Prediction of Therapeutic Efficacy of Gabapentin by Hull Airway Reflux Questionnaire in Chronic Refractory Cough

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Research

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Abstract

Background

Gabapentin is recommended for the treatment of chronic refractory cough. This study aims to identify its therapeutic predictors in a prospective clinical study.

Methods

179 patients with chronic refractory cough were treated with gabapentin. Prior to the therapy, all patients were assessed by Hull Airway Reflux Questionnaire (HARQ) and inhaled capsaicin test. When the treatment ended and cough resolution was confirmed, a stepwise logistic regression analysis was performed to identify the therapeutic predictors for gabapentin and to establish the prediction equation.

Results

Gabapentin treatment achieved a therapeutic success rate of 66.5%. HARQ scores were significantly higher in responders than non-responders to gabapentin (29.79 ± 9.58 vs 21.95 ± 7.83, t = -3.685, P = 0.000), which were positively related to the therapeutic efficacy of gabapentin (r = 0.433, P < 0.01). The optimal cutoff point of 21.5 in HARQ presented with a moderate ability to predict gabapentin efficacy, with a sensitivity of 84.6% and specificity of 63.6%. Multiple logistic regression identified items of “A tickle in your throat, or a lump in your throat” (OR= 7.927, P=0.005), “Cough when you get out of bed in the morning” (OR=7.016, P=0.045) and “Cough with eating” (OR=6.689, P=0.011) as independent predictors. The established logistic regression equation predicted ³ 80% of the treatment success rate of gabapentin, which was verified by consequent preliminary revalidating study in 59 patients.

Conclusions

HARQ may be useful to screen patients with chronic refractory cough most likely responsive to gabapentin, and help improve the therapeutic success.

Trial registration

http://www.chictr.org/; No.: ChiCTR-ONC-13003123

Background

Chronic refractory cough (CRC) is a clinically significant disorder where the etiologies of chronic cough remain unknown despite comprehensive laboratory investigations or cough is resistant to subsequent specific therapies even though the causes are identified[1, 2]. It is also called as cough hypersensitivity syndrome[1–3]. The management of CRC remains a challenge.

Gabapentin, a lipophilic structural analog of the inhibitory gamma-aminobutyric acid, is a neurotransmitter widely used for the treatment of neuropathic pain[4]. Recently, gabapentin has well been

demonstrated for its antitussive effectiveness in patients with CRC[5] and has become a recommended therapy in the latest ACCP and ERS cough guidelines[2, 6]. However, its therapeutic efficacy is suboptimal since approximately 40% of patients fail to gabapentin treatment[7, 8]. Therefore, it is imperative to screen patients most likely responsive to gabapentin therapy to improve the success rate and avoid potential adverse effects.

Hull Airway Reflux Questionnaire (HARQ), a validated and patient self-administered assessment tool for cough hypersensitivity syndrome[9], has been confirmed for its diagnostic accuracy and favorable responsiveness to treatment[10–12]. We have hypothesized that the HARQ would predict the therapeutic efficacy of gabapentin in treating CRC, and investigated its usefulness in a prospective clinical study.

Methods

Patients

187 patients with CRC were recruited from our respiratory clinic between April 2014 and April 2019. According to the established step-by-step algorithm[13],CRC was only established after the other common etiologies such as cough-variant asthma, upper-airway cough syndrome, eosinophilic bronchitis and cough due to reflux were excluded by negative laboratory work-up including sinus imaging, lung function, histamine bronchial provocation, fractional exhaled nitric oxide, induced sputum cytology and esophageal impedance-pH monitoring, and subsequent failure to therapeutic trials specific to these etiologies [13]. Moreover, the participants had to be between 18 and 70 years old and without known contraindication to gabapentin. Women in pregnancy or lactation and current smokers or ex-smokers within 2 years were excluded. None of the participants had a history of acute upper respiratory tract infection during the last 2 months prior to the recruitment. The procedure of the study was approved by the Ethics Committee of Tongji Hospital (No. LL(H)-13-171) and registered with the Chinese Clinical Trials Register (http://www.chictr.org/) under the registration number ChiCTR-ONC-13003123. Written informed consent was obtained from all participants.

