

# Construction of a nomogram predictive model for patients with liver rupture undergoing surgical intervention

Gen-Fei Zhu, M.D.,<sup>1</sup> Xiao-Qing Wu, M.D.,<sup>1</sup> Yang Chen, M.D.,<sup>2</sup> Feng Jiang, M.D.<sup>2</sup>

<sup>1</sup>Department of General Surgery, Zhejiang Hospital, Zhejiang Province-China

<sup>2</sup>Department of General Surgery, Affiliated Xiaoshan Hospital, Hangzhou Normal University, Zhejiang Province-China

## ABSTRACT

**BACKGROUND:** The incidence of blunt abdominal injury has significantly increased, and the liver is one of the most commonly damaged organs. In this study, we explored and established a nomogram model for patients with liver ruptures undergoing surgical treatment.

**METHODS:** A retrospective analysis was conducted for 66 adult patients with liver rupture, who were admitted to our hospital from January 2011 to October 2018. These patients were classified into two groups, according to whether the patient had surgery: surgery group (41 cases) and non-surgical group (25 cases). The following data were collected from these two groups of patients: gender, age, injury mechanism, liver damage, laboratory test results, and hospitalization. Multivariate logistic regression analysis was performed to screen the risk factors of patients who require surgical treatment, establish a predictive model based on the selected indicators, and draw the nomogram. Receiver operating characteristic curves and the calibration curve were used to evaluate the predictive value of the model.

**RESULTS:** Compared to the non-surgical group, the body temperature decreased, the heart rate increased, the injury severity score grade increased, the blood urea nitrogen, blood uric acid, creatinine (Cr), arterial partial pressure of oxygen, alkali excess, blood lactic acid and creatine kinase isoenzymes MB (CK-MB) increased, and the HCO<sup>-</sup> and Glasgow Coma Scale (GCS) coma scores decreased for patients in the surgical group (all,  $p < 0.05$ ). The logistic regression analysis revealed that Cr, arterial partial pressure of oxygen, HCO<sup>3-</sup>, CK-MB, and the Glasgow coma score were the influencing factors for surgical intervention for liver rupture. The nomogram model constructed based on these five indicators had a good degree of discrimination (area under the curve = 0.971, 95% CI: 0.896–0.997) and accuracy.

**CONCLUSION:** A nomogram model established based on Cr, arterial partial pressure of oxygen, HCO<sup>3-</sup>, CK-MB, the GCS, and other parameters can accurately predict the surgical treatment of patients with liver rupture.

**Keywords:** Liver rupture; logistic model; nomogram; retrospective analysis; surgical treatment.

## INTRODUCTION

With the rapid development of China's economy, and transportation and construction industry, the incidence of blunt abdominal injury has significantly increased, and the liver is one of the most commonly damaged organs.<sup>[1]</sup> The liver is an organ rich in blood supply. Once injured, lacerations, intraparenchymal hematoma, intra-abdominal hemorrhage, or shock can manifest at the early stage, and severe cases can lead to death.<sup>[2,3]</sup> Since the 1990s, the treatment con-

cept of liver rupture has been changed from surgical treatment to conservative treatment. Although most patients with blunt liver trauma can be cured by conservative treatment, there are still some patients who need surgery.<sup>[4]</sup> In addition, after conservative treatment, liver rupture is prone to rebleeding, delayed rupture leading to hemorrhagic shock, etc. Therefore, the timing of surgical intervention during clinical decision-making is very important. Furthermore, a practical and readable surgical intervention timing model is needed.

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Address for correspondence: Feng Jiang, M.D.

No. 728, Yucai North Road, Hangzhou 311200, Zhejiang Province, China Hangzhou - China

Tel: +86-571-83865816 E-mail: zjhzxh2020@163.com

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At present, few studies have reported on predicting models for surgical intervention timing for liver rupture. Furthermore, there is increasing consensus on the hemodynamic evaluation indicators for trauma. The consensus on circulatory shock and hemodynamic monitoring by the task force of the European Society of Intensive Care Medicine<sup>[5]</sup> considers that blood lactate >3 mmol/L and central venous blood oxygen saturation (ScvO<sub>2</sub>) <70% often indicate poor prognosis for patients. Another study considered that the continuous dynamic monitoring of arterial blood lactate and lactate clearance is of great significance for the early diagnosis, guidance of treatment, and prognostic evaluation of shock.<sup>[6]</sup> In addition, the residual level of alkali in shock patients is an indirect sensitive indicator to assess the severity and duration of acidosis caused by tissue hypoperfusion.<sup>[7]</sup> However, these above hemodynamic indicators are for trauma patients, are not specific for liver rupture, and are not individualized. Furthermore, the definition of hemodynamic stability was not clearly defined. Moreover, the review and observation of various indicators have a significant correlation with the clinical experience of the attending physician.

