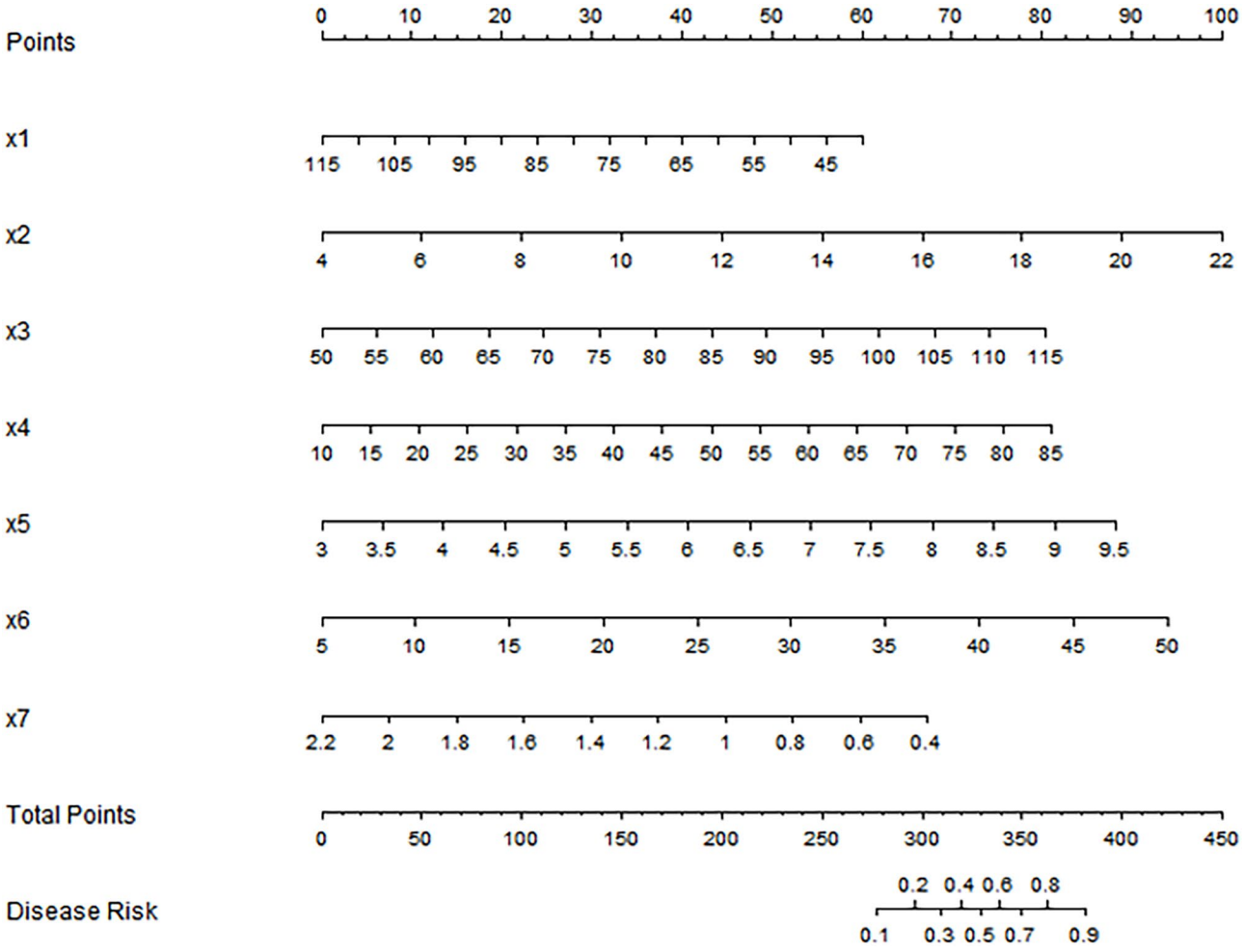

Fig. 1 Nomogram prediction model for therapeutic effects of compound digestive enzymes in patients with functional dyspepsia. Note: x1: PGI; x2PGII; x3: VIP; x4; PRDX1; X5: WBC count; X6: AST x7: high density lipoprotein cholesterol. Note: The higher the total score, the higher the predicted probability on the vertical axis, indicating a greater likelihood that the patient will not respond to compound digestive enzyme treatment. Note: PGI = Pepsinogen I; PGII = Pepsinogen II; VIP = Vasoactive Intestinal Peptide; PRDX1 = Peroxiredoxin 1;WBC count = White Blood Cell Count; AST = Aspartate Aminotransferase; HDL-C = High-Density Lipoprotein Cholesterol

