Effective factors of peroral endoscopic myotomy for treatment of achalasia

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Abstract

Introduction: Achalasia (AC) is an esophageal motility disorder clinically manifested as dysphagia.
Aim: To investigate the effective factors of peroral endoscopic myotomy (POEM) for AC treatment.
Material and methods: A total of 182 AC patients treated between August 2019 and September 2020 were enrolled to receive POEM. They were assigned to an effective group (n = 143) and an ineffective group (n = 39). Their clinical data were recorded. The biochemical indices were determined.
Results: Compared with the ineffective group, the Eckardt score and incidence of reflux 1 year after the operation were lower in the effective group, and the effective rate 6 months and 1 year after the operation was higher (p < 0.05). Significant differences were observed in drinking history, Eckardt score 1 year after the operation, hemoglobin (Hb), alanine aminotransferease (ALT), white blood cells (WBC), interleukin-6 (IL-6) and high sensitivity C-reactive protein (hs-CRP) between the two groups (p < 0.05). The Eckardt score 1 year after the operation, WBC, IL-6 and hs-CRP were lower, while the levels of Hb and ALT were higher in the effective group than those in the ineffective group. Multivariate logistic analysis revealed that drinking history, Eckardt score at 1 year after the operation, Hb, ALT, WBC, IL-6, and hs-CRP were independent factors affecting the therapeutic effect of POEM on AC. The results were well fitted by evaluation discrimination and calibration of the nomogram model, with good consistency.
Conclusions: POEM is safe, feasible and effective for AC treatment, based on factors such as drinking history, Eckardt score 1 year after the operation, Hb, ALT, WBC, IL-6, and hs-CRP.

Key words: effective facto, peroral endoscopic myotomy, achalasia.

Introduction

Achalasia (AC), an esophageal motility disorder, mainly affects young and middle-aged people, clinically manifested as dysphagia, gastric juice reflux, vomiting, and weight loss [1]. The disease is caused by the absence of esophageal peristalsis and impairment of relaxation function of the lower esophageal sphincter [2–4], seriously impacting the patients' quality of life. According to current research, immunity, heredity, infection and certain inflammatory factors are associated with its initiation. However, there is a lack of specific treatment measures for AC. Drug therapies for AC mainly include calcium antagonists and nitrates, which have no obvious efficacy and do not change the course of disease, so they are rarely adopted at present. Nevertheless, in clinical surgery, peroral endoscopic myotomy (POEM), a new minimally invasive technique for submucosal myotomy through tunnel endoscopy, is feasible [5–8]. Since the application of POEM in clinical treatment of AC was reported in 2010, the postoperative symptom remission rate of patients has been high, so it has been in the spotlight [9, 10].

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Aim

The therapeutic effect of POEM in the treatment of AC has been recognized by the medical profession. However, the factors associated with the efficacy have not been reported so far. In this study, therefore, the effective factors of POEM in the treatment of AC were investigated, so as to find out the effective evidence of the treatment outcome.

Material and methods

Subjects

A total of 182 AC patients treated between August 2019 and September 2020 were enrolled to receive POEM. According to the treatment outcomes, the patients were divided into an effective group (n = 143) and an ineffective group (n = 39). In the effective group, there were 79 males and 64 females, with an age of 42.36 ±11.57 years. Their course of disease was 0.26–416 months, and their preoperative Eckardt score was 5.21 ±1.31 points. In the ineffective group, there were 25 males and 14 females, with an age of 43.04 ±10.91 years, a course of disease of 0.19–420 months, and a preoperative Eckardt score of 5.18 ±1.06 points. No significant differences were found in the general data of patients between the two groups (p < 0.05).

Effectiveness evaluation was conducted during follow-up at 1 day after the operation using the Eckardt score, which consisted of dysphagia, reflux, frequency of chest pain, and weight loss. The Eckardt score at 1 day after the operation ≤ 3 points or decreased by > 3 points compared with that before the operation indicated effectiveness; otherwise, symptom recurrence was considered.

Related criteria

The inclusion criteria involved: (1) patients with clinical symptoms and recurrent AC diagnosed by esophageal manometry, barium radiography of upper digestive tract or gastroscopy, (2) those ≥ 18 years old, and (3) those who received POEM in our hospital.

The exclusion criteria were as follows: (1) patients with incomplete clinical data, (2) those with a malignant tumor, or (3) those who could not undergo POEM due to other diseases. This study was approved by the Ethics Committee, and all the patients and their families signed the informed consent.

