World Journal of

Gastrointestinal Surgery

World Journal of Gastrointestinal Surgery

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ABOUT COVER

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AIMS AND SCOPE

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ORIGINAL ARTICLE

Retrospective Study

Low serum albumin may predict poor efficacy in patients with perforated peptic ulcer treated nonoperatively

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Author contributions: Liang TS and Yang DG were responsible for designing the study and reviewing the manuscript; Liang TS and Zhang BL drafted the manuscript; Liang TS and Zhao BB collected the clinical data and abstracted the data; Liang TS and Zhang BL were responsible for revising the manuscript; All authors have read and approved the final manuscript.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of Liaocheng People's Hospital.

Informed consent statement: As this is a retrospective study, signed informed consent was unnecessary.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

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Abstract

BACKGROUND
Nonoperative management (NOM) is a promising therapeutic modality for patients with perforated peptic ulcer (PPU). However, the risk factors for poor efficacy and adverse events of NOM are a concern.

AIM
To investigate the factors predictive of poor efficacy and adverse events in patients with PPU treated by NOM.

METHODS
This retrospective case-control study enrolled 272 patients who were diagnosed with PPU and initially managed nonoperatively from January 2014 to December 2018. Of these 272 patients, 50 converted to emergency surgery due to a lack of improvement (surgical group) and 222 patients were included in the NOM group. The clinical data of these patients were collected. Baseline patient characteristics and adverse outcomes were compared between the two groups. Logistic regression analysis and receiver operating characteristic curve analyses were conducted to investigate the factors predictive of poor efficacy of NOM and adverse outcomes in patients with PPU.

RESULTS
Adverse outcomes were observed in 71 patients (32.0%). Multivariate analyses revealed that low serum albumin level was an independent predictor for poor efficacy of NOM and adverse outcomes in patients with PPU.

CONCLUSION
Low serum albumin level may be used as an indicator to help predict the poor efficacy of NOM and adverse outcomes, and can be used for risk stratification in patients with PPU.

Key Words: Perforated peptic ulcer; Peptic ulcer disease; Nonoperative treatment; Risk factor

Core Tip: Risk factors are associated with a poor efficacy in patients with perforated peptic ulcer (PPU) treated by nonoperative management (NOM), and can be used for risk stratification in patients with PPU. Serum albumin level is an important predictor of the poor efficacy of NOM.

INTRODUCTION

Perforation is a serious complication of peptic ulcer disease (PUD) with a morbidity rate between 6.2% and 27%[1-3]. Patients with perforated peptic ulcer (PPU) tend to be young male smokers residing in developing countries, while patients in developed countries tend to be elderly with associated use of steroid or non-steroidal anti-inflammatory drugs and multiple comorbidities[4]. The incidence of PPU has significantly decreased worldwide, especially in high-income countries[5], and only 2%-14% of PUD patients present with an acute abdominal perforation[6]. The reason for this overall progress is the introduction of new drugs (H2 receptor antagonists and proton pump inhibitors [PPIs]) and the diagnosis and management of *Helicobacter pylori* infection[4,7,8].

PPU is still one of the most common causes of abdominal pain in the emergency department and requires prompt diagnosis and treatment. Nonoperative treatment should be considered in patients with uncomplicated PPU, which prevents surgery and its resultant morbidity. Studies have demonstrated that approximately 40%-80% of patients with PPU will heal spontaneously, and most patients with uncomplicated PPU can benefit from nonoperative management (NOM)[5,9-11]. Prognostic factors that can enhance recovery, and reduce morbidity and mortality should be identified and investigated further.

The aim of this study was to evaluate the relationship between risk factors and clinical outcome, and identify which factors can be used for risk stratification in patients with PPU.