evaluate the degree of gastric mucosal atrophy, but there is currently a lack of specific cutoff values for enzyme therapy response in FD patients; The median PGI in the ineffective treatment group in this study was 65.2 ng/mL (Q1-Q3: 52.1–78.4), and PGII was 14.3 ng/mL (Q1-Q3: 11.2–17.5), but these values need to be validated for their discriminatory efficacy in a larger sample. For VIP and PRDX1, existing literature has not established threshold criteria related to FD treatment outcomes. This study found that when VIP ≥ 55 pg/mL, the risk of ineffective treatment increased by 1.82 times (95% CI: 1.23–2.69); When PRDX1 ≥ 2.1 ng/mL, OR = 1.67(95% CI: 1.09–2.55), But the stability of these critical values requires further calibration with multi center data. Future research needs to combine ROC curve optimization analysis or clinical decision curve (DCA) to determine the optimal cutoff values for each biomarker, in order to enhance the clinical practicality of the model. In addition, predictive models that integrate biomarker combinations (such as column chart total score thresholds) also need to clearly divide risk stratification, providing more intuitive reference for clinical doctors to develop personalized treatment plans.

PGI and PGII in the pepsinogen family are mainly secreted by the main cells of the gastric body and fundus, mucous neck cells, as well as the pyloric gland of the gastric antrum and the Brunner gland of the duodenum [9]. Under normal circumstances, PGI and PGII maintain relatively stable levels. Once PGI decreases, it may indicate a dysfunction in the secretion function of the gastric body and gastric fundus mucosa, leading to insufficient basal secretion of digestive enzymes in the stomach [10]. Even if compound digestive enzymes are supplemented, it may still be difficult to fully exert the effects of the medication due to the damaged digestive environment in the stomach. The elevation of PGII is often closely related

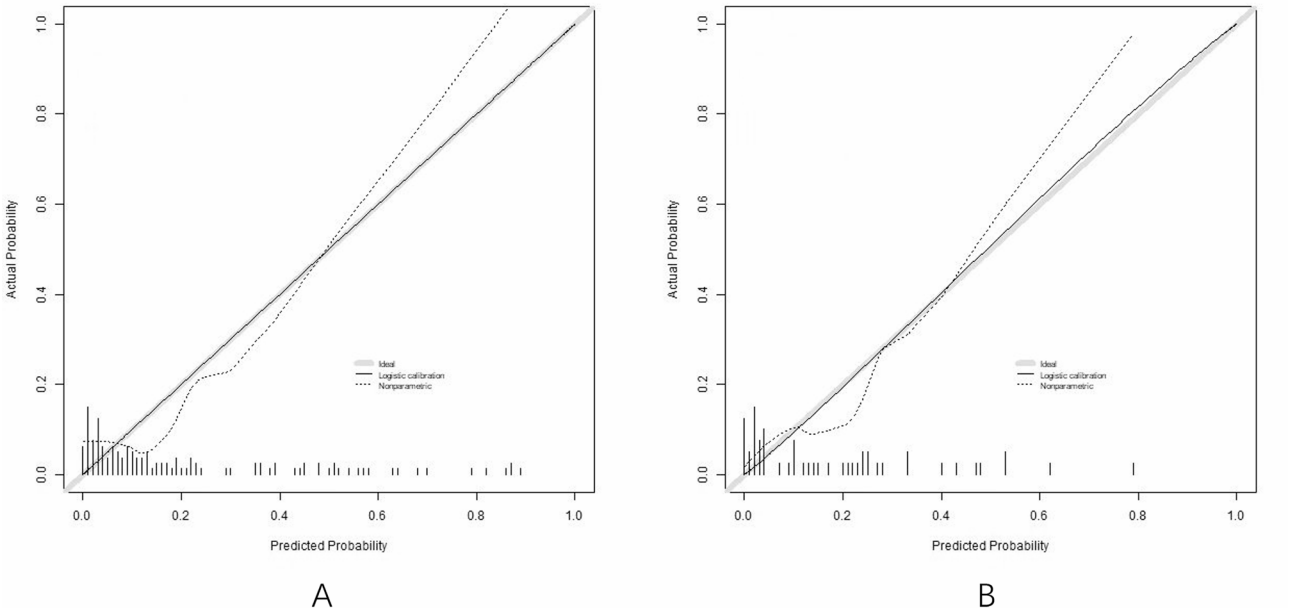

Fig. 2 Calibration curve (**A** is the training set, and **B** is the verification set)

