International Journal of Pharmacology

ISSN 1811-7775

science alert

ansinet
Asian Network for Scientific Information

OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2023.852.861

Research Article
Establishing a Predictive Model for the Treatment Prognosis of Acute Pancreatitis Based on Biomarkers

Xiaoqing Wu, Shanshan Zhai, Desheng Chen, Chen Li and Jun Duan

Department of Intensive Care Unit, China-Japan Friendship Hospital, Beijing 100029, China

Abstract

Background and Objective: Acute pancreatitis is a common digestive system disease with poor clinical treatment effectiveness. The aim of this study was to explore the correlation between serum ApoB/ApoA1, CRP, lipase and other indicators with the severity of acute pancreatitis and to construct a predictive model for adverse prognosis risk. Person. **Materials and Methods:** The study enrolled 142 patients with acute pancreatitis (AP) who received a combination of octreotide and early enteral nutrition. Based on the follow-up results of 28 days, the patients were divided into two groups: Good prognosis and poor prognosis. Statistical analysis was conducted using SPSS 26.0. Draw a column chart model and calibration curve using the RMS package, use Stata to draw the model ROC curve and use the rmda program package in Rstudio to draw the clinical decision curve. **Results:** This study established a predictive model and the Bootstrap method resulted in a C-index of 0.884, indicating that the line chart risk prediction model has good predictive ability. The decision curve shows that the threshold probability range of the model is 0.01~1.00 and its net return rate is >0. **Conclusion:** High APACHE II score, elevated ApoB/ApoA1, elevated CRP and elevated LPS are independent risk factors for poor prognosis in AP patients treated with octreotide combined with early enteral nutrition. The risk prediction model constructed based on this has good predictive ability for poor prognosis in patients.

Key words: Acute pancreatitis, octreotide, early enteral nutrition, prognosis risk column chart prediction model

Citation : Wu, X., S. Zhai, D. Chen, C. Li and J. Duan, 2023. Establishing a predictive model for the treatment prognosis of acute pancreatitis based on biomarkers. Int. J. Pharmacol., 19: 852-861.

Corresponding Author: Jun Duan, Department of Intensive Care Unit, China-Japan Friendship Hospital, Beijing 100029, China Tel: +86-13691362130

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

Funding: This work was supported by Major epidemic prevention and control of key clinical specialty projects of Beijing (2022) (No. 2022-ZX-007).

INTRODUCTION

The incidence rate of acute pancreatitis (AP) has increased in recent years, with a case fatality rate of about 5%[1,2]. The AP mild patients account for about 80%, with mild symptoms and can recover within 7 weeks after treatment, the prognosis is relatively good and the case fatality rate is within 3%[3]. However, if the disease is delayed, it is easy to further develop to moderate severe or severe disease, inducing metabolic dysfunction and organ failure and seriously threatening the life safety of patients. Timely administration of targeted measures is crucial for the outcome and prognosis of patients. Early enteral nutrition support can avoid damage to the intestinal barrier and reduce infectious complications[4]. However, octreotide can directly protect the pancreatic parenchyma cell membrane. In addition, it is also important to improve the prediction efficacy of the prognosis of AP. When in the acute reaction period, the persistent systemic inflammatory reaction can damage the target organs and then aggravate the condition, which has been verified in clinical practice. Apolipoprotein B/Apolipoprotein A1 (ApoB/ApoA1) is a comprehensive indicator that reflects the balance of lipid metabolism and inflammation[5,6]. Studies have pointed out that C-Reactive Protein (CRP) can play an important role in body immune regulation and inflammatory response or is associated with the occurrence and development of AP[7]. Lipase (LPS) originates from pancreatic tissue, which is clinically recognized as a specific diagnostic index of AP[8]. At present, many clinical studies on ApoB/ApoA1, CRP, LPS and AP mainly analyze the relationship with the degree of disease and there are few reports on patient prognosis evaluation and the construction of relevant prediction models is rarer. Therefore, in this study, AP patients receiving octreotide combined with early enteral nutrition treatment were selected to analyze the relationship between ApoB/ApoA1, CRP, LPS and the degree of disease, explore the risk factors of the prognosis of patients with poor and build a risk prediction model, aiming to provide data support for clinical diagnosis and treatment.

MATERIALS AND METHODS

General information: A total of 142 AP patients admitted to the China-Japan Friendship Hospital from July, 2020 to July, 2023 were selected as the subjects of this study. Inclusion criteria: Meet the clinically relevant diagnostic criteria and confirmed by laboratory examination and imaging tests[9,10], with related symptoms, such as dyspepsia, abdominal pain and abdominal distension; clinical data is not missing. Exclusion criteria: With malignant tumor, vital organ insufficiency, admission over 48 hrs. This study was approved by the Ethics Committee of China-Japan Friendship Hospital. The research objects were informed and they signed a fully-informed consent form.