MATERIALS AND METHODS

Study population

This was a single-center retrospective case-control study. Patients who were diagnosed with PPU by computed tomography (CT) scan and treated by NOM on admission between January 2014 and December 2018 at Liaocheng People's Hospital (Shandong, China) were enrolled in the study. The following patients were considered suitable for NOM: Patients with an empty stomach at the time of perforation and who were in good general condition, patients with tolerable abdominal pain, limited peritonitis with no manifestations of shock on admission, or a CT scan of the abdomen revealed that free air or liquid was limited to 1-2 zones. Those who were accepted for emergency surgery on admission or had suspected gastric cancer were excluded. Patients with severe liver disease or renal disease were also excluded. The patients were divided into two groups based on whether vital parameters are normal and the findings of peritonitis or septic shock: The nonoperative management group (NOM group) and the surgical management group (surgical group). This study was approved by the Ethics Committee of Liaocheng People's Hospital. As it was a retrospective

study, signed informed consent was not necessary.

Data collection
All patient data were obtained from electronic charts. Demographic data such as gender and age were collected. A medical history of hypertension, diabetes mellitus, and smoking status was recorded. Clinical variables such as duration of abdominal pain, physical examinations, and vital signs were evaluated. Laboratory variables including leukocyte count, hemoglobin, serum albumin, procalcitonin (PCT) concentration, and C-reactive protein (CRP) were collected.

Nonoperative management
Nonoperative treatment of patients with PPU consisted of fasting, hemodynamic resuscitation, nasogastric suction, appropriate antibiotics, and antisecretory therapy with PPIs and somatostatin and repeated clinical assessment. If there was no significant improvement in the patient's condition within 12 h, operative treatment was considered. Clinical improvement was defined as a composition of improvements in vital signs and abdominal signs. They were managed by an experienced surgeon. Water-soluble contrast imaging was performed in all patients to determine whether the perforation had sealed. Gastroscopy and *Helicobacter pylori* examination were recommended within 1 mo after the patient had completely recovered.

Statistical analyses
Continuous variables are expressed as the mean ± SD or median (interquartile range) as appropriate. Categorical variables are expressed as the number and percentage. The Student's *t*-test or Mann–Whitney *U* test was used to compare the continuous data as appropriate. The χ^2 or Fisher's exact test was used to compare the categorical data. Logistic regression analyses were used to identify clinical data, which were independent predictors for clinical failure of NOM or adverse outcomes in patients with PPU. Unadjusted variables with a *P* value < 0.05 in the univariate analyses were subsequently included in the multivariate logistic regression model. To assess the predictive ability of clinical data, a receiver operating characteristic (ROC) curve was performed and the area under the curve (AUC) was calculated. All statistical tests were two-tailed, and differences were considered significant when *P* < 0.05.

RESULTS

Baseline characteristics of the study patients
Between January 2014 and December 2018, 306 patients with PPU were admitted to the Gastrointestinal Surgery Department of our hospital. A total of 272 patients with PPU who were initially managed nonoperatively were included in the analysis, and 50 of them were converted to surgery. Finally, 222 patients received nonoperative treatment. The baseline characteristics of the patients are summarized in Table 1. The proportion of patients older than 70 years, with pain duration prior to admission ≥ 12 h and body temperature ≥ 38 °C was higher in the surgical group than in the NOM group. The levels of PCT and CRP and the proportion of patients with serum albumin < 30 g/L were higher in the surgical group than in the NOM group.

Comparison of clinical adverse outcomes between the surgical group and NOM group
In this study, the incidence of adverse outcomes was 30% in the surgical group and 25.2% in the NOM group; there were no significant differences between the two groups (*P* = 0.487). However, the length of hospital stay in the surgical group was longer than that in the NOM group (*P* < 0.001; Table 2).

Logistic regression analyses of predictors of poor efficacy of NOM and adverse outcomes in patients with PPU
For the prediction of poor efficacy of NOM, variables including age ≥ 70 years, pain duration prior to admission ≥ 12 h, and serum albumin < 30 g/L were entered into the multivariate logistic regression model. The results showed that serum albumin < 30 g/L was an independent indicator for poor efficacy of NOM (adjusted odds ratio [OR]: 5.073, 95%CI: 2.527-10.184, *P* < 0.001). In addition, pain duration prior to admission ≥ 12 h independently predicted poor efficacy of NOM (Table 3).

