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Prediction of therapeutic efficacy of gabapentin by Hull Airway Reflux Questionnaire in chronic refractory cough

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Abstract

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

Methods: A total of 179 patients with CRC were treated with gabapentin. Prior to the therapy, all patients were assessed by Hull Airway Reflux Questionnaire (HARQ) and inhaled capsaicin challenge. 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 66.48%. HARQ scores were significantly higher in responders than non-responders to gabapentin (29.79 ± 9.58 *versus* 21.95 ± 7.83, $t = -3.685$, $p < 0.001$), which were positively related to the therapeutic efficacy of gabapentin ($r = 0.433$, $p < 0.001$). The optimal cutoff point of 21.50 in HARQ presented with a moderate ability to predict gabapentin efficacy, with a sensitivity of 84.60% and specificity of 63.60%. 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 83.72% of the treatment success rate of gabapentin, which was verified by consequent preliminary revalidating study in 59 patients.

Conclusion: HARQ may be useful to screen patients with CRC most likely responsive to gabapentin, and help improve the therapeutic success.

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

Keywords: chronic refractory cough, cough sensitivity, gabapentin, predictive factors, questionnaire

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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 used widely for the treatment of neuropathic pain.[4] Recently, gabapentin has well been demonstrated for its antitussive effectiveness in patients with CRC and has become a recommended therapy in the latest American College of Chest Physicians (ACCP) and European Respiratory Society (ERS) cough guidelines.[2,5,6]

However, its therapeutic efficacy is suboptimal since approximately 40% of patients fail to respond 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.

The Hull Airway Reflux Questionnaire (HARQ) – a validated and patient self-administered assessment tool for cough hypersensitivity syndrome – has been confirmed for its diagnostic accuracy and favorable responsiveness to treatment.[9–11] We 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

A total of 187 patients with CRC were recruited from our respiratory clinic between April 2014 and April 2019. According to the established step-by-step algorithm,[12] CRC was established only 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 despite the relevant supportive findings of laboratory investigations.[12] 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 intolerable. 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.*,[13] which rates daytime and nighttime cough on a 6-point scale from 0 to 5 (zero indicates no cough; five indicates the most severe cough). Therapeutic success was defined as cough control (cough disappeared) or improvement (cough symptom score decreased by $\geqslant$50%) after gabapentin treatment.[8,14–16]

Cough sensitivity was assessed by inhaled capsaicin challenge and the validated Chinese version of HARQ.[17] The former was performed according to the protocol described by Fujimura *et al.* but adapted to the ERS guidelines,[18,19] and cough thresholds C2 and C5 were defined as the minimum concentration of capsaicin stimulating $\geqslant$2 or $\geqslant$5 coughs, respectively. HARQ was developed by Morice *et al.* and becomes available for clinical use free of charge in 38 different languages on the website http://www.issc.info/.[9] It 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 of standard care. After collection of general information and evaluation of cough symptom scores, both HARQ scores 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).