Treatment methods: At admission, the enrolled subjects were given symptomatic treatment, such as anti-infection, maintenance of electrolyte balance, gastrointestinal decompression and fluid resuscitation. At the same time, early enteral nutrition support was given. Under gastroscopy, the nutrition tube was placed into the jejunum through the nasal cavity and the enteral nutrition solution was infused with daily calories of 83.74 kJ/(kg/day) and nitrogen of 0.2 g/(kg/day). On this basis, jointly use octreotide (manufacturer: Novartis Pharmaceutical Co., Ltd., Approval No.: H20150364, specification content: 1 mL: 0.1 mg×5 pieces/box), 0.5 mg/day, add 250 mL normal saline mixed, 25 μg/hrs continuous intravenous pump, 1/day.

Study methods:

- Baseline data of the participants were collected, covering gender, age, Body Quality Index (BMI), underlying diseases, smoking, drinking, Acute Physiology and Chronic Health Status Score (APACHE), heart rate and blood pressure
- Determination of serological indicators level. All subjects received 5 mL of venous blood drawn on admission and centrifuged at 3000 r min^{-1} for 15 min, the supernatant was separated and stored in 80°C for testing. Automatic biochemical analyzer (LW C400), including triglyceride (TG), total cholesterol (TG), Low Density Lipoprotein (LDL) and HDL, C-Reactive Protein (CRP), ApoB and ApoA1 were measured by immunoturbidimetry and ApoB/ApoA1 ratio, LPS was determined by enzyme-linked immunosorbent test
- Follow-up prognosis. All subjects were followed for 28 days and recorded for 28 days of prognosis. Respiratory insufficiency, hypocalcemia and death can be judged as a poor prognosis. The group were divided into good prognosis and poor prognosis according to follow-up prognosis. Analyze the influencing factors of poor prognosis of AP patients with octreotide combined with early enteral nutrition therapy and construct a predictive model

Statistical analysis: Statistical analysis was performed using SPSS 26.0 lines. Count data were expressed as, line n (%) x^2 $\bar{x}\pm s$ M(P_{25}, P_{75}) Mann-Whitney U test, If the measurement data conform to normal distribution, it is expressed as (), using t-test, or non-parametric rank sum test, through univariate Logistic and multivariate Lasso regression, the independent risk factors of AP patients are analyzed by multivariate Logistic regression. Apply GraphPad Prism 8.0 to draw the model ROC curve, use the RMS package in R version 4.2.0 to draw the column chart model and calibration curve and use the RMDA program package to draw the clinical decision curve. Inspection level $\alpha = 0.05$, take both sides.

RESULTS

Outnosis of 142 AP patients: Of the 142 patients with AP, through No Octreotide combined with early enteral nutrition treatment, after 28 days of follow-up, 41 patients had a poor prognosis rate of 28.87% as shown in Table 1.

Comparison of the baseline data between the two groups: The age and APACHE scores of the two groups were different, the age and APACHE score of the poor prognosis group were higher than the good prognosis group, the difference was statistically significant ($p<0.05$) and of the BMI of the poor prognosis group was lower than the good prognosis group ($p<0.1$), besides, the other data of the two groups were not different ($p>0.05$) as shown in Table 2.

Comparison of the serological index levels between the two groups: There was no difference in TG, TC, LDL and HDL levels between the two groups ($p>0.05$) and the difference in ApoB/ApoA1, CRP and LPS between the two groups. The ApoB/ApoA1, CRP and LPS levels were higher than the good prognosis group, which was statistically significant ($p<0.05$) as shown in Table 3.

Correlation between ApoB/ApoA1, CRP and LPS and APACHE score: Pearson Correlation analysis showed that ApoB/ApoA1, CRP, LPS and APACHE score were significantly positive correlation ($p<0.05$) as shown in Table 4 and Fig. 1.

Table 1: Outnosis of 42 AP patients

Prognostic situation	n	Constituent ratio (%)
Eusemia	101	71.13
Prognosis mala	41	28.87
Respiratory insufficiency	13	9.15
Hypocalcemia	16	11.27
Die	12	8.45
Amount to	142	100.00

Component ratio refers to the percentage of people who experience various prognostic situations in the total number of people

Table 2: Comparison of the baseline data between the two patient groups

Project	Class	Group with good prognosis (n = 101)	Group with poor prognosis (n = 41)	χ^2/t	p-value
Sex	Man	57	28	1.706	0.191
	Woman	44	13		
Age/year		53.51±6.94	56.85±7.06	2.585	0.011
BMI kg m^{-2}		23.51±3.52	22.36±3.17	1.814	0.072
Hypertension	Not have	85	33	0.280	0.597
	Have	16	8		
Diabetes mellitus					
	Not have	81	30	0.844	0.358
	Have	20	11		
Coronary disease					
	Not have	99	38	2.445	0.118
	Have	2	3		
Smoking situation					
	Not have	78	28	1.230	0.267
	Have	23	13		
Drinking					
	Not have	82	29	1.868	0.172
	Have	19	12		
APACHE score		6.32±1.31	9.07±1.81	8.861	0.000
Heart rate (times min^{-1})		93.67±8.32	94.15±9.03	0.300	0.765
Systolic blood pressure (mm Hg)		120.39±13.63	122.05±15.41	0.634	0.527
Diastolic blood pressure (mm Hg)		68.33±5.97	67.85±6.54	0.416	0.678