Gabapentin treatment

According to a gradual dose escalation schedule[8], gabapentin (Hengrui Pharmaceutical Co., Ltd., Jiangsu, China) was given with a starting dose of 100 mg, three times daily, then increased by 100 mg each time every 3 days, until a maximum dose of 900 mg daily (300 mg, three times) was reached or the side effects became intolerant. The treatment was maintained for 8 weeks in patients with a favorable response but discontinued at the end of week 4 for patients unresponsive to gabapentin. Thereafter, the patients were instructed to follow a 3-week dose reduction schedule, with a 300 mg decrease weekly, resulting in gabapentin cessation at the end of week 12.

Outcome assessment

Cough severity was evaluated by the validated Chinese version of cough symptom scores described by Hsu et al. [14], which rates daytime and nighttime cough on a six-point scale from 0 to 5 (0 indicates no cough; 5 indicates the most severe cough). The therapeutic success was defined as cough control (cough disappeared) or improvement (cough symptom score decreased by ≥50%) after gabapentin treatment[8, 15-17].

Cough sensitivity was assessed by inhaled capsaicin test and the validated Chinese version[10] of HARQ. the former was perfomed according to the protocol described by Fujimura et al. [18] but adapted to the ERS guidelines[19] and cough thresholds C2 and C5 were defined as the minimum concentration of capsaicin stimulating ≥2 or ≥5 coughs, respectively. HARQ was developed by Morice et al.[9] and consisted of 14 items involving the cough trigger or aggravating factors and concomitant symptoms. Patients were required to recall how these items (questions) affected their life in the preceding month and rate them on a 6-point scale with scores of 0-5. The total score ranges from 0 to 70. Higher HARQ scores indicate higher cough sensitivity.

Research procedure

This was a single-center observational study. After the collection of general information and evaluation of cough symptom scores, both HARQ score and cough sensitivity to capsaicin were obtained, followed by the initiation of gabapentin treatment. Patients were followed up every 2 weeks, and the therapeutic efficacy of gabapentin was assessed each time. Then, stepwise logistic regression was performed to relate the HARQ scores and its items to the therapeutic response of gabapentin. (Figure 1).

Statistical analysis

The normally distributed data were expressed as mean ± SD, whereas skewed data were represented as median (inter-quartile range). C2 and C5 were logarithmically transformed and expressed as geometric mean ± SD. For data comparisons between responders and non-responders, the unpaired student's *t*-test, chi-square test, and Mann–Whitney *U*-test were employed where applicable. Univariate regression analysis was performed to screen significant variables, then forward stepwise multiple logistic regression analysis was used to identify independent predictors for therapeutic efficacy (P_{in}=0.05 and P_{out}=0.1). Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive value of HARQ. Software (SPSS 21.0, Chicago, IL, USA) was applied for statistical calculation. A P value < 0.05 was accepted as statistically significant.

Results

Treatment efficacy

Of 187 patients with CRC meeting the inclusion criteria, 8 patients refused to participate, and 179 (95.7%) patients were recruited to receive gabapentin treatment. Their clinical characteristics are shown in

Table 1. 173 participants completed the study while 6 patients dropped out because of intolerable dizziness (n = 2) and lost follow-up (n = 4) and were recorded as failure to the therapy. The therapeutic success was achieved in 119/179 (66.5%) patients, with cough controlled in 29.1%, improved in 37.4%, and failed in 33.5% (Fig. 1). Therapeutic effects of gabapentin occurred within 1 week of treatment, maximized during the subsequent 8-week course and persisted during the dose reduction phase. Adverse effects reported by patients including somnolence (n = 31, 17.3%), dizziness (n = 23, 13.1%), fatigue (n = 19, 10.6%), nausea (n = 5, 2.8%), rash (n = 1, 0.6%) and hypomnesia (n = 1, 0.6%), were tolerable in most patients.