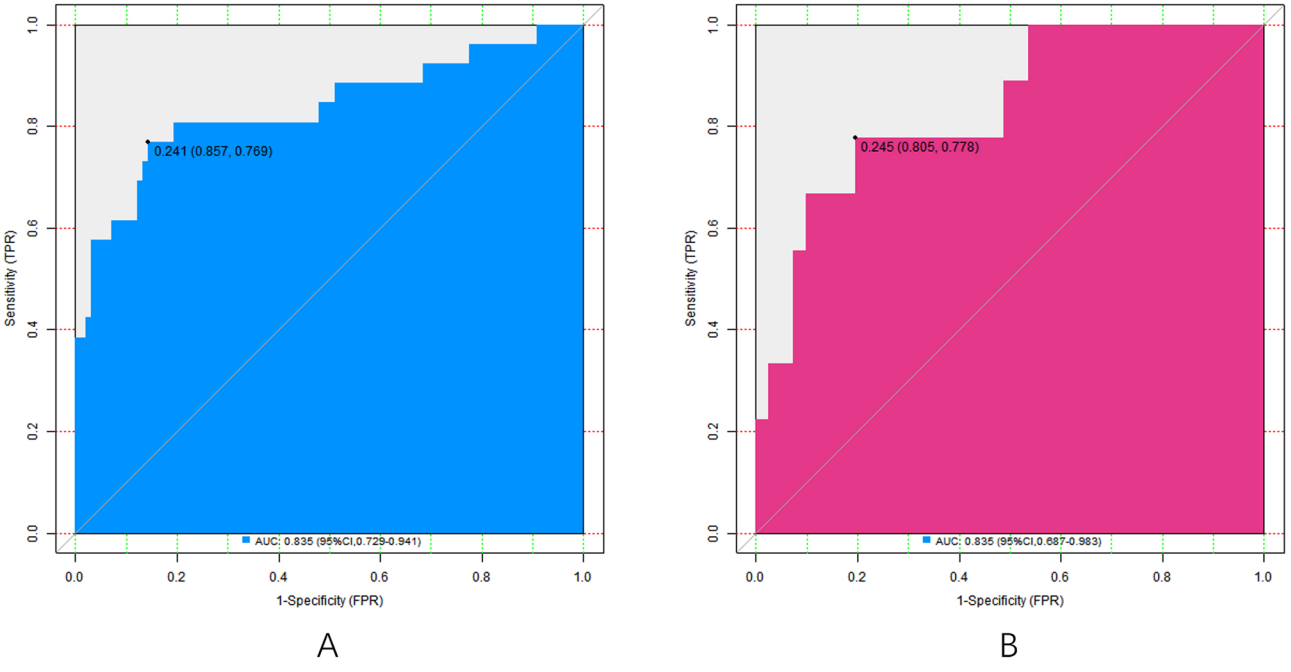

Fig. 3 ROC curve (**A** is the training set, and **B** is the verification set)

to pathological changes such as inflammation and atrophy of the gastric mucosa. These lesions of the gastric mucosa may disrupt the normal digestive microenvironment, interfere with the effective contact and action of compound digestive enzymes with food, and ultimately affect the therapeutic effect [11].

VIP, as an important neurotransmitter, is widely distributed in the gastrointestinal tract, and its abnormal elevation is clearly associated with gastrointestinal motility disorders in FD patients [12]. VIP activates VIP receptors (VPAC1/VPAC2) on smooth muscle cells, promoting the activation of the cAMP/PKA signaling pathway, leading to a decrease in the frequency of smooth muscle relaxation and peristalsis in the gastrointestinal tract [13]. In this study, elevated VIP levels may interfere with the efficacy of compound digestive enzymes through the following mechanisms: firstly, slowing down gastrointestinal peristalsis prolongs the emptying time of