$p<0.05$ indicates a statistical difference

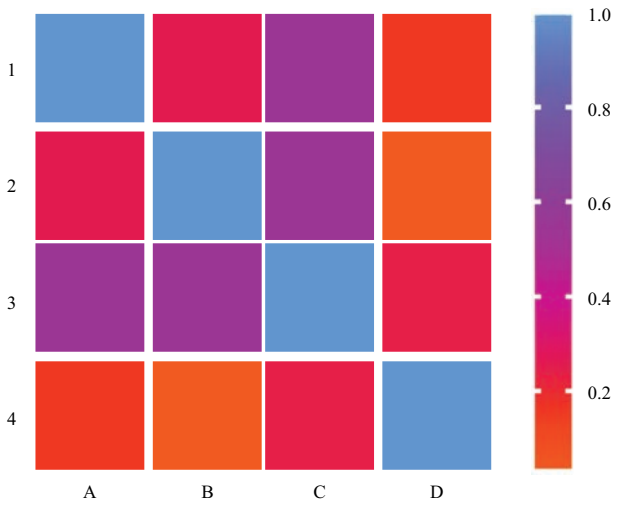

Fig. 1: Correlation matrix plot of ApoB/ApoA1, CRP and LPS and APACHE scores

Table 3: Comparison of the baseline data between the two patient groups

Project	Group with good prognosis (n =101)	Group with poor prognosis (n =41)	t	p-value
TG (mmol L^{-1})	4.59±1.11	4.64±1.19	-0.238	0.812
TC (mmol L^{-1})	4.37±0.95	4.42±1.03	-0.277	0.782
LDL (mmol L^{-1})	2.35±0.86	2.31±0.81	0.255	0.799
HDL (mmol L^{-1})	1.25±0.37	1.22±0.35	0.456	0.650
ApoB/ApoA1	0.64±0.22	0.75±0.27	2.525	0.013
CRP (mg L^{-1})	81.36±11.39	102.16±15.42	-8.863	0.000
LPS (U L^{-1})	376.71±66.28	443.85±87.56	-2.314	0.022

p<0.05 indicates a statistical difference, TG: Triglyceride, TC: Total cholesterol, LDL: Low density lipoprotein, HDL: High density lipoprotein, ApoB/ApoA1: Apolipoprotein B/Apolipoprotein A1, CRP: C-reactive protein, LPS: Lipase, ±Represents the distribution of data, that is, the distance between data points and the average value

Table 4: Correlations between ApoB/ApoA1, CRP and LPS and APACHE scores

Variable	Parameter	APACHE score	ApoB/ApoA1	CRP	LPS
APACHE score	r	1	0.251	0.544	0.198
	P		0.003	0.000	0.009
	N	142	142	142	142
ApoB/ApoA1	r	0.251	1	0.541	0.030
	P	0.003		0.000	0.724
	N	142	142	142	142
CRP	r	0.544	0.541	1	0.237
	P	0.000	0.000		0.005
	N	142	142	142	142
LPS	r	0.198	0.030	0.237	1
	P	0.009	0.724	0.005	
	N	142	142	142	142

p<0.05 indicates a statistical difference, ApoB/ApoA1: Apolipoprotein B/Apolipoprotein A1, CRP: C-reactive protein and LPS: Lipase

Patients with AP have a poor prognosis when treated with octreotide combined with early enteral nutrition univariate screening: Univariate Logistic regression analysis showed that age, BMI, APACHE score, ApoB/ApoA1, CRP and LPS may be related factors for the poor prognosis of AP patients with octreotide combined with early enteral nutrition therapy (p<0.01), as shown in Table 5. Screening by the multivariate Lasso regression model showed that the above six indicators could be included in the risk prediction model, as shown in Fig. 2 and 3.

Patients with AP have a poor prognosis when treated with octreotide combined with early enteral nutrition of the multivariate logistic-analysis: The above variables were included in the multivariate Logistic regression model and the variables were screened as "backward". The analysis showed that high APACHE score, ApoB/ApoA1, CRP and LPS were Patients with AP have a poor prognosis when treated with octreotide combined with early enteral nutrition independent risk factors (p<0.05) as shown in Table 6.

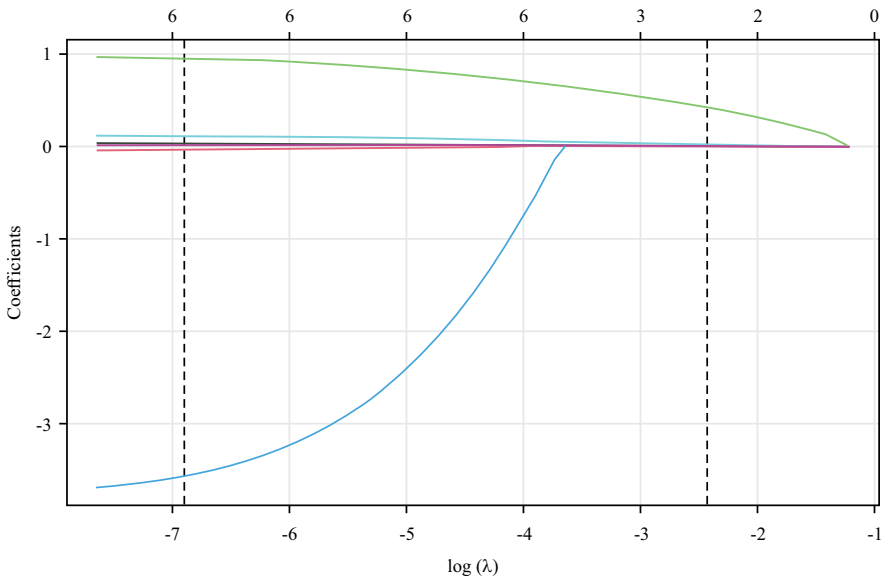

Fig. 2: Relationship between the penalty coefficient and the variables in the model