Table 1
Clinical characteristics of patients with chronic refractory cough

Characteristics	Value
Sex (male/female)	76/103
Age (yr)	45.7 ± 16.0[a]
Cough duration (mo)	18.0 (61.0) [b]
VAS	10.00 (1.00) [b]
Cough symptom score	
Daytime	3.00 (1.00) [b]
Nighttime	1.00 (1.00) [b]
FEV1 (% predictive value)	102.76 ± 13.49 [a]
FVC (% predictive value)	106.55 ± 16.14 [a]
FEV1/FVC (%)	82.44 ± 9.38 [a]
PD20-FEV1 < 7.8 mol (n, %)	21 (11.73%)
FeNO (ppb)	18.49 ± 12.24 [a]
Induced sputum cytology	
Eos > 2.5% (n, %)	35 (19.55%)
HARQ	25.85 ± 9.84[a]
C2	1.22 ± 6.95[c]
C5	2.26 ± 17.48[c]

a. mean ± SD; b. medians (25%-75% interquartile); c. geometric mean±SD; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; PD20-FEV1: cumulative provocative dose of histamine causing a 20% fall in FEV1; FeNO: fractional exhaled nitric oxide; Eos: eosinophils

Difference In Harq Score Between Responders And Non-responders

Responders to gabapentin rated higher HARQ scores than non-responders, especially in items including “Retching or vomiting when you cough”, “A tickle in your throat, or a lump in your throat,” “Cough with eating,” “Cough when you get out of bed in the morning,” and “Cough brought on by singing or speaking.” However, the scores of other variables were comparable between the two groups. (Table 2)

Table 2
Comparison of variables between patients responsive and non-responsive to gabapentin

Variables	responsive	unresponsive	Test results
Age (yr)	45.27 ± 15.48[a]	46.95 ± 17.88 [a]	t = 0.386,P = 0.700
Sex (male/female)	52/67	24/36	χ^2 = 0.223,P = 0.637
FEV1 (% predictive value)	104.97 ± 13.62 [a]	98.05 ± 12.33 [a]	t=-1.670,P = 0.102
FVC (% predictive value)	109.19 ± 15.32 [a]	100.93 ± 16.93 [a]	t=-1.667,P = 0.103
FEV1/FVC (%)	81.94 ± 9.21 [a]	83.51 ± 9.97[a]	t = 0.531,P = 0.598
PD20-FEV1 < 7.8 mol (n, %)	16(13.4%)	5(8.3%)	χ^2 = 1.007,P = 0.316
FeNO (ppb)	18.9 ± 13.8[a]	17.6 ± 8.35 [a]	t=-0.336,P = 0.738
Induced sputum cytology			
Eos > 2.5% (n, %)	27(22.69%)	8(13.33%)	χ^2 = 2.220,P = 0.136
Cough symptom score			
Daytime	3.00(1.00) [b]	3.00(1.00) [b]	Z=-0.775,P = 0.439
Nighttime	1.00(1.00) [a]	1.00(1.00) [a]	Z=-0.404,P = 0.686
cough threshold to inhaled capsaicin			
C2	1.33 ± 6.78[c]	0.98 ± 7.59 [c]	Z=-1.210,P = 0.226
C5	2.35 ± 17.81[c]	2.04 ± 17.09 [c]	Z=-0.481,P = 0.631

*P < 0.1; a. mean ± SD; b. medians (25–75% interquartile); c. geometric mean ± SD; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; PD20-FEV1: cumulative provocative dose of histamine causing a 20% fall in FEV1; FeNO: fractional exhaled nitric oxide; Eos: eosinophils