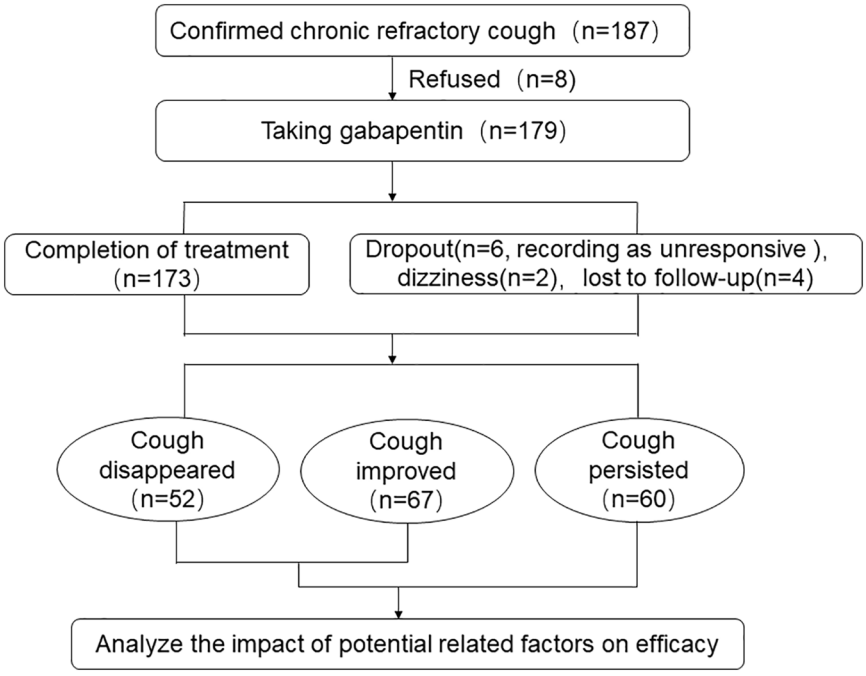

Figure 1. CONSORT flow diagram of this study.
CONSORT, consolidated standards of reporting trials

Statistical analysis

The normally distributed data were expressed as mean ± standard deviation (SD), whereas skewed data were represented as median [interquartile range (IQR)]. C2 and C5 were transformed logarithmically 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 refused to participate, and 179 (95.72%) were recruited to receive gabapentin treatment. Their clinical characteristics are shown in Table 1. A total of 173 participants completed the study while 6 dropped out because of intolerable dizziness ($n=2$) and loss to follow up ($n=4$) and were recorded as failure to the therapy. Therapeutic success was achieved in 119/179 (66.48%) patients, with cough controlled in 29.05%, improved in 37.43%, and failed in 33.52% (Figure 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. Cough relapsed in 22 patients (12.29%) within 3 weeks after cessation of therapy. Adverse effects reported by patients, including somnolence ($n=31$, 17.32%), dizziness ($n=23$, 12.85%), fatigue ($n=19$, 10.61%), nausea ($n=5$, 2.79%), rash ($n=1$, 0.56%) and hypomnesia ($n=1$, 0.56%), were tolerable in most patients.

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 1. Clinical characteristics of patients with CRC.

Characteristics	Value
Sex (male/female)	76/103
Age (years)	45.69 ± 16.01[a]
Cough duration (months)	18.00 (61.00)[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*, %) Impedance-pH monitoring	35 (19.55%)
AET > 6% (*n*, %)	24 (13.41%)
Reflux episodes per 24 h > 80 (*n*, %)	11 (6.15%)
SAP > 95% (*n*, %)	7 (3.91%)
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% IQR).
[c]Geometric mean ± SD.
AET, acid exposure time; CRC, chronic refractory cough; Eos, eosinophils; FEV1, forced expiratory volume in 1 s; FeNO, fractional exhaled nitric oxide; FVC, forced vital capacity; HARQ, Hull airway reflux questionnaire; IQR, interquartile range; PD20-FEV1, cumulative provocative dose of histamine causing a 20% fall in FEV1; ppb, parts per billion; SAP, the symptom association probability; SD, standard deviation.

Factors associated with the therapeutic efficacy of gabapentin

HARQ scores 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).

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 34.80% in gabapentin efficacy (Cox and Snell R^2), could screen 83.90% 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 (AUC). When adopting $p \geqslant 0.5714$, the logistic regression equation had a good ability to discriminate responders from non-responders with a sensitivity of 84.62%, specificity of 82.61%, positive predictive value of 76.00%, and negative predictive value of 89.19%, respectively (Figure 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 83.72%, which was obviously superior to 12.50% (2/16) in the patients predicted to be unresponsive to gabapentin ($\chi^2 = 25.802$, $p < 0.001$).

Discussion

In this study, gabapentin eliminated or attenuated the cough in about two-thirds of patients with CRC, and achieved a therapeutic success comparable with that of previous research.[5,7,8] Central nervous system-related side effects for the therapy were common but less frequent than those reported by Ryan *et al.*,[5] which can be explained by the lower dose of gabapentin used in the study. Nevertheless, the side effects were tolerable and rarely resulted in treatment interruption. Moreover, HARQ might be a useful predictor of the therapeutic efficacy of gabapentin in treating CRC.