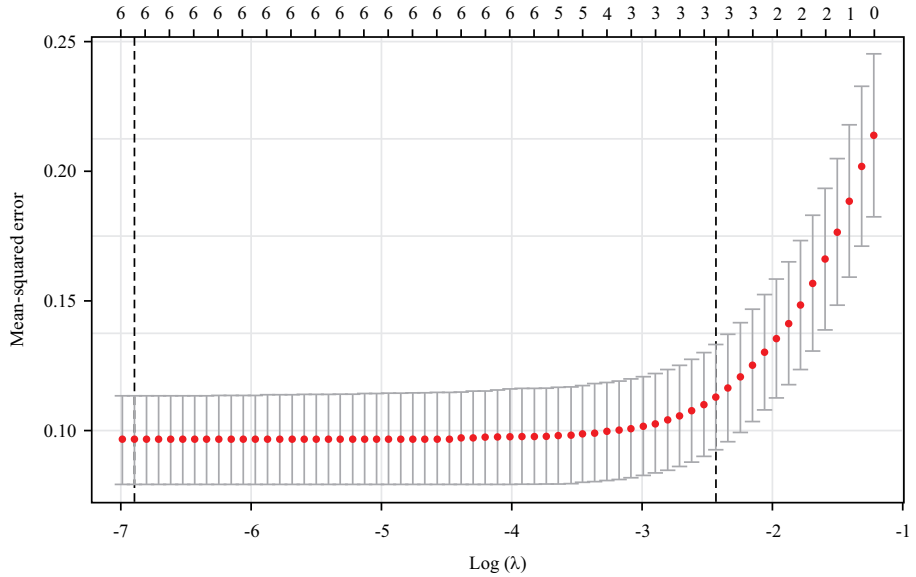

Fig. 3: Results of the multivariate Lasso regression

Table 5: Univariate logistic regression analysis of poor prognosis of AP patients with octreotide combined with early enteral nutrition therapy

Project	B	SE	OR	95% CI	Z	p-value
Age	0.073	0.029	1.075	1.075 (1.018-1.142)	2.485	0.013
BMI	-0.102	0.057	0.903	0.903 (0.803-1.007)	-1.782	0.075
APACHE grade	1.106	0.188	3.022	3.022 (2.166-4.556)	5.882	0.000
ApoB/ApoA1	2.048	0.842	7.751	7.751 (1.567-43.38)	2.432	0.015
CRP	0.127	0.022	1.136	1.136 (1.091-1.192)	5.692	0.000
LPS	0.012	0.003	1.012	1.012 (1.006-1.018)	4.053	0.000

p<0.05 indicates a statistical difference, BMI: Body mass index, ApoB/ApoA1: Apolipoprotein B/Apolipoprotein A1, CRP: C-reactive protein and LPS: Lipase

AP patients have a poor prognosis construction and calibration of the prediction model of the occurrence risk nomogram: Based on the results of multivariate Logistic analysis, the risk nomogram prediction model of poor prognosis of AP patients was constructed according to various risk factors, as shown in Fig. 4.

