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• *BRIEF REPORTS* •

Applications of gray relational analysis in gastroenterology

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Abstract

AIM: To introduce the basic methods of gray relational analysis (GRA) and to illustrate its applications in gastroenterology.

METHODS: With the essential formulae of GRA and several typically practical examples, the procedure of GRA was introduced. Examples were drawn from the gastroenterological studies. Thus the trait of GRA could be demonstrated.

RESULTS: The superiority of GRA in gastroenterological study was proved by the examples.

CONCLUSION: GRA can be applied mechanically or flexibly in gastroenterology.

Key words: Gray relational analysis; Gastroenterology

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INTRODUCTION

Gray relational analysis (GRA) was initiated by Professor Ju-Long Deng, the famous scientist and founder of gray system theory, Huazhong University of Science and Technology[1]. Previous applications of GRA in medical researches were mostly in cardiology[2-7]. In our viewpoint, it is very useful to introduce GRA to gastroenterologists.

MATERIALS AND METHODS

Essential formulae of GRA

Let X be the gray relational factor set, $x_0 \in X$ be the consulting sequence, $x_i \in X$ (i = 1, 2,…, m; $m \geqslant 2$, as the comparative factors) be the comparative sequence, x_0 and x_i are named factor sequences. The $x_0(k)$ and $x_i(k)$ are the values of x_0 and x_i at k point (k = 1, 2,…, n; $n \geqslant 3$). Thus, the formulae of gray relational coefficient $\gamma(x_0(k), x_i(k))$ and gray relational grade $\gamma(x_0,x_i)$ are the following:

$$\gamma(x_0(k),x_i(k))=\frac{\min\limits_i\min\limits_k|x_0(k)-x_i(k)|+\zeta\max\limits_i\max\limits_k|x_0(k)-x_i(k)|}{|x_0(k)-x_i(k)|+\zeta\max\limits_i\max\limits_k|x_0(k)-x_i(k)|} \quad \text{and} \quad \gamma(x_0,x_i)=\frac{1}{n}\sum_{k=1}^{n}\gamma(x_0(k),x_i(k))$$

The gray relational order, based on the gray relational grade $\gamma(x_0,x_i)$ which represents the strength of relationship between x_0 and x_i, can be constructed. In the formula, $\min\limits_i\min\limits_k|x_0(k)-x_i(k)|$ and $\max\limits_i\max\limits_k|x_0(k)-x_i(k)|$ are the absolute values of the minimum and maximum from the differences between $x_i(k)$ and $x_0(k)$. $x_i(k)$ and $x_0(k)$ are the values at point k in the x_0 and x_i, the sequences without dimension. Here, ζ = 0.5.

Dis-dimension method Let $x=(x(1), x(2),…, x(n))$ be the sequence with dimension. Thus, $f: x \rightarrow \chi$,

$$f(x(k))=\frac{x(k)}{x^*}=\chi(k),\ k=1,2,k\ldots,n;\ \chi(k)\in s(1) \quad \text{where } x^*\in\left\{x(1),\max_k x(k),\min_k x(k),\frac{1}{n}\sum_{k=1}^{n}x(k)\right\};$$

Consider parameter sequence $x_i=(x_i(1),x_i(2), …,x(n))$, where i=1, 2,…,N;

$$\begin{aligned} y_{(1)} &= (x_1(1),x_2(1),\cdots,x_N(1));\\ y_{(2)} &= (x_1(2),x_2(2),\cdots,x_N(2));\\ &\cdots\cdots\\ y_{(n)} &= (x_1(n),x_2(n),\cdots,x_N(n)); \end{aligned}$$

Thus, $f: x_i \rightarrow \chi_i$, $f(x_i(k))=\dfrac{x_i(k)-\min y(k)}{\max y(k)-\min y(k)}=\chi_i(k),\chi_i(k)\in s(1).$

Here, $\max y(k)=\max\limits_i x_i(k),\ \min y(k)=\min\limits_i x_i(k),\ k\in K, K=1,2,k\ldots,n.$

Evaluation matrix of GRA Suppose $x_{0j} \in x_0$ be a group of the consulting factors, j = 1, 2,…, e. Thus, there is the gray relational matrix R about x_0 and x_i as the following:

$$\mathrm{R}(x_0,x_i)=\begin{bmatrix} \gamma(x_{01},x_1) & \gamma(x_{02},x_1) & \cdots & \gamma(x_{0e},x_1) \\ \gamma(x01_1,x_2) & \gamma(x0_2,x_2) & \cdots & \gamma(x_{0e},x_2) \\ \cdots & \cdots & \cdots & \cdots \\ \gamma(x_{0_1},x_m) & \gamma(x0_2,x_m) & \cdots & \gamma(x_{0_e},x_m) \end{bmatrix}\begin{matrix}\gamma(x_{0j},x_1)\\ \gamma(x_{0_j},x_2)\\ \cdots\\ \gamma(x_{0_j},x_m)\end{matrix}$$

GRA model of clinical trial Let $x_i \in X$, $x_i=(x_i(1), x_i(2), …, x_i(n))$ be the observing parameter sequences of group i or case i; i=1, 2,…, m, $m \geqslant 2$, as the number of trial group or trial case.