Table 1 Comparison of baseline patient characteristics between the two groups, *n* (%)

Variables	Surgical group *n* = 50	NOM group *n* = 222	*P* value
Age in yr, average (median)	66.5 (15.8)	58.0 (21.3)	< 0.001
≥ 70 yr	19 (38.0)	44 (19.8)	0.006
Male, *n* (%)	32 (64.0)	162 (73.0)	0.205
Hypertension	16 (32.0)	45 (20.3)	0.072
DM	11 (22.0)	28 (12.6)	0.087
Smoking	26 (52.0)	83 (37.4)	0.057
Alcohol consumption	18 (36.0)	56 (25.2)	0.122
NSAIDs use	16 (32.0)	50 (22.5)	0.158
Pain duration prior to admission (median)	8.0 (9.0)	6.0 (6.0)	0.001
≥ 12 h	16 (32.0)	33 (14.9)	0.004
Heart rate (bpm) (median)	92.0 (24.0)	86.0 (18.0)	0.116
Body temperature (C) (median)	36.7 (1.2)	36.7 (0.7)	0.826
≥ 38 C	9 (18.0)	19 (8.6)	0.047
Hemoglobin (g/L)	116.8 22.7	126.5 22.2	0.006
< 90 g/L	7 (14.0)	15 (6.8)	0.090
WBC count (× 10^9/L) (median)	9.5 (6.6)	10.5 (3.3)	0.479
≥ 12 × 10^9/L	18 (36.0)	77 (34.7)	0.860
Procalcitonin (ng/mL) (median)	5.14 (10.03)	0.88 (3.96)	< 0.001
CRP (mg/L) (median)	151.28 (151.16)	68.46 (119.35)	< 0.001
Serum albumin (g/L)	27.5 4.65	33.7 6.79	< 0.001
< 30 g/L	32 (64.0)	54 (24.3)	< 0.001

CRP: C-reactive protein; DM: Diabetes mellitus; NOM: Nonoperative management; NSAIDs: Non-steroidal anti-inflammatory drugs; WBC: White blood cell.

Table 2 Adverse outcomes of patients with perforated peptic ulcer, *n* (%)

Complications	Surgical group, *n* = 50	NOM group, *n* = 222	*P* value
Wound infection	3 (6.0)	0	0.006
Respiratory infection	2 (4.0)	11 (5.0)	1.000
Urinary infection	4 (8.0)	9 (4.1)	0.415
Ascites	3 (6.0)	24 (10.8)	0.304
Pleural effusion	3 (6.0)	7 (3.2)	0.582
Abdominal abscess	0 (0)	5 (2.3)	0.588
Total complications	15 (30)	56 (25.2)	0.487
Length of hospital stay in d	12 (7)	9 (3)	< 0.001

NOM: Nonoperative management.

With regard to adverse outcomes, variables including age ≥ 70 years and serum albumin < 30 g/L were entered into the multivariate logistic regression model. The results showed that serum albumin < 30 g/L was also an independent indicator of adverse outcomes (adjusted OR: 2.945, 95%CI: 1.625-5.339, *P* <0.001) (Table 4). Thus,

Table 3 Logistic regression analysis for determining the independent predictors of poor efficacy of nonoperative management in patients with perforated peptic ulcer

Variable	OR	95%CI	*P* value	Adjusted OR	95%CI	*P* value
Age ≥ 70 yr	2.479	1.282-4.795	0.007	1.278	0.605-2.698	0.521
Male	0.658	0.344-1.260	0.207			
Hypertension	1.851	0.939-3.648	0.075			
Diabetes mellitus	1.954	0.898-4.253	0.091			
Smoking status	1.814	0.978-3.365	0.059			
Alcohol consumption	1.667	0.869-3.201	0.124			
NSAIDs use	1.619	0.826-3.171	0.160			
Pain duration prior to admission ≥ 12 h	2.695	1.339-5.427	0.005	2.495	1.163-5.352	0.019
Heart rate	1.018	0.998-1.037	0.071			
Body temperature ≥ 38 C	2.345	0.991-5.549	0.052			
Hemoglobin < 90 g/L	0.445	0.171-1.157	0.097			
WBC count ≥ 12 × 10^9/L	1.059	0.058-2.009	0.860			
Procalcitonin	1.027	1.000-1.056	0.052			
CRP	1.001	1.000-1.002	0.198			
Serum albumin < 30 g/L	5.331	2.876-10.635	< 0.001	5.073	2.527-10.184	< 0.001