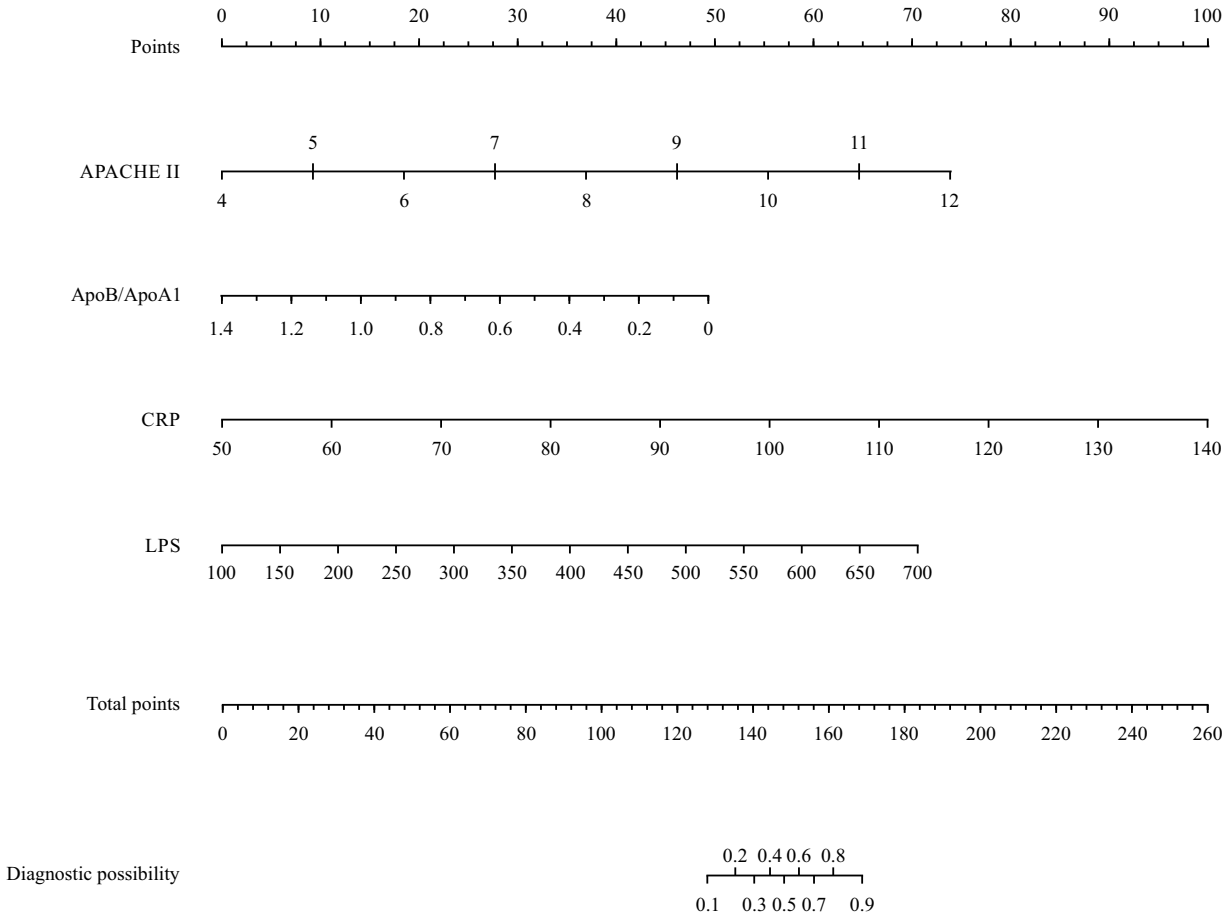

Fig. 4: Nomogram of risk of poor prognosis in AP patients with octreotide combined with early enteral nutrition