Variables	responsive	unresponsive	Test results
HARQ total scores	29.79 ± 9.58[a]	21.95 ± 7.83[a]	t=-3.685,P = 0.000*
Hoarseness or a problem with your voice	0.79 ± 1.11 [a]	0.77 ± 0.97 [a]	t=-0.078,P = 0.848
Clearing your throat	2.51 ± 1.73 [a]	2.14 ± 1.78 [a]	t=-0.808,P = 0.423
Excess mucus in the throat, or drip down the back of your nose	2.10 ± 1.85 [a]	2.18 ± 1.62 [a]	t = 0.168,P = 0.867
Retching or vomiting when you cough	2.23 ± 1.60 [a]	1.14 ± 0.99[a]	t=-3.300,P = 0.002*
Cough on first lying down or bending over	1.23 ± 1.69[a]	0.59 ± 1.26 [a]	t=-1.667,P = 0.099*
Chest tightness or wheeze when coughing	1.74 ± 1.50 [a]	1.14 ± 1.08 [a]	t=-1.824,P = 0.074*
Heartburn, indigestion, stomach acid coming up (or do you take medications for this, if yes score 5)	1.68 ± 1.92 [a]	1.36 ± 1.65 [a]	t=-0.655,P = 0.515
A tickle in your throat, or a lump in your throat	3.56 ± 1.35 [a]	2.41 ± 1.50 [a]	t=-3.077,P = 0.003*
Cough with eating (during or soon after meals)	2.10 ± 1.94 [a]	0.86 ± 1.39 [a]	t=-2.882,P = 0.006*
Cough with certain foods	1.90 ± 1.96 [a]	1.14 ± 1.32 [a]	t=-1.807,P = 0.076*
Cough when you get out of bed in the morning	3.21 ± 1.54 [a]	2.14 ± 1.73 [a]	t=-2.490,P = 0.016*
Cough brought on by singing or speaking (for example, on the telephone)	2.49 ± 1.59 [a]	1.68 ± 1.36 [a]	t=-2.000,P = 0.042*
Coughing during the day rather than night	2.44 ± 1.97 [a]	2.45 ± 1.85 [a]	t = 0.036,P = 0.971
A strange taste in your mouth	1.74 ± 1.79 [a]	1.09 ± 1.27 [a]	t=-1.657,P = 0.103

*P < 0.1; a. mean ± SD; b. medians (25–75% interquartile); c. geometric mean ± SD; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; PD20-FEV1: cumulative provocative dose of histamine causing a 20% fall in FEV1; FeNO: fractional exhaled nitric oxide; Eos: eosinophils

Factors Associated With The Therapeutic Efficacy Of Gabapentin

HARQ score showed a moderate positive correlation with the therapeutic efficacy of gabapentin ($r = 0.433$, $P < 0.01$). Its optimal cutoff value and discriminative item score are shown in Table 3. Among the significant factors identified by univariate logistic analysis, multivariate logistic regression revealed HARQ items of “A tickle in your throat, or a lump in your throat”, “Cough with eating” and “Cough when you get out of bed in the morning” were independent predictors of gabapentin efficacy (Table 4).

Table 3
The optimal cutoff value of factors influencing the efficacy of gabapentin on chronic refractory cough.

Variables	cut-off value	sensitivity	specificity	AUC	P value	95%CI
HARQ total scores	≥ 21.50	84.6%	63.6%	0.763	0.001	0.631–0.894
Retching or vomiting when you cough	≥ 2.50	46.2%	90.9%	0.703	0.009	0.574–0.832
A tickle in your throat, or a lump in your throat	≥ 3.50	61.5%	77.3%	0.721	0.004	0.587–0.855
Cough with eating	≥ 0.50	66.7%	63.6%	0.686	0.017	0.551–0.821
Cough when you get out of bed in the morning	≥ 1.50	82.1%	54.5%	0.678	0.022	0.532–0.824
Cough brought on by singing or speaking	≥ 2.50	69.2%	40.9%	0.651	0.052	0.511–0.790
Cough on first lying down or bending over	≥ 1.50	35.9%	86.4%	0.590	0.247	0.445–0.735
Chest tightness or wheeze when coughing	≥ 2.50	33.3%	86.4%	0.610	0.158	0.468–0.751
Cough with certain foods	≥ 3.50	28.2%	95.5%	0.611	0.154	0.470–0.752

Table 4
Univariate and multivariate logistic regression analysis of the efficacy of gabapentin on chronic refractory cough.

	Univariate			*multivariate*	
Variables	Ranges	OR(95%CI)	P value	OR(95%CI)	P value
HARQ total scores	≥ 21.50	14.403(3.135–36.005)	0.000*		
Retching or vomiting when you cough	≥ 2.50	7.418(1.852–43.744)	0.006*		
A tickle in your throat, or a lump in your throat (X_1)	≥ 3.50	10.506(2.182–23.755)	0.001*	7.927 (1.845–34.049)	0.005*
Cough with eating (X_3)	≥ 0.50	4.324(1.067–9.068)	0.038*	6.689(1.534–29.166)	0.011*
Cough when you get out of bed in the morning (X_2)	≥ 1.50	10.349(2.157–23.702)	0.001*	7.016(1.682–29.263)	0.045*
Cough brought on by singing or speaking	≥ 2.50	5.119(1.190–11.300)	0.024*		
Cough on first lying down or bending over	≥ 1.50	3.733(0.941–14.819)	0.061		
Chest tightness or wheeze when coughing	≥ 2.50	2.907(0.835–13.304)	0.088		
Cough with certain foods	≥ 3.50	9.778(1.178–81.154)	0.035*		
*P < 0.05					