CRP: C-reactive protein; NSAIDs: Non-steroidal anti-inflammatory drugs; PPU: Perforated peptic ulcer; WBC: White blood cell.

Table 4 Logistic regression analysis of predictors of clinical complications in patients with perforated peptic ulcer

Variables	OR	95%CI	*P* value	Adjusted OR	95%CI	*P* value
Age ≥ 70 yr	2.331	1.277-4.254	0.006	1.630	0.853-3.114	0.139
Male	1.390	0.777-2.488	0.268			
Hypertension	1.008	0.528-1.928	0.980			
Diabetes mellitus	1.729	0.842-3.550	0.136			
Smoking status	0.757	0.432-1.328	0.331			
Alcohol consumption	0.970	0.527-1.785	0.922			
NSAIDs use	0.977	0.519-1.839	0.941			
Pain duration prior to admission ≥ 12 h	1.316	0.667-2.594	0.428			
Heart rate	1.005	0.988-1.023	0.568			
Body temperature ≥ 38 C	0.586	0.214-1.606	0.299			
Hemoglobin < 90 g/L	0.590	0.236-1.471	0.257			
WBC count ≥ 12 × 10^9/L	0.787	0.441-1.405	0.418			
Procalcitonin	1.021	0.994-1.048	0.126			
CRP	1.000	0.999-1.001	0.933			
Serum albumin < 30 g/L	3.376	1.917-5.946	< 0.001	2.945	1.625-5.339	< 0.001

CRP: C-reactive protein; NSAIDs: Non-steroidal anti-inflammatory drugs; PPU: Perforated peptic ulcer; WBC: White blood cell.

serum albumin < 30 g/L was an independent risk factor for predicting the poor efficacy of NOM and adverse outcomes.

The performance of serum albumin in predicting the poor efficacy of NOM and adverse outcomes

The ROC curves for serum albumin in predicting poor efficacy of NOM and adverse outcomes are shown in Figure 1. The optimal cut-off value of serum albumin for predicting poor efficacy of NOM was 31.8 g/L, with 63% sensitivity and 82% specificity. The optimal cut-off value of serum albumin for predicting adverse outcomes was 29.9 g/L, with 76% sensitivity and 52% specificity. The AUC values for serum albumin for predicting poor efficacy of NOM and adverse outcomes was (0.774, 95%CI: 0.711–0.836) and (0.649, 95%CI: 0.572–0.727) ($P < 0.001$, respectively).

DISCUSSION

Our prediction models demonstrated the risk factors for poor efficacy of NOM and adverse outcomes in patients with PPU, and the AUC values verified their significance. Accumulating evidence has shown that serum albumin is not only a parameter of nutritional status but also a marker of acute inflammation and is associated with disease severity. Patients in the surgery group represented relatively serious infections. Therefore, the proportion of patients with serum albumin < 30 g/L was higher in the surgical group. Our results showed that serum albumin was an excellent risk predictor, not only for predicting poor efficacy of NOM but also for adverse outcomes. In addition, pain duration prior to admission ≥ 12 h was an independent risk factor for predicting poor efficacy of NOM.