Let $x_0 \in X$, $x_0 = (x_0(1), x_0(2),…, x_0(n))$ be the ideal parameter sequence of trial, the ideal values used to construct x_0 are chosen from x_i. Here, k=1, 2,…, n, $n \geqslant 3$, as the number of parameters in the sequences. Hence, the gray relational grade $g(x_0,x_i)$ acts as the reflection of approaching the ideal effects. Then, the formulae:

$$\gamma(x_i(k),x(k))=\frac{\min\limits_i\min\limits_k|x_i(k)-x(k)|+\zeta\max\limits_i\max\limits_k|x_i(k)-x(k)|}{|x_i(k)-x(k)|+\zeta\max\limits_i\max\limits_k|x_i(k)-x(k)|} \quad \text{and} \quad \gamma(x_0,x_i)=\frac{1}{n}\sum_{k=1}^{n}\gamma(x_0(k),x_i(k))$$

are called GRA model of clinical trial.

Table 1 Baseline values in four patients before treatment

No. (k)	Age (yr) (x_1)	Course of jaundice (mo) (x_2)	Toughness degree of liver (x_3)	Liver below costal arch (cm) (x_4)	Liver below xiphoid (cm) (x_5)	Splenomegaly (cm) (x_6)
1	55	5.0	3	3	6	0
2	43	2.0	2	3	7	1
3	27	0.7	2	6	4	4
4	48	1.0	3	2	0	2

Table 2 Hepatic functions in four patients before and after albendazole treatment

No. (k)	Bilirubin (μmol/L) (x_7)		One minute bilirubin (μmol/L) (x_8)		ALP (IU) (x_9)		GOT (x_{10})		A/G (g/L) (x_{11})	
	Before	After	Before	After	Before	After	Before	After	Before	After
1	89.2	14.2	11.3	2.1	176.6	28.4	30.0	30.0	45.5/37.5	44.2/27.5
2	60.2	8.9	8.0	0.5	58.0	51.0	76.0	30.0	41.0/56.0	45.1/33.9
3	62.0	8.9	23.4	0.9	481.0	10.6	72.0	63.0	28.0/54.0	48.0/36.0
4	212.9	17.0	129.2	1.9	463.0	247.0	135.0	30.0	33.0/45.0	45.0/27.0

Examples

GRA on small sample data background The objective of this study was to evaluate the relationship between the baseline condition of patients with alveococcosis and the therapeutic effects by using albendazole regularly. Four patients with complete data who were diagnosed clinically and complicated by obstructive jaundice were enrolled in this study. Albendazole was orally given twice daily for over 1 year with a dosage of 20 mg/kg each day in all cases. Baseline values of the observation parameters are shown in Table 1. The effects of albendazole on hepatic functions are shown in Table 2.

Analysis Step 1: To calculate the improved ratio of hepatic functions. The improved ratio was calculated by using the formula:

$$r = \frac{|a - b|}{a}$$

Here, r = improved ratio, a = parameter value before treatment, b = parameter value after treatment.

The calculated values of the improved ratio are listed in Table 3.

Step 2: Correlation analysis Let x_7-x_{11} be the dependent variables, let x_1-x_6 be the independent variables, correlation analysis was performed using the statistical analysis system (version 6.12). The results of correlation analysis are shown in Table 4, indicating that the correlation between dependent variables and independent variables was not significant.

Step 3: GRA Let $x_{0j} \in x_0$ be a group of the consulting factors, j = 7, 8, 9, 10, 11 as the consulting factors, let x_1-$x_6 \in x_i$, i = 1, 2, 3, 4, 5, 6 be the comparative factors. GRA was operated by using GRA program that we edited in the statistical analysis system (version 6.12). Dis-dimension process was the averaging method. Thus, the gray relational matrix R about x_0 and x_i is as follows:

Table 3 Improved ratio of hepatic functions after treatment

k	x_7	x_8	x_9	x_{10}	x_{11}
1	0.84081	0.81416	0.83902	0.00000	0.32468
2	0.85216	0.93750	0.12069	0.60526	0.81711
3	0.98074	0.96154	0.97796	0.12500	1.57141
4	0.92015	0.98529	0.46652	0.77778	1.27274

$$R(x0_j,xi)= \begin{array}{c} \\ \gamma(x0_j,x1) \\ \gamma(x0_j,x2) \\ \gamma(x0_j,x3) \\ \gamma(x0_j,x4) \\ \gamma(x0_j,x5) \\ \gamma(x0_j,x6) \\ \\ \end{array} \begin{array}{c} \begin{array}{ccccc} \gamma(x7,xi) & \gamma(x8,xi) & \gamma(x9,xi) & \gamma(x10,xi) & \gamma(x11,xi) \end{array} \\ \begin{bmatrix} 0.83086 & 0.84450 & 0.68009 & 0.59362 & 0.68935 \\ 0.65564 & 0.63919 & 0.58232 & 0.57313 & 0.56608 \\ 0.82607 & 0.82195 & 0.68418 & 0.56399 & 0.75575 \\ 0.75198 & 0.78167 & 0.75162 & 0.49046 & 0.77538 \\ 0.66376 & 0.67106 & 0.64311 & 0.58631 & 0.52690 \\ 0.65423 & 0.65564 & 0.62717 & 0.59336 & 0.76081 \end{bmatrix} \\ \begin{array}{ccccc} 0.73042 & 0.73567 & 0.66217 & 0.56681 & 0.67905 \end{array} \end{array} \begin{array}{c} \\ 0.72768 \\ 0.60327 \\ 0.73039 \\ 0.71112 \\ 0.61823 \\ 0.65824 \\ \\ \end{array}$$

The GRA results revealed in the gray relational factor set that the superior consulting factors were x_7 and x_8, the superior comparative factors were x_1, x_3 and x_4.

GRA for four therapeutic strategies of duodenal ulcer related to Helicobacter pylori

Background The purpose of this project was to evaluate the effects of four therapeutic strategies on duodenal ulcer (DU) related to *Helicobacter pylori* (*H pylori*). Forty-nine male and nine female patients with DU were complicated by *H pylori*-positivities proved by endoscopic examination and *H pylori* test, and had no gastric or complex ulcer. Their ages were 24-62 years (average 37.1±6.5 years). All the subjects had no obvious complications or other systemic disorders. They did not take antibiotics, bismuth agents or restrain acids/antacids for 2 wk preceding the study.

Table 4 Results of correlation analysis

	x_7	x_8	x_9	x_{10}	x_{11}
x_1	−0.81774	−0.59309	−0.27907	0.10911	−0.77759
	0.1823	0.4069	0.7209	0.8909	0.2224
x_2	−0.78666	−0.98054	0.15755	−0.56181	−0.98954
	0.2133	0.0195	0.8425	0.4382	0.0105
x_3	−0.31909	−0.37737	0.15463	0.06341	−0.45498
	0.6809	0.6226	0.8454	0.9366	0.5450
x_4	0.66573	0.12652	0.63044	−0.59213	0.40379
	0.3343	0.8735	0.3696	0.4079	0.5962
x_5	−0.56410	−0.60064	−0.11905	−0.52589	−0.57561
	0.4359	0.3994	0.8810	0.4741	0.4244
x_6	0.97814	0.72219	0.38317	0.03476	0.90090
	0.0219	0.2778	0.6168	0.9652	0.0991

Note: The upper numbers are the correlation coefficients between corresponding variables and the lower numbers are the P values.

Table 5 Raw data in four groups

Group (i) / k	n	n	Disappearance of symptoms		Eradication of *H pylori*		Active mucitis fading		Ulcer cure	
			Rate (%) (1)	Time (d) (2)	n	Rate (%) (3)	n	Rate (%) (4)	n	Rate (%) (5)
A (x_1)	14	14	100	3.8	11	78.6	9/13	69.2	12	85.7
B (x_2)	15	15	100	3.6	10	66.7	9/13	69.2	11	73.3
C (x_3)	14	10	71.4[a]	6.8	11	78.6	9/12	75	9	64.3
D (x_4)	15	15	100	3.7	2	13.3[b]	3/12	25	9	60
Ideal (x_0)			100	3.6		78.6		75		85.7

[a]P<0.05, [b]P<0.01 *vs* other groups; i=A, B, C, D=1, 2, 3, 4; k=1, 2, 3, 4, 5.