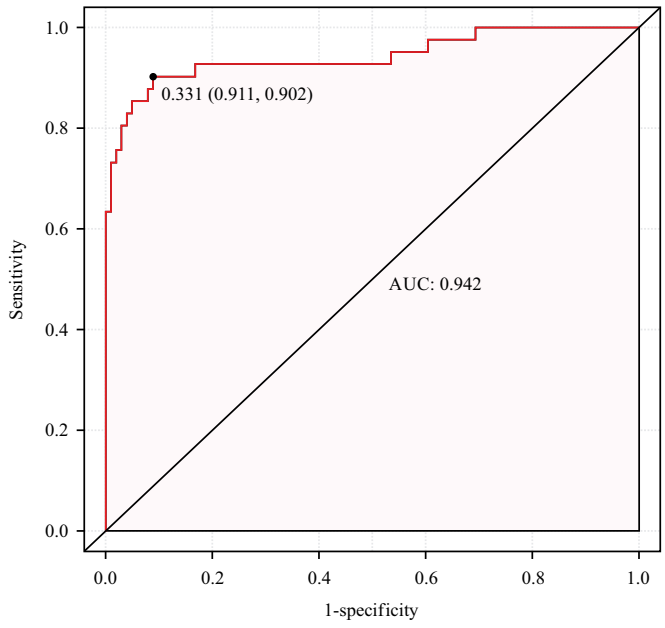

Fig. 5: ROC curves of the risk prediction model

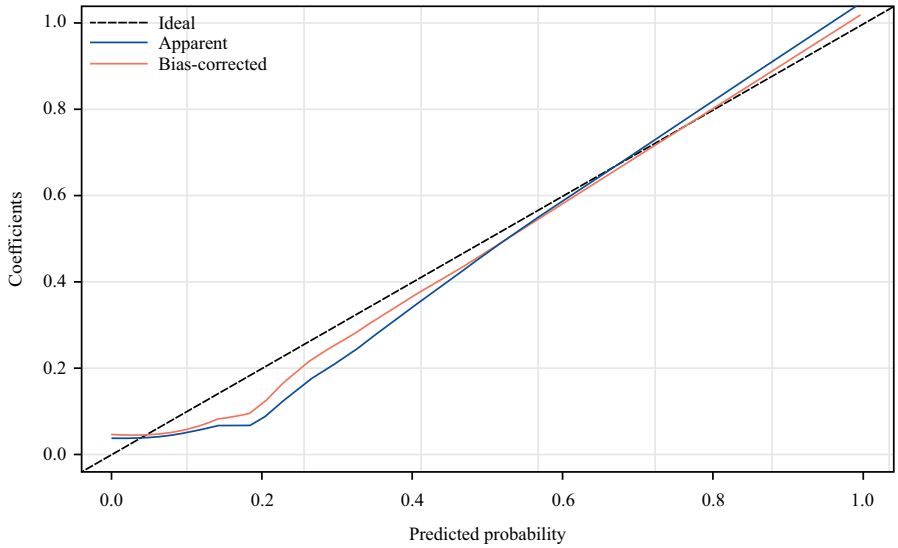

Fig. 6: Calibration curve of the nomogram risk prediction model

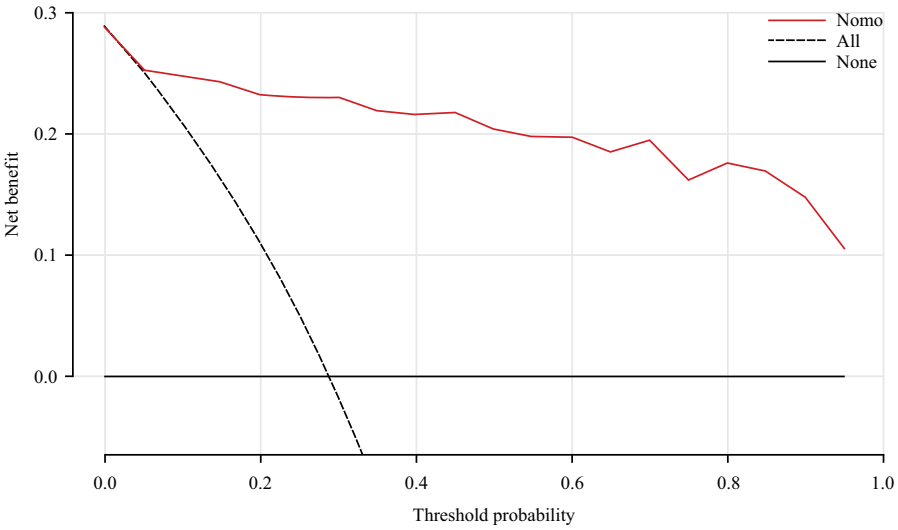

Fig. 7: Decision curve of the nomogram risk prediction model

Table 6: Multivariate Logistic regression analysis of AP patients with octreotide combined with early enteral nutrition therapy

Project	B	SE	OR	95% CI	Z	p-value
APACHE grade	0.995	0.241	2.704	2.704 (1.769-4.627)	4.130	0.000
ApoB/ApoA1	-3.798	1.807	0.022	0.022 (0.001-0.677)	-2.101	0.036
CRP	0.120	0.033	1.127	1.127 (1.062-1.212)	3.606	0.000
LPS	0.013	0.004	1.013	1.013 (1.005-1.022)	3.068	0.002

p<0.05 indicates a statistical difference, ApoB/ApoA1: Apolipoprotein B/Apolipoprotein A1, CRP: C-reactive protein and LPS: Lipase

The risk of poor prognosis of AP patients was obtained according to the nomogram risk prediction model, which was used as the test variable and the group as the status variable. The ROC curve analysis showed that the model AUC was 0.942 (95% CI: 0.8912~0.9929), sensitivity was 90.2 and 91.1% specificity and 0.813 Youden index when cut-off = 0.331 (Fig. 5). The internal verification of Bootstrap method (B = 1000) shows that the prediction curve of Bias-

corrected basically coincides with the Ideal line and the C-index is 0.884. The risk prediction model of this nomogram has good prediction ability, as shown in Fig. 6. The decision curve shows that the threshold probability of this model ranges from 0.01 to 1.00, with a net yield >0 and both above the two invalid lines (Fig. 7).

DISCUSSION

Pancreatitis is predominantly acute in clinical practice. The acute pancreatitis can be accompanied by and organ failure, posing a significant threat to patient safety. Severe cases of acute pancreatitis often exhibit extensive pancreatic necrosis, which increases susceptibility to secondary infection and subsequently leads to multiple organ failure, shock and potential fatality. Studies have reported that the case fatality rate for severe acute pancreatitis can exceed 50%, but early treatment has shown promise in reducing it to 20%[11,12]. Patients with severe acute pancreatitis experience compromised metabolic capacity, heightened protein degradation and oxygen consumption rates and disrupted negative nitrogen balance, hence early enteral nutrition support therapy is clinical practice. Octreotide exhibits various physiological activities including reduction of inflammatory mediators and inhibition of secretion, effectively mitigating the adverse effects caused by endotoxins. This study to investigate the risk factors associated with poor prognosis among patients with atitis receiving octreotide combined with early enteral nutrition.