In 1946, Taylor proposed the famous "Taylor method" in the NOM of PPU, and concluded that 28 PPU patients receiving NOM showed a lower mortality rate than patients receiving direct simple closure with an omental patch[12]. The first randomized trial performed by Crofts *et al*[10] revealed that 72% of patients treated by NOM had lower morbidity and mortality compared to the surgical group. Several retrospective studies have reported that the NOM technique has a higher success rate in well-selected patients[13]. Moreover, surgical treatment did not show an advantage with regard to morbidity and mortality compared to NOM[5,9,10]. According to World Society of Emergency Surgery guidelines, patients with PPU were suggested to avoid endoscopic treatment such clipping, fibrin glue sealing, or stenting. This approach needs further validation, as it may not be effective in perforated ulcer cases due to fibrotic tissue with loss of compliance. In our study, approximately 81.6% (222/272) of patients received NOM, and the incidence of non-fatal complications was similar to that for those who converted to surgery. These data are in accordance with previous studies and indicate that NOM is a feasible approach[9,14]. However, NOM for PPU is still controversial and has not been widely adopted. In many hospitals, surgical treatment is the preferred choice, and NOM is just an alternative for patients who are not suitable or unwilling to undergo surgery[6]. This study tried to determine the risk factors that will help clinicians select patients with PPU who will experience poor efficacy. Based on logistic regression analysis, two parameters were significantly correlated with poor efficacy of NOM: serum albumin < 30 g/L and pain duration prior to admission ≥ 12 h. With regard to adverse outcomes, only serum albumin < 30 g/L was an independent risk predictor. Furthermore, the AUC values showed that serum albumin had moderate power in predicting clinical outcomes.

Serum albumin has been used as a diagnostic marker for malnutrition in clinical practice for several years as it can reflect the nutritional status of patients[15]. The current evidence shows that serum albumin is not only a parameter of nutritional status, but also a marker of acute inflammation and is associated with disease severity [16]. In a prospective study including 2465 patients who were admitted to the emergency department, the mortality rate was higher in patients with low levels of serum albumin than those with normal serum albumin levels[17]. A previous study showed that PPU patients with low levels of serum albumin at presentation may predict the need for gastric resection, and elevated serum albumin levels can increase the success rate of NOM[18]. Consistent with a previous study, our findings showed that serum albumin < 30 g/L can predict the need for surgical management in patients with PPU who were initially treated nonoperatively. This study is the first to demonstrate that serum albumin is also an independent risk factor for adverse outcomes in patients with PPU. In patients with perforations, the production of acute phase proteins and inflammatory factors will lead to a further decline in serum albumin. Fluids leak slowly from intravascular to interstitial spaces causing local swelling, which induce difficult healing in patients with low levels of serum albumin. Routine measurement of serum albumin on admission, can be used for risk strati-
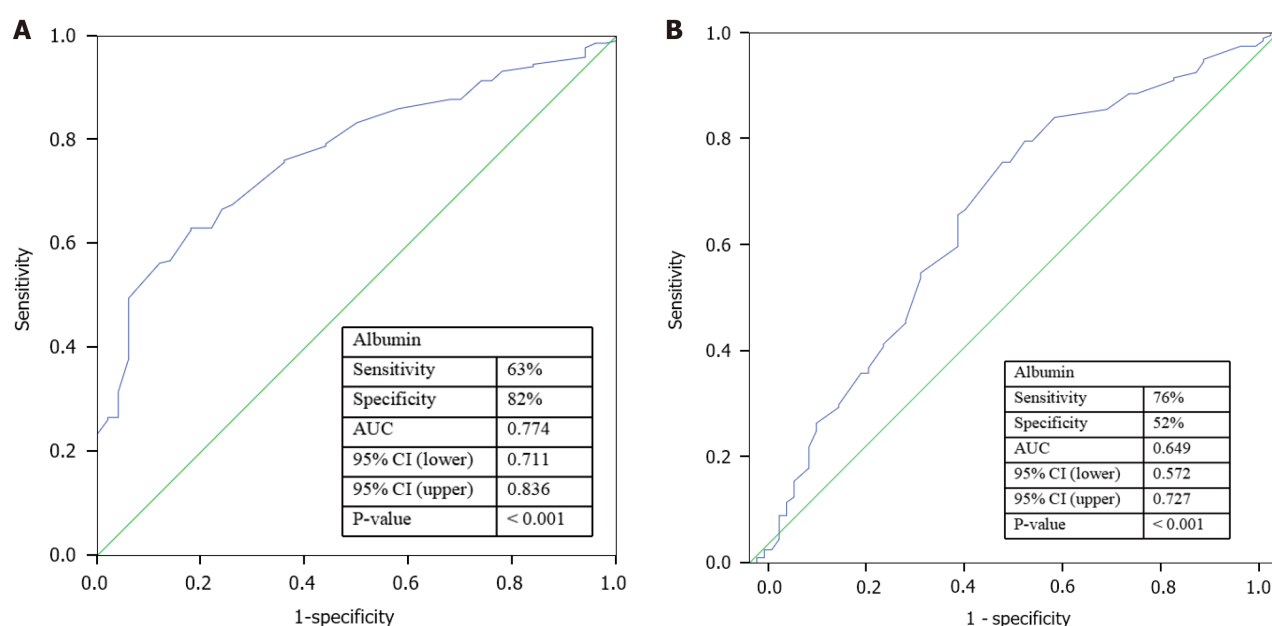
Figure 1 The receiver operating characteristic curves. A: The receiver operating characteristic (ROC) curves for serum albumin in predicting poor efficacy of nonoperative management (NOM); B: The ROC curves for serum albumin in predicting adverse outcomes of NOM. AUC: Area under the curve.