Table 6 Gray relational coefficients between ideals (x_0) and other groups (x_i)

Group (i) / k	Disappearance of symptoms		Eradication of *H pylori*	Active mucitis fading	Ulcer cure
	Rate (%) (1)	Time (d) (2)	Rate (%) (3)	Rate (%) (4)	Rate (%) (5)
A (1)	1	0.9175	1	0.8481	1
B (2)	1	1	0.7328	0.8481	0.7547
C (3)	0.6302	0.4099	1	1	0.6407
D (4)	1	0.9569	0.3333	0.3932	0.6013

Materials

Step 1: Data collection Grouping and therapeutic strategies: All the subjects were randomly divided into four groups. Group A had 14 cases that were treated with a triple therapeutic strategy of tinidazole (Livzon), Lizhu Dele/colloidal bismuth subcitrate (Livzon Pharmaceutical Factory, Zhuhai) and omeprazole (Sanye Pharm). Group B had 14 cases that were treated with a triple therapeutic strategy of metronidazole (Tongji Meiji), amoxicillin (Baiyunshan, Guangzhou) and omeprazole (Sanye Pharm). Group C had 14 cases that were treated with a triple therapeutic strategy of metronidazole (Tongji Meiji), amoxicillin (Baiyunshan, Guangzhou) and De-Nol/colloidal bismuth subcitrate (Yamanouchi Europe). Group D had 15 cases that were treated with a single therapeutic strategy of omeprazole (Sanye Pharm). There were no significant differences between groups in age or sex distribution. The dose of tinidazole was 1.0 mg b.i.d, Lizhu Dele/colloidal bismuth subcitrate 110 mg q.i.d, omeprazole 20 mg q.d, amoxicillin 0.5 mg q.i.d, metronidazole 0.2 mg t.i.d, De-Nol/colloidal bismuth subcitrate 120 mg q.i.d. Lizhu Dele/colloidal bismuth subcitrate and De-Nol/colloidal bismuth subcitrate were taken orally 30 min ante cibum or before sleep. The others were taken orally 30 min post cibum. Lizhu Dele/colloidal bismuth subcitrate, De-Nol/colloidal bismuth subcitrate and omeprazole were given for 2 wk and the others for 1 wk.

Endoscopic examination and *H pylori* test All the subjects underwent endoscopic examination and *H pylori* test. After pharynx local anesthesia, gastroduodenal endoscopy was performed in all subjects taking a left lateral position by Q30 electronic endoscope system. Images were screened and rinsed, washing-cell specimen muter representatives were taken from the site of ulcer lesion during endoscopy. At normal temperature, the specimen muter representatives were put in the *H pylori* fast test box containing reagents (the PLA Higher Medical School, Lanzhou, China). After 24 h, the reagents that appeared in rose were defined as positive, and those that remained unchanged in color were defined as negative.

Estimation criteria All patients were asked to return for a check-up in a month after treatment. They were evaluated under four aspects: (1) Disappearance of symptoms (all baseline symptoms including pyrosis, epigastric pain, abdominal distension, acid suffusion and belching of gas, etc. disappeared). (2) Eradication of *H pylori* (the specimen muter representatives in *H pylori* test double boxes became negative, and one of them being positive was thought that eradication of *H pylori* infection was not achieved). (3) Active mucitis fading (the original hyperemia, erosion, edema in the duodenal mucosa were not seen endoscopically). (4) Ulcer cure (the duodenal ulcer vanished or pitted, and abated, dilated or unchanged ulcers in the ulcer area were defined as uncured).

Step 2: Raw data of four groups are listed in Table 5.

Step 3: GRA Let the ideal sequence x_0, $x_0(k) \in x_0$, k = 1, 2, 3, 4, 5, be the consulting factor sequences. Let x_i, $x_i(k) \in x_i$, i = 1, 2, 3, 4, 5, 6, be the comparative factor sequences. GRA was operated using GRA program that we edited in the statistical analysis system (version 6.12). Thus, the gray relational coefficients between x_0 and x_i are as follows (Table 6).

The gray relational grades to ideals of four groups were: γ_{0A}, i.e., γ_{01} = 0.95312; γ_{0B}, i.e., γ_{02} = 0.86712; γ_{0C}, i.e., γ_{03} = 0.73616; γ_{0D}, i.e., γ_{04} = 0.65694.

Thus the gray relational order was $x_1 > x_2 > x_3 > x_4$; i.e., strategy A $\succ$ strategy B $\succ$ strategy C $\succ$ strategy D.

GRA on serum markers of liver fibrosis

Background Serum procollagen type III (PC III), prolidase (PLD), and hyaluronic acid (HA), are of diagnostic significance in liver fibrosis. To find out the markers with early diagnostic value of liver fibrosis via GRA, 100 patients with chronic liver diseases including 28 patients with chronic persistent hepatitis (CPH), 21 patients with chronic active hepatitis (CAH), and 51 patients with liver cirrhosis (LC), were studied. Thirty HBVM-negative subjects with normal liver biochemical test served as controls. The clinical materials of the subjects are listed in Table 7.