Observation indices

The clinical data of patients were recorded, including drinking history, Eckardt score, gender, age, course of disease, smoking history, incision length, operation time, fasting time, hospital stay, medical expenses, and histories of diabetes mellitus, hypertension and drug allergy. In addition, the biochemical indices of the patients were detected, including hemoglobin (Hb), alanine aminotransferase (ALT), white blood cell count (WBC), interleukin-6 (IL-6), hypersensitive C-reactive protein (hs-CRP), red blood cell count (RBC), triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and mean platelet volume (MPV).

Methods

Before the operation, all patients were given general anesthesia via endotracheal intubation. During the operation, a transparent cap was placed at the front end of the endoscope, and indigo carmine epinephrine saline solution was injected under the mucosa of the left wall at 8–10 cm above the cardia. After the local mucosa was fully lifted, the mucous layer was cut open with a knife (KD-620LR) to form a transverse incision, which was then separated by the knife (KD-620LR) to form a tunnel extending to 2–3 cm below the cardia. Thereafter, the esophageal circular muscle and part of the longitudinal muscle along the left wall of the esophagus in the tunnel was cut open with the knife (KD-620LR), and the fibrous membrane was kept intact. After the bleeding in the tunnel was addressed and rinsed, the entrance of the tunnel was clamped longitudinally with a metal titanium clamp. After no active bleeding was assured, the endoscope was withdrawn, followed by placement of the gastric tube [11–14] (Photo 1).

Statistical analysis

SPSS 22.0 software was utilized for statistical analysis. The measurement data were represented as x ± SD and compared by t-test. The numerical data were expressed as rate and compared by χ^2 test. A multivariate logistic regression model was employed for analysis. P < 0.05 indicated that a difference was statistically significant.
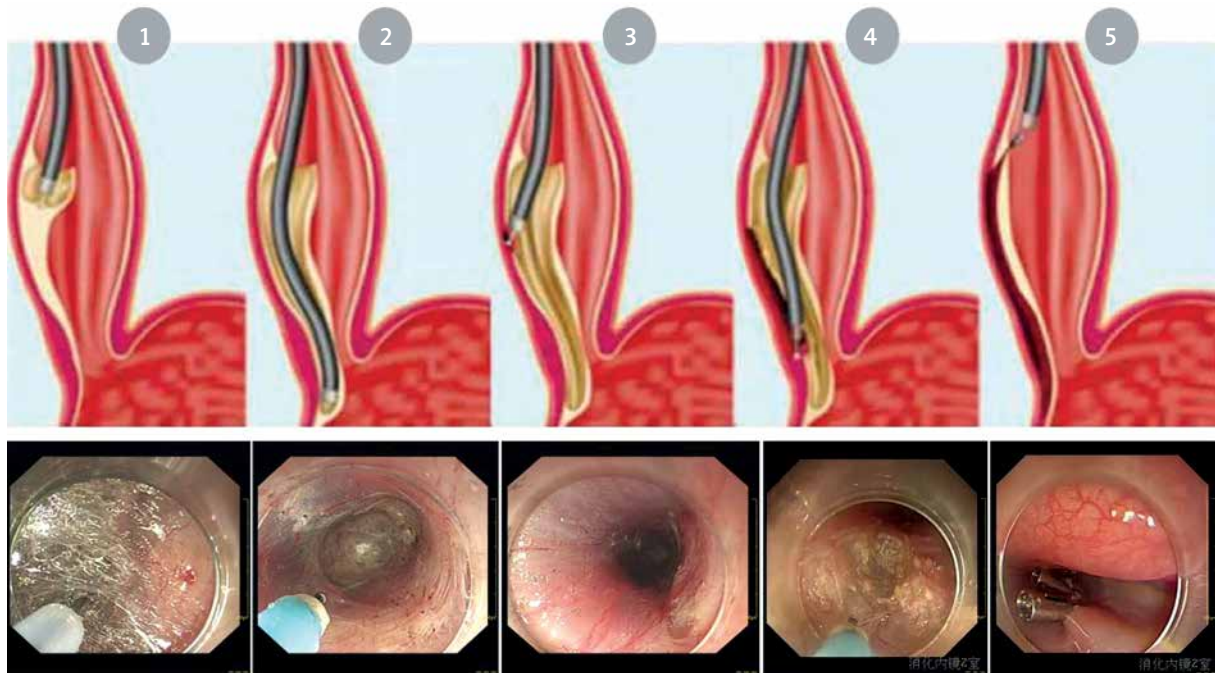
Photo 1. POEM procedure. Upper row: Schematic diagram of POEM; lower row: corresponding endoscopic views. **1** – mucosal incision; **2** – separation of submucosa and establishment of the submucosal tunnel; **3–4** – myotomy; **5** – hemostasis

POEM – peroral endoscopic myotomy.