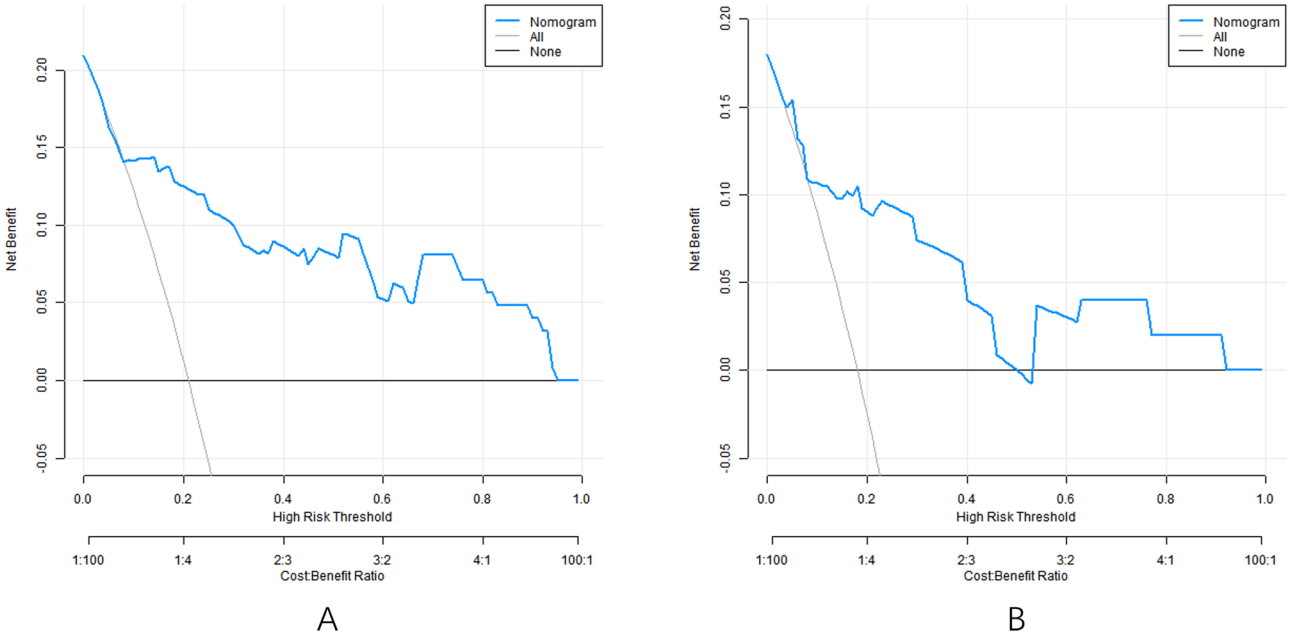

Fig. 4 Decision curve (**A** is the training set, and **B** is the verification set)

food in the stomach, resulting in insufficient contact time between compound digestive enzymes and food, which cannot fully exert their role in decomposing carbohydrates, proteins, and fats. Secondly, VIP can inhibit the secretion of gastric acid and pepsinogen, weaken the initial digestive capacity in the stomach, and thus affect the synergistic effect of compound digestive enzymes in the intestine [14]. In addition, VIP can also regulate intestinal mucus secretion, and abnormal changes in mucus layer thickness or composition may hinder the diffusion of enzyme molecules to substrates, reducing digestion efficiency [15]. It is worth noting that VIP has a bidirectional regulatory effect with inflammatory factors (such as IL-1 β), and its elevated levels may further exacerbate the inflammatory microenvironment of the gastrointestinal tract, forming a vicious cycle of 'motility disorders inflammation enzyme reduction'.

PRDX1, as an important member of the peroxidase reductase family, is closely related to oxidative stress and inflammatory response in FD patients [16]. Under normal circumstances, PRDX1 maintains the redox homeostasis of gastrointestinal mucosa by clearing reactive oxygen species (ROS) such as hydrogen peroxide. However, changes in the gut microenvironment of FD patients, such as dysbiosis of the gut microbiota and impaired mucosal barrier function, can induce compensatory elevation of PRDX1, but its antioxidant capacity is still insufficient to neutralize excessive ROS. Research has shown that the sustained accumulation of ROS can activate the NF - κ B signaling pathway, causing infiltration of inflammatory cells (such as macrophages and neutrophils) in the intestinal mucosal lamina propria, leading to the release of pro-inflammatory factors such as IL-6 and TNF - α [17]. These inflammatory mediators not only directly inhibit the activity of digestive enzymes such as pepsin and trypsin, but also damage the mitochondrial function of gastrointestinal epithelial cells, reduce cellular energy supply, and indirectly weaken the catalytic efficiency of compound digestive enzymes [18]. In addition, overexpression of PRDX1 can upregulate the activity of matrix metalloproteinases (MMPs), accelerate the degradation of the gastrointestinal mucosal basement membrane, disrupt the binding sites between digestive enzymes and substrates, and ultimately affect the therapeutic effect of compound digestive enzymes.