Table 7 Clinical materials of the subjects (mean±SD)

Groups	Number of subjects	Age (yr)	Number of males
Controls	30	31.7±7.2	19
CPH	28	35.2±9.1	20
CAH	21	34.9±6.9	16
LC	51	45.1±11.4	41

Clinical materials Examination of PC III, PLD and HA PC III was assayed by using a commercially available radioimmunoassay (Chongqing Institute of Phymatosis, Chongqing). The activity of PLD was assayed by using a commercially available ultraviolet spectrophotometry (Third Military Medical University, Chongqing). Serum HA was assayed by using a commercially available radioimmunoassay (Shanghai Institute of Navy Medicine, Shanghai). PC III, PLD and HA in controls were regarded as the normal upper limits, and the sensitivity of each marker was calculated. The results are shown in Table 8.

Table 8 Sensitivity of serum PC III, PLD and HA

Marker	CPH	CAH	LC
PCIII	28.6	100.0	88.2
PLD	0.0	57.1	90.2
HA	7.1	76.2	94.2

GRA Step 1: To construct the ideal sequence The ideal sequence was constructed according to the pathological changes of liver diseases. There was no liver fibrosis in CPH, and so the sensitivity of an ideal marker value for the diagnosis of CPH should be zero. Whereas there was early liver fibrosis in CAH, and so the sensitivity of an ideal marker value for CAH should be 100%. The average value of the sensitivity of PC III, PLD and HA in LC was 90.9%, which can be chosen as the sensitivity of an ideal marker value for LC. So, the ideal sequence was x_0 = (0, 100, 90.9).

Step 2: To identify the comparative sequences The observed parameter sequences of i (i = 1, 2, 3 = sensitivity of PC III, sensitivity of PLD and sensitivity of HA) were x_i, x_1, x_2, $x_3 \in x_i$. Thus, the parameter sequences were x_1 = (28.6, 100, 88.2), x_2 = (0, 57.1, 90.2), x_3 = (7.1, 76.2, 94.2), which served as the comparative sequences. x_0, $x_i \in X$, was the GAR factor set.

Step 3: GRA operation GRA was performed using the GRA program that we edited in the statistical analysis system (version 6.12). The results were: $\gamma(x_0,x_1) = 0.7733$, $\gamma(x_0,x_2) = 0.7667$, $\gamma(x_0,x_3) = 0.7$. So the gray relational order was: $\gamma(x_0,x_1)>\gamma(x_0,x_2)>\gamma(x_0,x_3)$; i.e., $x_1 \succ x_2 \succ x_3$.

In conclusion, The GRA showing superiority to statistical methods in some cases can be applied mechanically or flexibly in gastroenterology.

DISCUSSION

Through GRA, serum PC III was identified as the marker with early diagnostic value of liver fibrosis. This example provides a new insight into the study of liver diseases and illustrates a practical application of GRA.

Since the discovery of *H pylori* in 1983, a wealth of data about DU related to *H pylori* has been accumulated, and the therapeutic strategies of duodenal ulcer have been changed. There is evidence that ulcer cure and reduction of recurrence could be achieved by effective antibiotic therapy. Such colloidal bismuth subcitrates as Lizhu Dele or De-Nol can form a protective bismuth-protein membrane which can promote healing of the ulcer and prevent recurrence of ulcer. The results of GRA showed that the gray relational order of the comprehensive effects in terms of the symptom disappearance, eradication of *H pylori*, active mucitis fading and ulcer cure is strategy A $\succ$ strategy B $\succ$ strategy C $\succ$ strategy D, and strategy A is the best of four strategies which showed no differences from the previous reports.

Alveococcosis is as harmful as a malignant tumor. Untreated cases had a 5-year mortality rate of 70% and 10-year of 93%. The severity is related to jaundice. Patients with alveococcosis had a low diagnostic and hospitalization rate. There is a shortage of clinical samples, and not suitable for statistical analysis. The first time report on alveococcosis had no statistical analysis. The GRA results indicated that jaundice parameter bilirubin and 1-min bilirubin were the superior consulting factors, which suggest the main effect of albendazole on alveococcosis. The relevant factors with severity of the disease such as age, degree of liver toughness and liver below costal arch were the superior comparative factors, which suggest that the effects of albendazole on alveococcosis were partially restricted by the baseline conditions of patients. This example provides objective evidence and demonstrates that GRA is superior to statistical analysis for small sample data.

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