The poor prognosis of AP may lead to pancreatic exocrine insufficiency, pancreatic necrosis, pancreatic insufficiency, complications and other conditions, which may harm the health of patients. Therefore, attention should be paid to ensuring the prognosis of patients in the process of treatment. In this study, 142 AP patients with the No Octreotide combined with early enteral nutrition treatment, after 28 days of follow-up, 41 patients had a poor prognosis rate of 28.87%. It is relatively close to the above conclusion. The ApoB is one of the key molecules in cholesterol and lipid metabolism. It is mainly found in LDL and Very Low-Density Lipoprotein (VLDL), which can assist lipoprotein to enter the blood vessel wall, produce a stimulating effect on macrophages and induce inflammatory response. The ApoA1 is one of the major components of HDL and plays an important role in lipid metabolism *in vivo*. It binds to HDL particles to help its synthesis and transport cholesterol in the body. The ApoA1, by binding to the ABC-A1 transporter protein, promotes cholesterol outflow from the tissue cells and transports it to the liver for metabolism. This process is known as the reverse transport of cholesterol, which helps remove the excess cholesterol in the body, thus protecting cardiovascular health. The ApoB/ApoA1 is a comprehensive indicator that can reflect the balance of lipid metabolism and the balance of pro-inflammatory/anti-inflammatory response in the body. The CRP is an acute temporal protein that is mainly synthesized by the liver. It is a non-specific inflammatory marker that rises rapidly during inflammation or tissue damage and usually peaks within concentrations in the blood for hours[13,14]. After effective treatment and inflammation control, the level of CRP gradually returned to normal levels. It can be used as one of the indicators to judge the treatment effect and predict the prognosis[15]. The LPS can catalyze the hydrolysis of fat, mainly in the synthesis of pancreatic follicle cells. When this cell is damaged, LPS is released and its level in serum is significantly increased[14]. In this study, the levels of ApoB/ApoA1, CRP and LPS in the poor prognosis group were higher than those of the good prognosis group, suggesting that ApoB/ApoA1, CRP and LPS may be involved in the development and development of AP. The APACHE II score is a scoring system used to assess patient severity and predict prognosis and is often used in intensive care patients. Analysis of the relationship between ApoB/ApoA1, CRP, LPS and APACHE II score showed that ApoB/ApoA1, CRP, LPS and APACHE scores, so that ApoB/ApoA1, CRP and LPS were closely related to the degree of disease in AP patients.

Further to explore the AP patients via risk factors for poor prognosis of octreotide combined with early enteral nutrition therapy was found that high APACHE score, elevated ApoB/ApoA1, CRP and LPS were patients with AP have a poor prognosis when treated with octreotide combined with early enteral nutrition Independent risk factors. The APACHE II score can reflect the level of systemic inflammatory response and the degree of organ function damage. The high APACHE II score indicates that the systemic inflammatory response and organ damage are more severe, more complex disease and higher risk of poor prognosis. Some studies show that a high APACHE II score is associated with increased mortality in AP patients[16]. The increase of ApoB or the decrease of ApoA1 reflects the imbalance of inflammatory balance and the number of inflammatory factors and the inflammatory mediator cascade waterfall effect, resulting in systemic inflammatory response syndrome; on the other hand, the increase of ApoB/ApoA1 also indicates the disorder of lipid metabolism in pancreatic inflammatory state, which is closely related to the pathophysiological process of AP[17]. Elevated CRP reflects the severity of the inflammatory response, which in AP patients is one of the core pathophysiological

processes[18]. High CRP levels are often accompanied by the presence of infection and clinical complications further aggravate the risk of poor prognosis. The LPS activity is usually low and elevated LPS may suggest impaired pancreatic tissue. The LPS may be associated with an inflammatory response and a Systemic Inflammatory Response Syndrome (SIRS)[19]. The AP is caused by an inflammation of the pancreas, which may lead to the development of a systemic inflammatory response. Systemic inflammatory response may cause multiple organ failure and a poor prognosis. Based on the above risk factors, a nomogram prediction model for the risk of poor prognosis of AP patients with octreotide combined with early enteral nutrition was established and the ROC analysis of the model found that the AUC was 0.942 (95% CI: 0.8912~0.9929), when cut-off = 0.331, the sensitivity was 90.2 and 91.1% and the Youden index was 0.813. In the internal validation of Bootstrap method, C-index is 0.884 and the nomogram risk prediction model has good prediction ability. The decision curve shows that the threshold probability ranges of this model range from 0.01 to 1.00 and its net yield is >0. These results suggested that the risk prediction model has good prediction efficacy for poor prognosis of AP patients. Clinical risk of poor prognosis of AP patients is evaluated according to these risk factors and effective prevention is conducted for high risk patients in advance to improve patient prognosis.

CONCLUSION

The ApoB/ApoA1, CRP and LPS are closely related to the degree of disease condition in patients with acute pancreatitis. High APACHE score, ApoB/ApoA1, CRP and LPS were Patients with AP have a poor prognosis when treated with octreotide combined with early enteral nutrition Independent risk factors, the risk prediction model constructed from this point has good predictive ability for poor patient prognosis or can be used as a reference for clinical diagnosis and treatment decisions.

SIGNIFICANCE STATEMENT

This paper studied the correlation between serum ApoB/ApoA1, CRP, lipase and the severity of acute pancreatitis and explored the predictive model of octreotide combined with early enteral nutrition therapy. This study is of great significance for clinical doctors to better understand the pathogenesis and condition evaluation of acute pancreatitis, provide a more scientific basis for the formulation of treatment plans and help improve the treatment effect and prognosis of acute pancreatitis.