Stepwise logistic regression led to a significant equation: Logit (P) = − 2.612 + 2.070X_1 + 1.948X_2 + 1.901X_3, where X_1 represented the score of “A tickle in your throat, or a lump in your throat”, X_2 represented the score of “Cough when you get out of bed in the morning ”and X_3 represented the score of “Cough with eating”. The equation accounted for the variation of 34.8% in gabapentin efficacy (Cox & Snell R^2), could screen 83.9% of subjects correctly. Its good calibration was verified by the Hosmer–Lemeshow test ($\chi^2(6) = 5.979$, P = 0.426). ROC analysis revealed a moderate area under the curve. When adopting P ≥ 0.5714, the logistic regression equation had a good ability to discriminate responders from non-responders with the sensitivity of 84.6%, the specificity of 82.6%, the positive predictive value of 76% and the negative predictive value of 89.2%, respectively. (Fig. 2).

Revalidating Prediction Equation

We preliminarily revalidated the established prediction equation in 59 patients with CRC from May 2019 and June 2020. Among 43 patients predicted to be responsive to gabapentin, cough resolution was actually achieved in 36 patients, with a therapeutic success rate of 83.7%, which was obviously superior to 12.5% (2/16) in the patients predicted to be unresponsive to gabapentin ($\chi^2 = 25.802$, $P < 0.001$).

Discussion

In the study, gabapentin eliminated or attenuated the cough in about two-thirds of patients with CRC, and achieved a comparable therapeutic success with the previous researches[5, 7, 8]. Central nervous system-related side effects were common for the therapy although they were tolerable and rarely resulted in the treatment interruption. Moreover, HARQ might be a useful predictor of the therapeutic efficacy of gabapentin in treating CRC.

Cough hypersensitivity in patients with CRC is characterized by clinical features including abnormal laryngeal sensations in the throat (laryngeal paresthesia), the exaggerated cough response to the threshold or subthreshold-level exposure to a known tussigen (hypertussia) and cough triggered by non-tussive stimuli (allotussia) [20, 21]. Therefore, to restore normal cough sensitivity and inhibit pathological cough under the premise of preserving the protective effect of cough reflex are an ideal therapeutic strategy. The rationale for gabapentin treating CRC is the similar central hypersensitivity of chronic cough to neuropathic pain and the proven efficacious effectiveness of gabapentin in chronic pain [22–25]. Our study has supported that gabapentin is an effective regimen for CRC, as indicated by a favorable response to gabapentin in the majority of recruited patients.

HARQ has originally been designed as an aid to diagnosis rather than a quality-of-life tool for cough hypersensitivity syndrome. Several lines of evidence have shown HARQ can detect cough hypersensitivity with a high sensitivity and specificity, and clearly separate the coughers from the non-coughers when adopting cutoff values as ≥ 12.75–13[9–11, 26]. However, CRC does not differ from the other common etiologies of chronic cough except for cough due to reflux in cough hypersensitivity identified by HARQ[9], reflecting a single coherent clinical entity of chronic cough[27]. In the study, we have demonstrated that HARQ may be helpful to screen patients with CRC suitable for gabapentin therapy as it had a moderate good ability to predict the therapeutic efficacy of gabapentin when adopting 21.5 as a cutoff point.