The nomogram model was based on single- and multiple-factor regression analysis. Multiple variables were selected to predict the probability of a certain clinical outcome. Then, the individual predictive value was obtained, and this was used to guide the clinical diagnosis and treatment decisions. This is a personalized and visual statistical model for predictive analysis.<sup>[8]</sup> At present, this is being used for liver cancer,<sup>[9]</sup> stomach cancer,<sup>[10]</sup> and breast cancer,<sup>[11]</sup> in which the survival rate of patients is predicted. The present study collected the clinical data of patients with liver rupture and established a nomogram model to predict the timing of patients who received surgical intervention, to provide a reference for the treatment options of such patients.

## MATERIALS AND METHODS

### Patients

A retrospective analysis was conducted on the clinical data of 66 adult patients with liver rupture, who were admitted to our hospital from January 2011 to October 2018. The age of these patients was between 20 and 78 years old, with an average age of 41.42±13.73 years old. Among these patients, 51 patients were male and 15 patients were female. The major cause of liver injury was a traffic accident (23 cases), followed by fall from height (15 cases), heavy object injury (11 cases), knife stabbing (15 cases), and other injuries (five cases). Patients were classified into two groups, according to whether they received surgical treatment: Surgical group (41 cases) and non-surgical group (25 cases) based on the American Association for the Surgery of Trauma (AAST) liver damage grading scale. The study was carried out in accordance with the Declaration of Helsinki and approved by the Ethics Committee

of Affiliated Xiaoshan Hospital, Hangzhou Normal University on 04.09.2020, (no.2020-007). The requirement for informed consent was waived due to the retrospective nature of the study.

### Inclusion and Exclusion Criteria

#### Inclusion Criteria

Enrolled patients who underwent puncture laboratory and imaging examinations and were diagnosed with traumatic liver rupture by trauma examination; patients with clinical manifestations, such as coma, hematuria, vomiting, abdominal distension, and right upper abdominal pain were included in the study.

#### Exclusion Criteria

Combined with other abdominal organ injuries, patients with incomplete clinical data were excluded from the study.

### Data Collection

The following data were collected from these two groups of patients: gender, age, cause of injury, time from injury to consultation, combined organ injury, body temperature, heart rate, systolic blood pressure (SBP), Glasgow coma scale (GCS) score, hematocrit (HCT), AAST grade, injury severity score (ISS), red blood cell (RBC) count, hemoglobin (Hb), platelet (PLT) count, blood urea nitrogen (BUN), creatinine (Cr), blood lactate, ScvO<sub>2</sub>, alkali excess, alanine aminotransferase (ALT), aspartate aminotransferase (AST), RBC transfusion, perihepatic effusion, blood volume in the abdominal cavity, operation time, surgical blood loss, total hospital stay, and the determination of whether the injury is combined with peritoneal irritation sign, the determination of whether vasopressors were used, and other information.

### Statistical Analyses

R (version 3.5.2) was used to process the data. The mainly used R packages were mice, glm, predict, Resource Selection, rms, etc. The Kolmogorov–Smirnov test was used for normality distributed data. Normally distributed data were expressed as mean±standard deviation (mean±SD). An independent sample t-test was used for comparisons between groups. Non-normally distributed measurement data are expressed in median and quartile (M [P25, P75]). Wilcoxon rank-sum test was used for comparisons between groups. The count data were expressed in percentage (%), and X<sup>2</sup>-test was used for comparisons between groups. Multivariate logistic regression was used to analyze the influencing factors of liver rupture patients who underwent surgical treatment. The R software (version 4.0.4) was used to construct the nomogram to predict the surgical treatment of patients with liver rupture. The receiver operating characteristic (ROC) curve and area under the curve (AUC) were used to indirectly evaluate the predictive performance of the model. The inspection level was  $\alpha=0.05$ .

## RESULTS

### Comparison of the General Information of Groups

Compared to the non-surgical group, the body temperature decreased, the heart rate increased, and the ISS classification

and BUN increased in patients in the surgical group. Furthermore, the blood uric acid, Cr, arterial partial pressure of oxygen, alkali excess, blood lactic acid, and CK-MB increased, while the HCO<sub>3</sub><sup>-</sup> and GCS scores decreased, and the differences were statistically significant (all,  $p < 0.05$ ). For these