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

Variables	Responsive	Unresponsive	Test results
Age (years)	45.27 ± 15.48[a]	46.95 ± 17.88[a]	$t = 0.386$, $p = 0.700$
Sex (male/female)	52/67	24/36	$\chi^2 = 0.223$, $p = 0.637$
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 (13.45%)	5 (8.33%)	$\chi^2 = 1.007$, $p = 0.316$
FeNO (ppb)	18.90 ± 13.80[a]	17.60 ± 8.35[a]	$t = -0.336$, $p = 0.738$
Induced sputum cytology			
Eos > 2.5% (*n*, %)	27 (22.69%)	8 (13.33%)	$\chi^2 = 2.220$, $p = 0.136$
MII-pH			
AET > 6% (*n*, %)	14 (11.76%)	10 (16.67%)	$\chi^2 = 0.826$, $p = 0.363$
Reflux episodes per 24 h >80 (*n*, %)	9 (7.56%)	2 (3.33%)	$\chi^2 = 0.345$, $p = 0.776$
SAP > 95% (*n*, %)	11 (9.24%)	4 (6.67%)	$\chi^2 = 1.237$, $p = 0.340$
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]	$Z = -0.481$, $p = 0.631$
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]	$t = -3.077$, $p = 0.003$*

(Continued)

Table 2. (Continued)

Variables	Responsive	Unresponsive	Test results
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% IQR).
[c]Geometric mean ± SD.
AET, acid exposure time; Eos, eosinophils; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; HARQ, Hull airway reflux questionnaire; IQR, interquartile range; MII-pH, Multichannel intraluminal Multichannel intraluminal Multichannel intraluminal; PD20 - FEV1, cumulative provocative dose of histamine causing a 20% fall in FEV1; ppb, parts per billion; SAP, the symptom association probability; SD, standard deviation.

Table 3. The optimal cutoff value of factors influencing the efficacy of gabapentin on CRC.

Variables	Cut-off value	Sensitivity	Specificity	AUC	*p* value	95% CI
HARQ total scores	⩾21.50	84.60%	63.60%	0.763	0.001	0.631–0.894
Retching or vomiting when you cough	⩾2.50	46.20%	90.90%	0.703	0.009	0.574–0.832
A tickle in your throat, or a lump in your throat	⩾3.50	61.50%	77.30%	0.721	0.004	0.587–0.855
Cough with eating	⩾0.50	66.70%	63.60%	0.686	0.017	0.551–0.821
Cough when you get out of bed in the morning	⩾1.50	82.10%	54.50%	0.678	0.022	0.532–0.824
Cough brought on by singing or speaking	⩾2.50	69.20%	40.90%	0.651	0.052	0.511–0.790
Cough on first lying down or bending over	⩾1.50	35.90%	86.40%	0.590	0.247	0.445–0.735
Chest tightness or wheeze when coughing	⩾2.50	33.30%	86.40%	0.610	0.158	0.468–0.751
Cough with certain foods	⩾3.50	28.20%	95.50%	0.611	0.154	0.470–0.752

AUC, area under the curve; CI, confidence interval; CRC, chronic refractory cough; HARQ, Hull airway reflux questionnaire.

Cough hypersensitivity in patients with CRC is characterized by clinical features, including abnormal laryngeal sensations in the throat (laryngeal paresthesia), exaggerated cough response to threshold or subthreshold-level exposure to a known tussigen (hypertussia), and cough

Table 4. Univariate and multivariate logistic regression analysis of the efficacy of gabapentin on CRC.

Variables	Univariate			Multivariate	
	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*		

*$p < 0.05$.
CI, confidence interval; CRC, chronic refractory cough; HARQ, Hull airway reflux questionnaire; OR, odds ratio.