Results

Therapeutic effects of POEM on AC

No significant difference was found in the pre-operative Eckardt score between the two groups ($p > 0.05$). There were differences in the Eckardt score and incidence of reflux at 1 year after the operation, and the effective rate at 6 months and 1 year after the operation ($p < 0.05$). Moreover, the Eckardt score and incidence of reflux at 1 year after the operation were lower in the effective group than those in the ineffective group, and the effective rate at 6 months and 1 year after the operation was higher in the effective group than that in the ineffective group (Table I).

Univariate analysis results of therapeutic effects of POEM on AC

Significant differences were observed in drinking history, Eckardt score at 1 year after the operation, Hb, ALT, WBC, IL-6 and hs-CRP between the two groups ($p < 0.05$). Also, the Eckardt score at 1 year after the operation, WBC, IL-6 and hs-CRP were lower, while the levels of Hb and ALT were higher in the effective group than those in the ineffective group.

Table I. Therapeutic effect of POEM on AC

Group	n	Eckardt score [point]		Incidence of reflux 1 year after operation (%)	Effective rate after operation (%)	
		Before operation	1 year after operation		6 months	1 year
Effective	143	5.21 ±1.31	2.52 ±0.94	21.65	81.23%	73.41%
Ineffective	39	5.18 ±1.06	3.12 ±0.84	46.12	76.15%	69.86%
t/χ^2		0.121	3.228	2.612	3.214	3.697
P-value		0.452	0.001	0.000	0.001	0.001

AC – achalasia, POEM – peroral endoscopic myotomy.

Table II. Univariate analysis results of therapeutic effects of POEM on AC

Clinical feature	Effective group (*n* = 143)	Ineffective group (*n* = 39)	t/χ^2	*P*-value
Gender:			0.982	0.322
Male	79	25		
Female	64	14		
Age [years]	42.36 ±11.57	43.04 ±10.91	0.290	0.386
Course of disease [months]	186.25 ±23.11	185.94 ±22.81	0.065	0.474
Smoking history [n (%)]:			0.001	0.126
Yes	44	12		
No	99	27		
Drinking history:			4.964	0.026
Yes	49	21		
No	94	18		
Incision length [cm]	9.24 ±0.25	9.16 ±0.18	1.761	0.056
Operation time [min]	69.21 ±10.29	68.78 ±11.06	0.193	0.423
Fasting time [days]	2.16 ±0.23	2.14 ±0.16	0.445	0.328
Hospital stay [days]	5.23 ±1.21	5.14 ±1.16	0.364	0.358
Medical expenditure (ten thousand CNY)	2.13 ±0.17	2.06 ±0.15	0.094	0.119
Eckardt score at 1 year after operation [points]	2.52 ±0.94	3.12 ±0.84	3.228	0.001
History of diabetes mellitus:			0.014	0.907
Yes	38	10		
No	105	29		
History of hypertension:			0.006	0.937
Yes	56	15		
No	87	24		
History of drug allergy:			0.013	0.910
Yes	8	2		
No	135	37		
RBC [× 10^{12}/l]	4.09 ±0.35	4.14 ±0.62	0.476	0.317
Hb [g/l]	147.69 ±12.55	121.65 ±20.36	7.384	0.000
ALT [U/l]	30.92 ±2.69	29.16 ±2.55	3.220	0.001
TG [mmol/l]	3.47 ±1.02	3.36 ±1.24	0.465	0.322
LDL [mmol/l]	2.55 ±0.80	2.57 ±0.71	0.127	0.450
HDL [mmol/l]	3.69 ±0.55	3.58 ±0.77	0.788	0.216
MPV [fl]	0.32 ±0.02	0.32 ±0.04	0.001	0.124
WBC [× 10^9/l]	9.38 ±2.64	12.16 ±1.62	6.087	0.000
IL-6 [pg/ml]	229.69 ±40.94	289.35 ±39.65	7.100	0.000
hs-CRP [mg/l])	26.69 ±5.33	32.85 ±6.94	4.774	0.000

AC – achalasia, ALT – alanine aminotransferase, Hb – hemoglobin, HDL – high-density lipoprotein, hs-CRP – hypersensitive C-reactive protein, IL-6 – interleukin-6, LDL – low-density lipoprotein, MPV – mean platelet volume, POEM – peroral endoscopic myotomy, RBC – red blood cell count, TG – triglyceride, WBC – white blood cell count.