The central and peripheral components of cough hypersensitivity vary among the individual patient with chronic cough, and both can develop as a part of CRC. Considering the centrally acting nature of gabapentin, CRC patients with predominant central cough sensitization should have a higher possibility to respond to gabapentin. Although HARQ cannot definitely measure central sensitization, some items may imply central cough hypersensitivity. Itchy throat, a common trigger to cough[28], is involved in laryngeal sensory neuropathy and indicates laryngeal hypersensitivity as the sensitization of the central neural circuit helps to regulate chronic itchy sensation[29]. Therefore, it is not surprising that the HARQ items of “A tickle in your throat, or a lump in your throat” and “Cough with eating”, the respective

manifestation of laryngeal paresthesia and allotussia representing central hypersensitivity[20] scored higher in gabapentin responders than in non-responders, and were identified as two independent predictors of gabapentin efficacy. Our study has confirmed central cough hypersensitivity was a crucial factor predicting the therapeutic success of gabapentin in patients with CRC.

Gastroesophageal reflux can be a determinant of CRC since about 36% of patients with cough due to reflux are resistant to anti-reflux medicinal treatment[15] and need the neuromodulators as add-on therapy[7, 16, 30]. The underlying mechanisms include incomplete acid suppression, non-acid reflux, transient lower esophageal sphincter relaxations and esophageal hypersensitivity[30], which are generally associated with peripheral sensitization of cough reflex. However, the reflux reaching the proximal esophagus and laryngopharynx is often accompanied by laryngeal sensory neuropathy, a sign of central sensitization[31]. Despite the fact that cough due to reflux was excluded by negative findings of esophageal impedance-pH monitoring and failure to the subsequent trial of anti-reflux medicinal therapy, reflux as a precipitating factor of CRC was possible since the HARQ items of “Cough with eating” and “Cough when you get out of bed in the morning” hint airway reflux induced by gaseous reflux[32] in addition to cough hypersensitivity. When considering gabapentin resolves CRC associated with reflux[8], the two HARQ items became the therapeutic predictive factors of gabapentin has a potential reasonability.

Among the three independent predictors corresponding to HARQ items, the individual importance was almost equal. In fact, the findings in our study may reflect the multiple facets and non-prominent recognition features of central cough hypersensitivity[27]. Therefore, anyone of these factors alone is not powerful enough to select appropriate patients with CRC most likely responsive to gabapentin and to predict therapeutic success. With the established multivariate logistic regression equation, the overall prediction of the three independent factors for the therapeutic success of gabapentin can be more accurately estimated, leading to a convenient clinical decision making. When calculated P is ≥ 0.5714, more than 80% of the treatment success rate of gabapentin can predictably be achieved by the equation. By prior screen with HARQ, the treatable traits of CRC will be easy to be identified for gabapentin and the experienced adverse effects of the therapy without benefit will be minimized.

There were several limitations in the study. The cough hypersensitivity assessed by HARQ was inevitably affected by the subjectivity of the questionnaire, which limits the reliability of results. Since the determination of predictors for the therapeutic efficacy of gabapentin was performed by post-hoc analysis, we think the subjective inherence of the HARQ will not decrease the power of the conclusion because participants were blinded to the HARQ utilization, which was further supported by the preliminary results of our consequent revalidating study. Although the placebo effects of gabapentin cannot be ruled out, the study aimed to identify the therapeutic predictors of gabapentin, rather than to confirm its effectiveness in CRC. In fact, the usefulness of gabapentin for CRC has been fully established[2, 6]. The established logistic regression equation is indeed imperfect since it has only a moderate ability to predict the therapeutic success of gabapentin. However, it may significantly enhance the therapeutic efficacy of

gabapentin from 66.5–83.7%. We hope the prediction model will be persistently improved by further clinical study and practice in the future.

Conclusions

In conclusion, HARQ had a moderate ability to discriminate CRC patients responsive and unresponsive to gabapentin. Among the three independent predictors corresponding to HARQ items, the individual importance was almost equal. The established logistic regression equation predictably help achieve more than 80% of the treatment success rate of gabapentin. Therefore, HARQ might be useful to screen patients with CRC most likely responsive to gabapentin.

Abbreviations

Hull Airway Reflux Questionnaire (HARQ); Chronic refractory cough (CRC); Receiver operating characteristic (ROC).