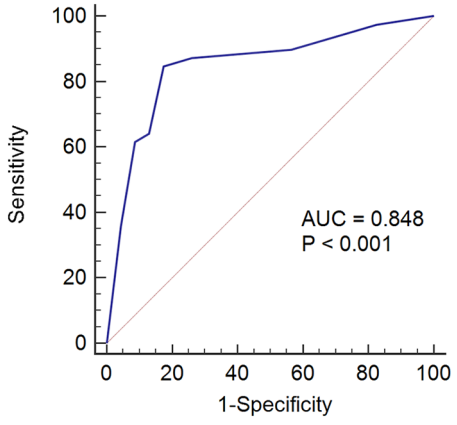

Figure 2. The internal accuracy of the logistic regression model assessed by ROC curve. The AUC was 0.848 (95% CI: 0.745–0.952; $p < 0.001$), which indicates that, for 84.8% of the paired participants (one responder, one non-responder), the responder scored higher. These results suggest that the logistic regression model used in this study had a moderate good ability to discriminate between responsive and unresponsive participants.
AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic.

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 is 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 was originally 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 coughers from non-coughers when adopting cutoff values as ⩾12.75–13.[9,10,17,26] 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-to-good ability to predict the therapeutic efficacy of gabapentin when adopting 21.50 as a cutoff point.

The central and peripheral components of cough hypersensitivity vary among individual patients 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 – is involved in laryngeal sensory neuropathy and indicates laryngeal hypersensitivity as the sensitization of the central neural circuit helps to regulate chronic itchy sensation.[28,29] 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, respectively,[20] scored higher in gabapentin responders than in non-responders, and were identified as two independent predictors of gabapentin efficacy. In contrast, the cough threshold C2 and C5 to inhaled capsaicin, which measures peripheral component of cough sensitivity, failed to present an ability to predict a favorable response to gabapentin treatment. Our study has confirmed that central rather than peripheral 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,[14] and need the neuromodulators as add-on therapy.[8,15,30] The underlying mechanisms include incomplete acid suppression, non-acid reflux, transient lower esophageal sphincter relaxations, esophageal hypersensitivity, and esophageal dysmotility,[30,31] which are generally associated with peripheral sensitization of cough reflex. However, the reflux reaching the proximal esophagus and laryngopharynx is often accompanied by abnormal laryngeal sensation – a sign of central sensitization.[32] 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, including an 8-week course of omeprazole 20 mg twice daily and domperidone 10 mg three times a day,[15] 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" strongly hint at airway reflux induced by gaseous reflux in addition to cough hypersensitivity.[33] 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, any one 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, overall prediction of the three independent factors for the therapeutic success of gabapentin can be more accurately estimated, leading to more convenient clinical decision making. When calculated p is $\geqslant 0.5714$, more than 80% of the treatment success rate of gabapentin can predictably be achieved by the equation. Prior screen with HARQ will allow the treatable traits of CRC to be identified easily for gabapentin, and experiencing adverse effects of therapy without benefit will be minimized.

A mild predominance of males in patients with chronic cough was reported in a study from Guangzhou, China.[34] On the contrary, females accounted for the majority of patients with CRC in this study. The inconsistency between the two studies may be explained by differences in patient selection due to there being only slightly more males in the cohort of patients with chronic cough.[34] Moreover, the gender distribution in the present study is in line with most studies and our previous observations. [35–37] The preponderance of the female patients with chronic cough can be attributed to the fact that women were more likely to see medical care because of embarrassment and the negative impact on quality-of-life provoked by cough-related urinary incontinence.[38]

There were several limitations to this study. 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 consider that subjective inherence of the HARQ will not decrease the power of the conclusions because participants were blinded to HARQ utilization, which was further supported by the preliminary results of our consequent revalidation study. Although the placebo effects of gabapentin cannot be ruled out, the study aimed to identify therapeutic predictors of gabapentin, rather than to again confirm its effectiveness in CRC. In fact, the usefulness of gabapentin for CRC has been fully established, leading to its recommendation for CRC treatment in clinical practice.[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 66.48% to 83.72%. We hope the prediction model will be persistently improved by further clinical study and practice in the future.

Conclusion

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, their individual importance was almost equal. The established logistic regression equation predictably helped achieve more than 80% of the treatment success rate of gabapentin. Therefore, HARQ might be useful to screen patients with CRC to identify those most likely responsive to gabapentin.

Author contributions

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

Availability of data and materials

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

Conflict of interest statement

The authors declare that there is no conflict of interest.

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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.

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Supplemental material

Supplemental material for this article is available online.

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