Table III. Variable assignment

Index	Variable assignment
History of drinking	No = 0; yes = 1
Eckardt score 1 year after operation	< 2.52 points = 2; 2.52–3.12 points = 1; > 3.12 points = 0
Hb	> 147.69 g/l = 2; 121.65–147.69 g/l = 1; < 121.65 g/l = 0
ALT	> 30.92 U/l = 2; 29.16–30.92 U/l = 1; < 29.16 U/l = 0
WBC	< 9.38×10^9/l = 2; 9.38–12.16×10^9/l = 1; > 12.16×10^9/l = 0
IL-6	< 229.69 pg/ml = 2; 229.69–289.35 pg/ml = 1; > 289.35 pg/ml = 0
hs-CRP	< 26.69 mg/l = 2; 26.69–32.85 mg/l = 1; > 32.85 mg/l = 0

ALT – alanine aminotransferase, Hb – hemoglobin, hs-CRP – hypersensitive C-reactive protein, IL-6 – interleukin-6, WBC – white blood cell count.

Table IV. Results of multivariate logistic regression analysis

Factor	SE	β	Wald χ^2	OR	95% CI
Drinking history	0.447	0.124	13.009	1.564	1.124–3.241
Eckardt score 1 year after operation	0.759	0.112	45.917	2.136	1.529–3.628
Hb	0.119	0.045	6.955	1.126	1.036–3.225
ALT	0.449	0.129	12.124	1.567	1.264–3.667
WBC	0.357	0.138	6.691	1.429	1.124–3.208
IL-6	0.617	0.167	13.665	1.854	1.033–3.338
hs-CRP	0.511	0.157	10.595	1.667	1.364–3.675

ALT – alanine aminotransferase, Hb – hemoglobin, hs-CRP – hypersensitive C-reactive protein, IL-6 – interleukin-6, WBC – white blood cell count.
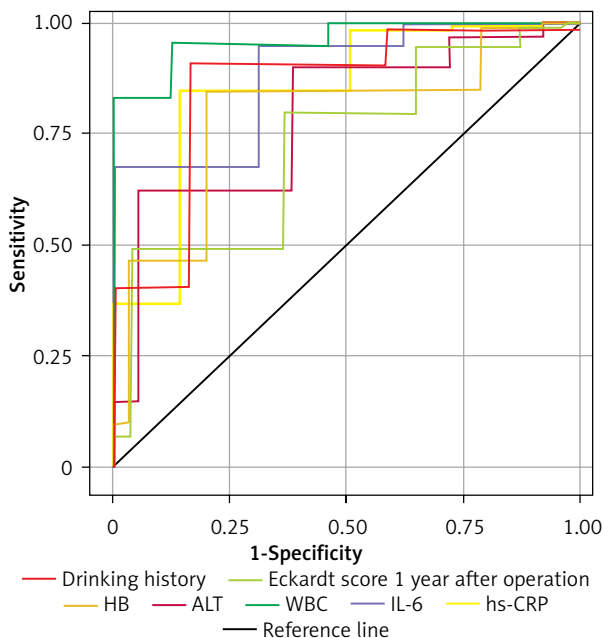

Figure 1. ROC curve of therapeutic effect of POEM on AC

AC – achalasia, POEM – peroral endoscopic myotomy, ROC – receiver operating characteristic.

Gender, age, course of disease, history of smoking, incision length, operation time, fasting time, hospital stay, medical expenses, histories of diabetes mellitus, hypertension and drug allergy, RBC, TG, LDL, HDL and MPV displayed no significant differences between the two groups ($p > 0.05$) (Table II).

Results of multivariate logistic regression analysis

The therapeutic effect of POEM on AC was taken as the dependent variable, and the factors with statistical significance ($p < 0.05$, screened out in univariate analysis) were taken as the independent variables (Table III). Multivariate logistic analysis revealed that drinking history, Eckardt score at 1 year after the operation, Hb, ALT, WBC, IL-6, and hs-CRP were independent factors affecting the therapeutic effect of POEM on AC (Table IV).