Declarations

Ethics approval and consent to participate

The procedure of the study was approved by the Ethics Committee of Tongji Hospital (No. LL(H)-13-171) and registered with the Chinese Clinical Trials Register (http://www.chictr.org/) under the registration number ChiCTR-ONC-13003123. Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Dr. Mengru Zhang was in charge of case collection, processing and statistical analysis of data, interpretation of the results and drafting the manuscript. Dr. Qiang Chen, Ran Dong and Li Yu participated in case collection and critical review of the manuscript. Dr. Zisheng Ai involved in processing and statistical analysis of data. Dr. Xianghuai Xu was in charge of program coordination and participated in study design, and critical review and correction of the manuscript. Dr. Zhongmin Qiu was in charge of study design, and review and correction of the manuscript. All the authors approved the final version of the manuscript.

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Figures

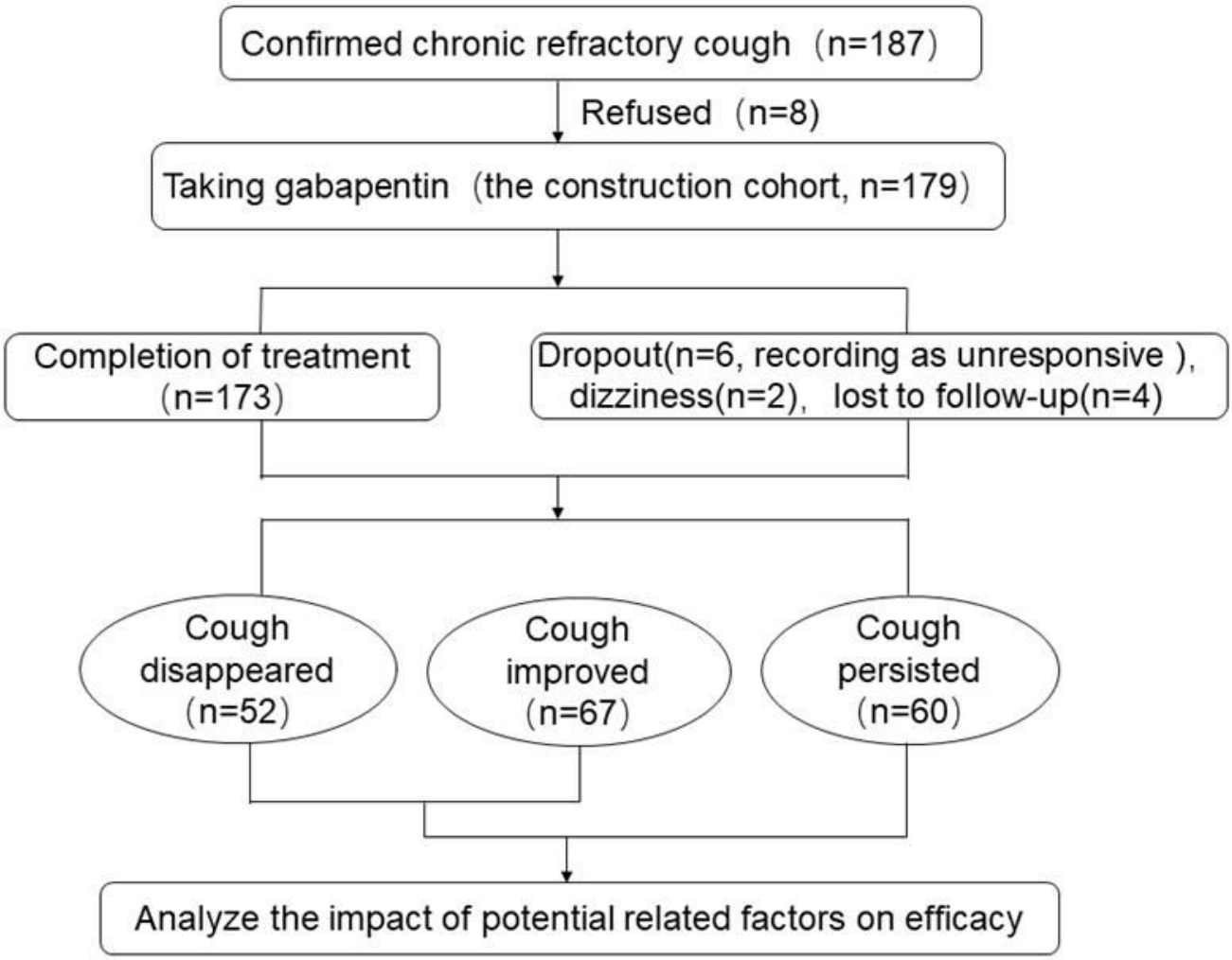

Figure 1

CONSORT (Consolidated Standards of Reporting Trials) flow diagram of this study.