fication in patients with PPU.

When the onset time of abdominal pain prior to admission is more than 12 h, pyrexia, hypotension and abdominal distension with acute circulatory collapse may be evident[19]. In our study, pain duration prior to admission ≥ 12 h was an independent risk factor for predicting poor efficacy of NOM. The data from our study were consistent with those observed in a previous study[20].

In our analysis, 81.6% of cases (222/272) received NOM with a complication rate of 32%, and patients who converted to surgery had a morbidity rate of 30%. In addition, our study also demonstrated that hospital stay was shorter in the NOM group than in the surgical group. Taken together, these findings show that NOM was safe and effective in patients with PPU. In addition, several risk factors have been confirmed to be significantly associated with poor efficacy of NOM and can be used for risk stratification in patients with PPU.

This study had several limitations. First, this was a single-center retrospective study, and the patients were treated by different doctors. Second, relevant indicators were analyzed only when the patient was admitted to the hospital, and the various indicators during hospitalization were not included. Third, there is currently no uniform standard for uncomplicated upper gastrointestinal perforation; thus, biases in patient selection may exist.

CONCLUSION

The use of NOM for PPU may be debated for some time. The advantages of NOM are obvious. It is important to stratify patients into high and low risk on admission. NOM is recommended in patients who are in good general condition with an empty stomach at the time of perforation. Low serum albumin is an independent risk factor that may predict adverse consequences of NOM for PPU.

ARTICLE HIGHLIGHTS

Research background

Nonoperative management (NOM) is a promising therapeutic modality for patients with perforated peptic ulcer (PPU). However, the risk factors for poor efficacy and adverse events of NOM are a concern.

Research motivation

Prognostic factors that could enhance recovery, and reduce morbidity and mortality should be identified and investigated further in patients with PPU.

Research objectives

The aim of this study was to evaluate the relationship between risk factors and clinical outcome, and identify which factors can be used for risk stratification in patients with PPU.

Research methods

Total 272 patients who were diagnosed with PPU and initially managed nonoperatively from January 2014 to December 2018 were enrolled. The clinical data of these patients were collected. Baseline patient characteristics and adverse outcomes were compared between the two groups.

Research results

Multivariate analyses revealed that low serum albumin level was an independent predictor for poor efficacy of NOM and adverse outcomes in patients with PPU.

Research conclusions

Low serum albumin level may be used as an indicator to help us predict poor efficacy of NOM and adverse outcomes, and can be used for risk stratification in patients with PPU.

Research perspectives

Low serum albumin is an independent risk factor that may predict adverse consequences of NOM for PPU.

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