Receiver operating characteristic (ROC) curves of therapeutic effects of POEM on AC

The ROC curve of therapeutic effect of POEM on AC was plotted, and the areas under the curve

Table V. ROC curve analysis results of therapeutic effect of POEM on AC

Index	AUC	Sensitivity (%)	Specificity (%)
History of drinking	0.871	79.1	80.9
Eckardt score 1 year after operation	0.727	78.3	84.2
Hb	0.722	78.8	79.2
ALT	0.837	81.7	86.6
WBC	0.915	80.8	82.2
IL-6	0.864	78.9	82.4
hs-CRP	0.855	81.3	81.8

AC – achalasia, ALT – alanine aminotransferase, Hb – hemoglobin, hs-CRP – hypersensitive C-reactive protein, IL-6 – interleukin-6, POEM – peroral endoscopic myotomy, ROC – receiver operating characteristic, WBC – white blood cell count.

(AUCs) of drinking history, Eckardt score at 1 year after the operation, Hb, ALT, WBC, IL-6, and hs-CRP were 0.871, 0.727, 0.722, 0.837, 0.915, 0.864, and 0.855 respectively. Their sensitivity was 79.1%, 78.3%, 78.8%, 81.7%, 80.8%, 78.9%, and 81.3%, respectively, and their specificity was 80.9%, 84.2%, 79.2%, 86.6%, 82.2%, 82.4%, and 81.8%, respectively (Figure 1, Table V).

Model establishment

A nomogram model for predicting the therapeutic effect of POEM on AC was constructed based on the results of multivariate regression analysis, which demonstrated that drinking history and ALT had the greatest influence on AC patients, followed by hs-CRP, Hb, IL-6, Eckardt score at 1 year after the operation, and WBC. After the clinicopathological information of each AC patient was imported into the nomogram model, the corresponding scores were obtained from the score scale. The scores of drinking history, Eckardt at 1 year after the operation, Hb, ALT, WBC, IL-6, and hs-CRP were 22, 13, 17, 22, 13, 16, and 17 points respectively, and the value corresponding to the total score (120 points) was 60.00%, which was the effective rate of POEM on AC (Figure 2).

Calibration and discrimination of model

The discrimination and calibration of the therapeutic effect of POEM on AC were evaluated. AUC for discrimination evaluation was 0.801 (95% CI: 0.736–0.891, $p < 0.001$), so the discrimination was good (Figure 3 A). The calibration curve of the prediction model had a clear and obvious band, with a certain discrimination ($p = 0.169$). It could be seen that the prediction probability of the model was close to the actual observation probability, showing a strong consistency (Figure 3 B).

Discussion

At present, there is no gender difference in the incidence of AC, and it frequently occurs at the age of 20–40 years. Due to unclarified etiology and mechanism, the therapeutic effect varies in patients. It has been proposed that [15, 16] mental factors, viral infections, autoimmunity, genetic factors and so on can lead to different therapeutic effects, but no specific influencing factors have been put forward. Although the etiology of AC has not been clarified yet, many investigations have demonstrated that the pathogenesis of AC is probably that genetically susceptible individuals suffered inflammation and a delayed immune response due to changes in environmental factors such as viral infection. For this reason, many inflammatory and immune indicators may affect the therapeutic effect. On the other hand, AC is treated by many means, and POEM is a common surgical method for the treatment of AC, despite its incompletely clarified therapeutic mechanism [17–20]. Some researchers believe that its therapeutic mechanism may have an association with the degree of sufficient myotomy and the healing degree of tissue fibrosis [21]. According to the study of Jacobson *et al.* [10], course of disease was an independent factor influencing the therapeutic effect of AC after POEM. Since the use of POEM in clinical treatment of AC in 2010, the postoperative symptom remission rate of patients has remained high. As a result, POEM has been in the spotlight.