White blood cell count, aspartate aminotransferase, and high-density lipoprotein cholesterol are also associated with the therapeutic effect of compound digestive enzymes. As a commonly used biomarker of inflammatory response, an increase in white blood cell count usually reflects the presence of infectious or non infectious inflammation in the body. This inflammation may not only affect the normal peristalsis and secretion of digestive fluids in the gastrointestinal tract, but also lead to congestion and edema of the gastrointestinal mucosa, further damaging the digestive environment [19]. AST mainly exists in liver cells and myocardial cells, and elevated serum AST levels indicate liver cell damage or changes in cell membrane permeability. As an important metabolic organ in the human body, liver dysfunction may affect the synthesis, metabolism, and regulation of digestive enzymes, indirectly affecting the effectiveness of compound digestive enzymes in the body [20]. HDL-C is not only an important indicator of lipid metabolism, but

also has anti-inflammatory, antioxidant, and endothelial integrity maintenance functions [21]. In the gastrointestinal tract, HDL-C can maintain mucosal microenvironment homeostasis by binding endotoxins and inhibiting inflammatory cell infiltration. Low levels of HDL-C may be accompanied by a decrease in local antioxidant capacity of the intestinal mucosa, exacerbating oxidative stress damage and thereby affecting the uptake and utilization efficiency of digestive enzymes by gastrointestinal epithelial cells [22]. It should be noted that the above explanations regarding the relationship between these indicators and treatment efficacy are mostly based on association analysis and hypothetical inference of existing research, rather than confirmed causal relationships.

There are many limitations to this study: the potential role of psychological factors was not fully considered when explaining the relationship between indicators and treatment outcomes; The sample size of the validation set is only 75 cases (accounting for 30% of the total sample size), which may overestimate the model's generalization ability; As a single center retrospective study, a single sample source can easily lead to selection bias; The FD subtype was not considered as the main research factor, and different subtypes may have different pathophysiological mechanisms and treatment responses; Only evaluating short-term effects for 4 weeks, due to research design and resource limitations, follow-up was not extended, making it impossible to determine long-term efficacy and whether the same predictive factors can predict sustained remission; Important influencing factors such as gene polymorphism and gut microbiota were not included; Moreover, there is a lack of placebo or control groups, and the model only indicates a causal relationship between biomarkers and overall treatment outcomes rather than specific drug treatment effects. Overinterpretation of the results should be avoided when applying them.

This study constructed a predictive model for the therapeutic effect of compound digestive enzymes based on serum PGI, PGII, VIP, PRDX1 and other indicators in FD patients. This provides a new tool and reference for clinical doctors to predict the therapeutic effect of compound digestive enzymes in the treatment of FD. PGI, PGII VIP、PRDX1、 White blood cell count, aspartate aminotransferase, high-density lipoprotein cholesterol and other indicators are closely related to the treatment effect and can be used as important indicators to predict the treatment effect. If the column chart prediction model constructed in this study is further validated and applied in clinical practice, it will have a significant impact on the treatment decision-making of functional dyspepsia (FD). When the column chart predicts a high probability of failure of compound digestive enzyme therapy in patients due to unfavorable biomarker characteristics, clinical doctors can refer to this result to adjust treatment strategies. For example, for such patients, clinical doctors may consider alternative therapies such as prokinetic drugs to improve gastrointestinal motility, alleviate postprandial bloating, early satiety, and other symptoms; Or use neuromodulators to regulate gastrointestinal nerve function, alleviate discomfort such as abdominal pain and burning sensation; For patients with Helicobacter pylori infection, timely eradication treatment should be carried out to eliminate the impact of infection factors on digestive symptoms; In addition, dietary intervention is also an important part, guiding patients to adjust their eating habits and reduce the intake of spicy, greasy and other stimulating foods, which can help alleviate symptoms of indigestion. In addition, combination therapy is also a feasible option. Clinical doctors can combine compound digestive enzymes with other drugs in the early stages of treatment to enhance the synergistic effect of different drugs and improve treatment efficacy. For example, combining compound digestive enzymes with prokinetic drugs can not only supplement digestive enzymes to promote food digestion, but also enhance gastrointestinal motility and accelerate food emptying. By adjusting the treatment plan based on the predicted results of the column chart and avoiding ineffective single treatment attempts, personalized treatment can be provided more accurately for patients, improving treatment efficiency and quality of life, truly realizing the application of precision medicine in the treatment of functional dyspepsia. However, due to limitations such as the lack of external validation in this study, the external applicability and accuracy of the model need to be further improved. Future research should explore these issues in depth to improve the clinical practicality of the model and provide more solid support for the precise treatment of FD, thereby improving the quality of life of patients and reducing the medical burden on society.

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Author contributions
Conception and design: Jiachao Pan and Wenqiang Ren. Method: Bo Zhang. Data Collection: Bo Zhang. Manuscript Writing: Jiachao Pan. Manuscript revision: Wenqiang Ren. Research supervision: Wenqiang Ren. All authors contributed to the article and approved the submitted version.

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Data availability
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee of The Central Hospital Affiliated to Shandong First Medical University (No. 2022JCH-021532), and

informed consent was obtained from all patients. This study was conducted in accordance with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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