REFERENCES

1. Charley, E., B. Dinner, K. Pham and N. Vyas, 2023. Diabetes as a consequence of acute pancreatitis. World J. Gastroenterol., 29: 4736-4743.
2. Iannuzzi, J.P., J.A. King, J.H. Leong, J. Quan and J.W. Windsor *et al*., 2022. Global incidence of acute pancreatitis is increasing over time: A systematic review and meta-analysis. Gastroenterology, 162: 122-134.
3. Takada, T., S. Isaji, T. Mayumi, M. Yoshida and Y. Takeyama *et al*., 2022. JPN clinical practice guidelines 2021 with easy-to-understand explanations for the management of acute pancreatitis. J. Hepato Biliary Pancreatic Sci., 29: 1057-1083.
4. Ramírez-Maldonado, E., S.L. Gordo, E.M. Pueyo, A. Sánchez-García and S. Mayol *et al*., 2021. Immediate oral refeeding in patients with mild and moderate acute pancreatitis: A multicenter, randomized controlled trial (PADI trial). Ann. Surg., 274: 255-263.
5. Reynoso-Villalpando, G.L., C. Sevillano-Collantes, Y. Valle, I. Moreno-Ruiz, J.R. Padilla-Gutiérrez and F.J. del Cañizo-Gómez, 2019. ApoB/ApoA1 ratio and non-HDL-cholesterol/HDL-cholesterol ratio are associated to metabolic syndrome in patients with type 2 diabetes mellitus subjects and to ischemic cardiomyopathy in diabetic women. Endocrinología Diabetes y Nutrición (Engl. Edn.), 66: 502-511.
6. Wang, X., Z. Wang, B. Li and P. Yang, 2020. Prognosis evaluation of universal acute coronary syndrome: The interplay between SYNTAX score and ApoB/ApoA1. BMC Cardiovasc. Disord., Vol. 20. 10.1186/s12872-020-01562-6.
7. Perrone, S., R. Brunelli, G. Perrone, I. Zannini and P. Galoppi *et al*., 2019. A successful term pregnancy with severe hypertriglyceridaemia and acute pancreatitis. Clinical management and review of the literature. Atherosclerosis Suppl., 40: 117-121.
8. Cueni, C., N. Hofer-Inteeworn, C. Kümmerle-Fraune, C. Müller and P.H. Kook, 2023. Progression of lipase activity and pancreatic lipase immunoreactivity in dogs hospitalized for acute pancreatitis and correlation with clinical features. Vet. Intern. Med., 37: 70-79.
9. Working Group IAP/APA Acute Pancreatitis Guidelines, 2013. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology, 13: e1-e15.
10. Banks, P.A., T.L. Bollen, C. Dervenis, H.G. Gooszen and C.D. Johnson *et al*., 2012. Classification of acute pancreatitis-2012: Revision of the Atlanta classification and definitions by international consensus. Gut, 62: 102-111.

11. Tian, G., L. Zhu, S. Chen, Q. Zhao and T. Jiang, 2022. Etiology, case fatality, recurrence, and severity in pediatric acute pancreatitis: A meta-analysis of 48 studies. Pediatr. Res., 91: 56-63.
12. Silva-Vaz, P., A.M. Abrantes, M. Castelo-Branco, A. Gouveia, M.F. Botelho and J.G. Tralhão, 2019. Murine models of acute pancreatitis: A critical appraisal of clinical relevance. Int. J. Mol. Sci., Vol. 20. 10.3390/ijms20112794.
13. Behling-Kelly, E., C.E. Haak, P. Carney, J. Waffle, K. Eaton and R. Goggs, 2022. Acute phase protein response and changes in lipoprotein particle size in dogs with systemic inflammatory response syndrome. Vet. Intern. Med., 36: 993-1004.
14. Ferreira, R.F., R.L. Dittrich, I.B. Zimmermann, B.B. Ljubic, V. Mrljak and P.D. Eckersall, 2021. Differential acute-phase protein responses in dogs seropositive or seronegative for *Neospora caninum*. Parasitol. Res., 120: 3529-3535.
15. Karabuga, B., E. Gemcioglu, E.K. Karabuga, S. Baser and O. Ersoy, 2022. Comparison of the predictive values of CRP, CRP/albumin, RDW, neutrophil/lymphocyte, and platelet/lymphocyte levels in determining the severity of acute pancreatitis in patients with acute pancreatitis according to the BISAP score. Bratislava Med. J., 123: 129-135.
16. Li, X.W., C.H. Wang, J.W. Dai, S.H. Tsao and P.H. Wang *et al*., 2023. Comparison of clinical outcomes between aggressive and non-aggressive intravenous hydration for acute pancreatitis: A systematic review and meta-analysis. Crit. Care, Vol. 27. 10.1186/s13054-023-04401-0.
17. Jin, J.L., D. Sun, Y.X. Cao, H.W. Zhang and Y.L. Guo *et al*., 2018. Intensive genetic analysis for Chinese patients with very high triglyceride levels: Relations of mutations to triglyceride levels and acute pancreatitis. eBioMedicine, 38: 171-177.
18. Georgakopoulou, V.E., A. Gkoufa, N. Garmpis, S. Makrodimitri and C.V. Papageorgiou *et al*., 2022. COVID-19 and acute pancreatitis: A systematic review of case reports and case series. Ann. Saudi Med., 42: 276-287.
19. Nauka, P.C., T.A. Weinstein, M.T. Dolinger, J.M. Miller, N. Kohn, S. Bitton and H.L.R. Rilo, 2019. Validation of lipase and systemic inflammatory response syndrome as prognostic indicators in pediatric acute pancreatitis: A retrospective analysis. J. Pediatr. Gastroenterol. Nutr., 68: 389-393.