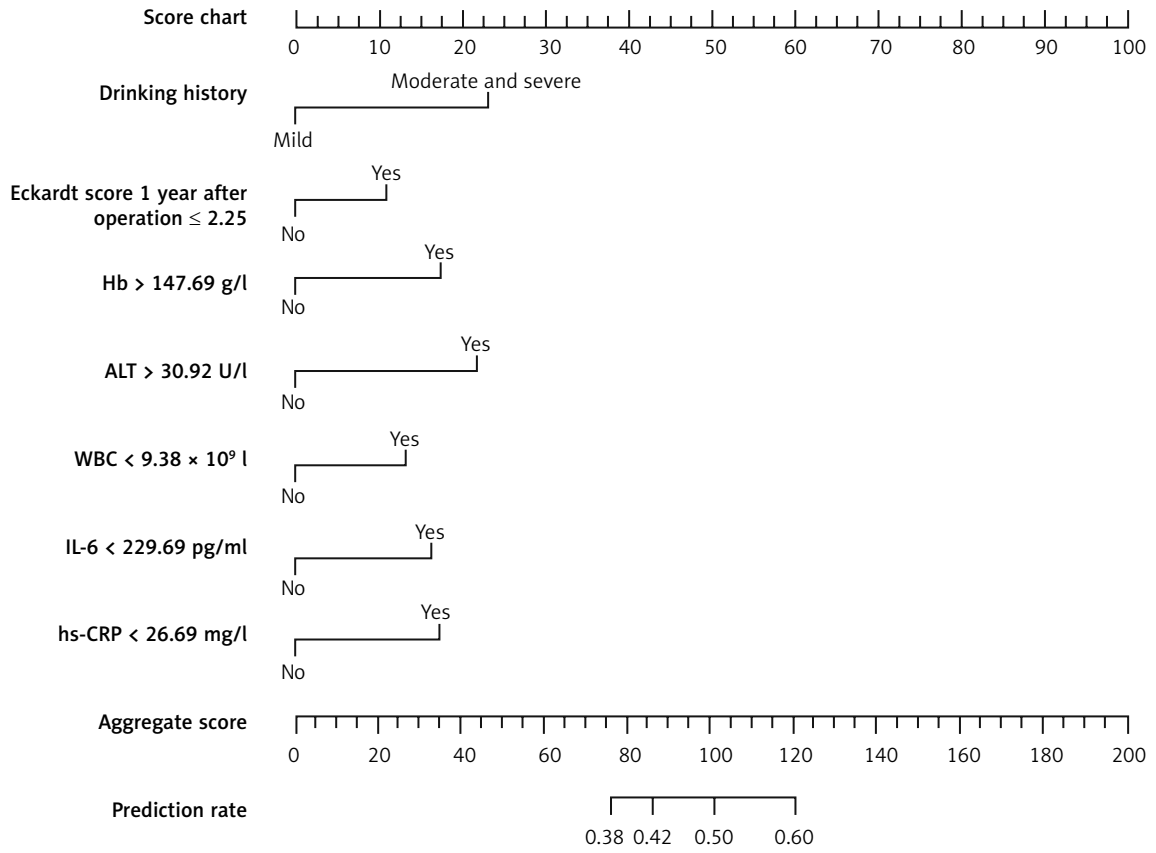In the present study, the effective factors of POEM in treating AC were investigated, and it was found

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Figure 2. Nomogram model for predicting therapeutic effect of POEM on AC

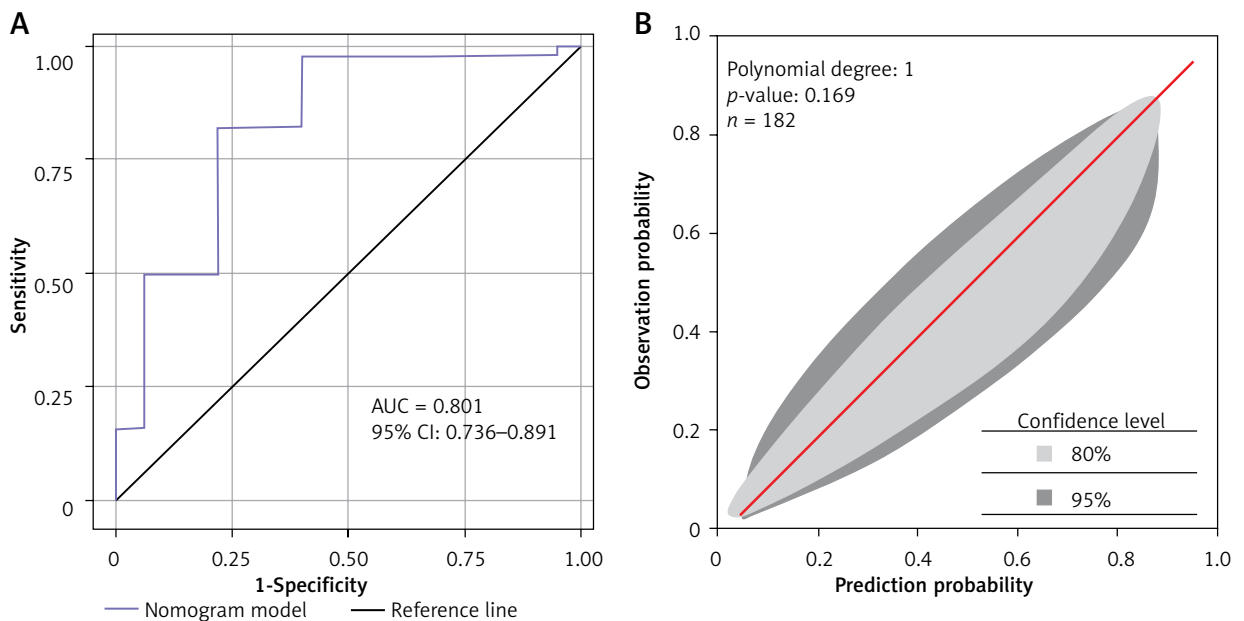*AC – achalasia, POEM – peroral endoscopic myotomy.*