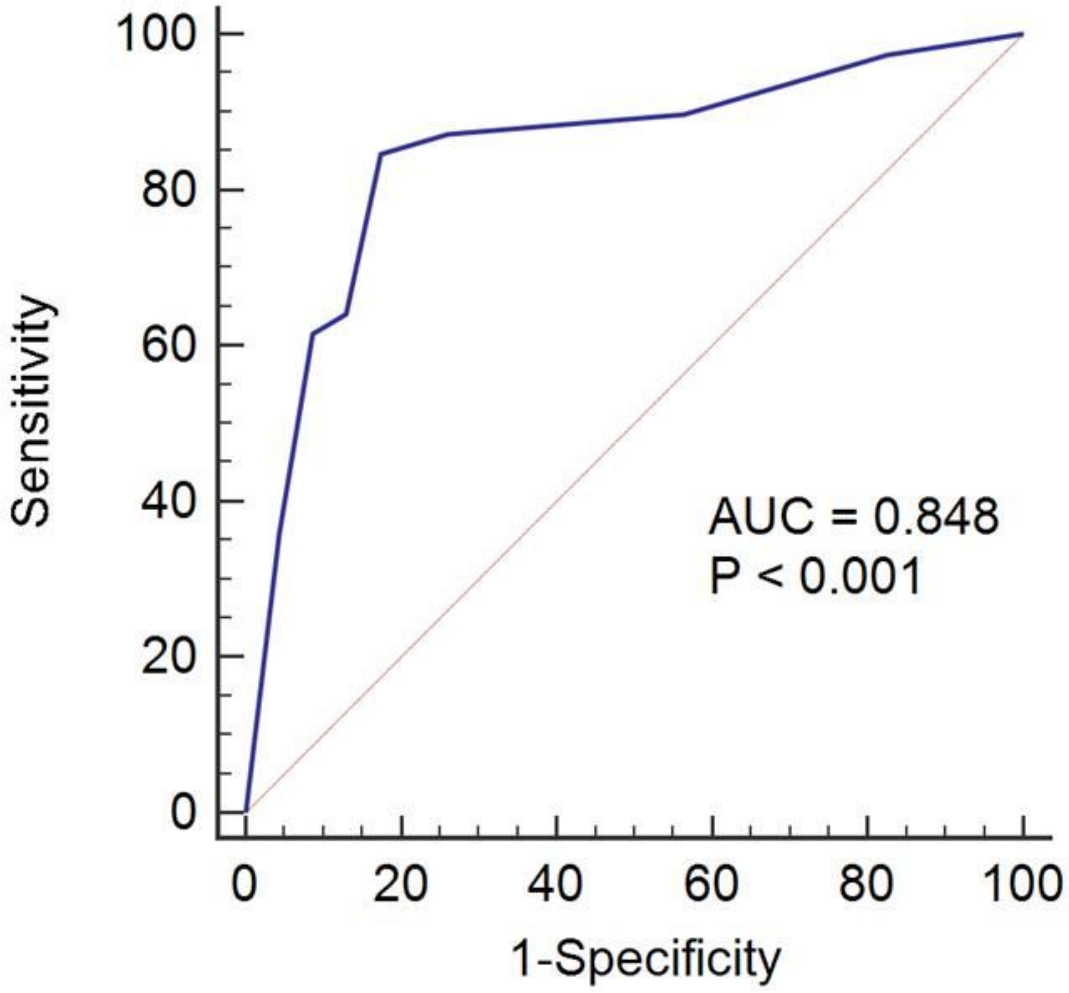

Figure 2

The internal accuracy of the logistic regression model assessed by Receiver operating characteristic (ROC) curve. The area under the curve (AUC) was 0.848 (95%CI: 0.745-0.952; P < 0.001), which indicates that for 84.8% of the paired participants (one responder, one non-responder), the responder scored higher. These results suggest that the logistic regression model used in this study had a moderate good ability to discriminate between responsive and unresponsive participants.