Figure 3. Calibration and discrimination of model predicting therapeutic effects of POEM on AC

AC – achalasia, POEM – peroral endoscopic myotomy.

that drinking history, Eckardt score at 1 year after the operation, Hb, ALT, WBC, IL-6, and hs-CRP were independent factors affecting the therapeutic effect of POEM on AC. Patients with a history of drinking may suffer more evident neuromuscular dysfunction in the esophagus and cardia due to stimulation by ethanol. Moreover, ethanol entering the human body will severely disturb normal gastrointestinal function of the patients, causing more serious difficulty in eating. Eckardt score at 1 year after the operation can reflect the recovery of patients on the aspects of dysphagia, reflux, frequency of chest pain, and weight loss. If the score slightly declines compared with that before the operation, the recovery mechanism is destroyed, and the therapeutic effect may be limited. Hb, an item in blood routine tests, can be transported to various tissues of the whole body after combination with oxygen in the lungs. If the content of Hb is below a certain value, the oxygen carriage capability will be weakened, and normal regulation of the neuromuscular function of the esophagus and cardia will fail, so the therapeutic effect will be unsatisfactory. ALT, usually a vital index reflecting the liver function, showed a certain value for the evaluation of the therapeutic effect of AC patients in this study, which may be caused by the difference in incision means. Due to the impact on the digestive function of patients, the metabolic level was repressed, leading to decreased enzyme activity. In addition, WBC, IL-6 and hs-CRP are all associated with inflammatory factors. According to a study [22], mechanical operations in surgery may result in some inflammatory cytokines in patients, aggravating nerve injury and impeding nerve repair. Meanwhile, it was found in this study that there were differences in the Eckardt score and incidence of reflux at 1 year after the operation, and the effective rate at 6 months and 1 year after the operation ($p < 0.05$). Moreover, the Eckardt score and incidence of reflux at 1 year after the operation were lower in the effective group than those in the ineffective group, and the effective rate at 6 months and 1 year after the operation was higher in the effective group than that in the ineffective group. The ROC curve of the therapeutic effect of POEM on AC indicated that the AUCs of drinking history, Eckardt score at 1 year after the operation, Hb, ALT, WBC, IL-6 and hs-CRP were 0.871, 0.727, 0.722, 0.837, 0.915, 0.864, and 0.855, respectively, and they had high fitting degrees, so they were influencing factors for the real therapeutic effect.

In addition, a nomogram model was constructed in this study to predict the therapeutic effect of POEM on AC. The discrimination and calibration of the model were assessed, and it was found that the AUC of discrimination evaluation was 0.801 (95% CI: 0.736–0.891, $p < 0.001$), so the discrimination was good. The calibration curve of the prediction model had a clear and obvious band, with a certain discrimination ($p = 0.169$). It could be seen that the prediction probability of the model was close to the actual probability observed, showing a strong consistency. There were also some limitations in this study requiring attention and improvement in future research: (1) This is a single-center study with a relatively small sample size, so it is hoped that multi-center studies with a larger sample size can be performed later to confirm the reliability of the results of this study. (2) It is difficult to explain the time sequence and causality between influencing factors and malignant changes in this cross-sectional study, so the results require verification by cohort studies.

Conclusions

POEM is safe, feasible and effective in the treatment of AC. More clinical research is needed to evaluate the therapeutic effect of POEM based on factors such as drinking history, Eckardt score at 1 year after the operation, Hb, ALT, WBC, IL-6, and hs-CRP.

Conflict of interest

The authors declare no conflict of interest.

References

1. Schlottmann F, Patti MG. Esophageal achalasia: current diagnosis and treatment. Expert Rev Gastroenterol Hepatol 2018; 12: 711-21.
2. Nelson M, Zhang X, Genta RM, et al. Lower esophageal sphincter muscle of patients with achalasia exhibits profound mast cell degranulation. Neurogastroenterol Motil 2021; 33: e14055.
3. Laurino-Neto RM, Herbella F, Schlottmann F, et al. Evaluation of esophageal achalasia: from symptoms to the chicago classification. Arq Bras Cir Dig 2018; 31: e1376.
4. Schlottmann F, Neto RML, Herbella FAM, et al. Esophageal achalasia: pathophysiology, clinical presentation, and diagnostic evaluation. Am Surgeon 2018; 84: 467-72.
5. Shea GE, Johnson MK, Venkatesh M, et al. Long-term dysphagia resolution following POEM versus Heller myotomy for achalasia patients. Surg Endosc 2020; 34: 1704-11.
6. Schaheen LW, Sanchez MV, Luketich JD. Peroral endoscopic myotomy for achalasia. Thorac Surg Clin 2018; 28: 499-506.

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7. Schlottmann F, Luckett DJ, Fine J, et al. Laparoscopic heller myotomy versus peroral endoscopic myotomy (POEM) for achalasia: a systematic review and meta-analysis. Ann Surg 2018; 267: 451-60.

8. Feng J, Ali RW, Hao JY, et al. Peroral endoscopic myotomy for esophageal motility disorders. Esophagus 2020; 17: 11-8.

9. Ponds FA, Fockens P, Lei A, et al. Effect of peroral endoscopic myotomy vs pneumatic dilation on symptom severity and treatment outcomes among treatment-naive patients with achalasia: a randomized clinical trial. JAMA 2019; 322: 134-44.

10. Jacobson BC, Lichtenstein DR. Peroral endoscopic myotomy (POEM) vs pneumatic dilation: establishing a new therapeutic option for achalasia. JAMA 2019; 322: 119-20.

11. Cappell MS, Stavropoulos SN, Friedel D. Updated systematic review of achalasia, with a focus on POEM therapy. Dig Dis Sci 2020; 65: 38-65.

12. Lee Y, Brar K, Doumouras AG, et al. Peroral endoscopic myotomy (POEM) for the treatment of pediatric achalasia: a systematic review and meta-analysis. Surg Endosc 2019; 33: 1710-20.

13. Ichkhanian Y, Vosoughi K, Aghaie Meybodi M, et al. Comprehensive analysis of adverse events associated with gastric peroral endoscopic myotomy: an international multicenter study. Surg Endosc 2021; 35: 1755-64.

14. Mohan BP, Ofosu A, Chandan S, et al. Anterior versus posterior approach in peroral endoscopic myotomy (POEM): a systematic review and meta-analysis. Endoscopy 2020; 52: 251-8.

15. Tustumi F, Bernardo WM, da Rocha JRM, et al. Esophageal achalasia: a risk factor for carcinoma. A systematic review and meta-analysis. Dis Esophagus 2017; 30: 1-8.

16. Gillies CL, Farrukh A, Abrams KR, et al. Risk of esophageal cancer in achalasia cardia: a meta-analysis. JGH Open 2019; 3: 196-200.

17. Kroch DA, Grimm IS. POEM for Achalasia. Am J Surg 2018; 84: 489-95.

18. Onimaru M, Inoue H, Fujiyoshi Y, et al. Long-term clinical results of per-oral endoscopic myotomy (POEM) for achalasia: first report of more than 10-year patient experience as assessed with a questionnaire-based survey. Endosc Int Open 2021; 9: E409-16.

19. Holmstrom AL, Hungness ES. POEM for esophageal achalasia. J Laparoendosc Adv Surg Techn 2020; 30: 635-8.

20. Wang Y, Di Zhou WX, Ge S. Modified protocol for enhanced recovery after surgery is beneficial for achalasia patients undergoing peroral endoscopic myotomy: a randomized prospective trial. Videosurgery Miniinv 2021; 16: 656-63.

21. Crespin OM, Liu LWC, Parmar A, et al. Safety and efficacy of POEM for treatment of achalasia: a systematic review of the literature. Surg Endosc 2017; 31: 2187-201.

22. Uchima H, Colan J, Marín I, et al. Underwater peroral endoscopic myotomy (u-POEM) after tension capnoperitoneum and capnothorax during POEM. Endoscopy 2020; 52: E396-7.