**Table 1.** Comparison of basic information between the two groups

Indices	Surgery Group (n=41)	Non-surgical Group (n=25)	t/z	p
Age	39.29±14.23	43.16±15.15	-0.813	0.300
Gender (Male/Female)	31/10	20/5	0.170	0.680
Peritoneal Irritation Sign (Positive/Negative)	25/16	9/16	3.879	0.049
Use of vasopressors (Yes/No)	30/11	24/1	5.441	0.020
Body temperature (°)	36.65±1.16	37.29±0.43	2.676	0.009
Time spent on primary diagnosis (min)	81.22±97.36	108.00±211.11	0.701	0.486
Heart rate (c. p. m.)	100.51±18.94	82.28±15.02	4.089	0.000
Injury Severity Score	37.63±11.44	31.84±6.64	2.302	0.025
White blood cell count (×10 <sup>9</sup> /L)	12.56±6.75	12.28±7.44	0.155	0.877
Neutrophil count (×10 <sup>9</sup> /L)	62.88±23.30	75.34±14.38	2.406	0.019
Red blood cell count (×10 <sup>9</sup> /L)	4.20±0.77	4.40±0.60	1.117	0.268
Hemoglobin (g/L)	133.66±22.84	136.08±21.12	0.430	0.669
Hemoglobin decrease within one hour (g/L)	38.03±19.26	12.96±8.00	6.161	0.000
Platelet count (×10 <sup>9</sup> /L)	225.22±74.34	212.72±57.82	0.718	0.475
C-reactive protein	3 (0,4.7)	4 (0.5,13.7)	0.823	0.410
Blood Na	140.89±3.84	141.03±2.47	0.168	0.867
K	3.66±0.48	3.85±0.39	1.702	0.867
Ca	2.14±0.41	2.15±0.16	0.085	0.932
Prothrombin time	12.88±2.30	12.56±1.18	0.649	0.518
International normalized ratio	1.09±0.19	1.06±0.09	0.787	0.434
Activated partial thromboplastin time	30.37±20.32	24.12±3.12	1.520	0.134
Thrombin time	19.20±3.48	18.25±2.07	1.234	0.222
D-dimer	16.73±17.74	12.12±14.63	1.091	0.279
Urea nitrogen	6.28±1.49	4.74±2.48	3.159	0.002
Uric acid	348.38±45.45	269.59±100.12	4.369	0.000
Creatinine	97.32±22.44	78.55±10.50	3.922	0.000
Arterial blood pH	7.27±0.15	7.36±0.09	2.808	0.007
Arterial oxygen partial pressure	129.56±76.13	92.67±13.71	2.392	0.020
Central venous oxygen saturation	93.78±15.38	97.49±1.98	1.199	0.235
Alkali excess	-8.47±5.90	-4.18±1.96	3.512	0.001
HCO <sub>3</sub> <sup>-</sup>	18.29±3.66	22.21±2.11	4.881	0.000
Blood lactic acid	3.89±2.48	2.38±0.61	2.995	0.004
Creatine kinase	385.44±188.84	310.31±198.90	1.537	0.129
Creatine kinase isoenzymes MB	111.47±87.90	34.51±36.87	4.151	0.000
Aspartate aminotransferase	383.00±343.47	289.19±318.16	1.106	0.279
Alanine aminotransferase	348.41±128.62	195.68±246.12	3.311	0.002
GCS Coma Scores	12.15±4.61	14.80±1.00	2.828	0.006
Surgical blood loss (mL)	1709±1509	0±0	5.648	0.000
Total hospital stay (d)	18.54±15.15	14.52±11.23	1.148	0.255

**Table 2.** The multivariate logistic regression results for liver rupture patients who require surgical intervention

Indices	$\beta$	SE	Wald $\chi^2$	p	OR	95%CI	
						Lower	Upper
Creatinine	0.114	0.050	5.162	0.023	1.121	1.016	1.238
Arterial partial pressure of oxygen	0.054	0.022	6.092	0.014	1.055	1.011	1.102
HCO <sub>3</sub> <sup>-</sup>	-0.681	0.262	6.755	0.009	0.506	0.303	.846
Creatine kinase isoenzymes MB	0.032	0.013	6.168	0.013	1.032	1.007	1.059
GCS Coma Scores	-0.424	0.248	2.913	0.028	0.654	0.402	0.865
Constant	3.211	6.719	0.228	0.633	24.797		

two groups of patients, the differences in age, gender ratio, time spent on primary diagnosis, white blood cell count, neutrophil count, RBC count, Hb, Hb decrease within 1 h, PLT count, C-reactive protein, blood Na, blood K, blood Ca, prothrombin time, international normalized ratio, activated partial thromboplastin time, thrombin time, and D-dimer level were not statistically significant (all,  $p > 0.05$ ; Table 1).

### The Multivariate Logistic Regression Results for Liver Rupture Patients Who Require Surgical Intervention

According to the univariate analysis results, which include body temperature, ISS grade, urea nitrogen, uric acid, Cr, arterial blood pH, arterial oxygen partial pressure, HCO<sub>3</sub><sup>-</sup>, blood lactic acid, alkali excess, CKMB, GCS score, peritoneal irritation sign (positive = 1, negative = 0), and the use of vasopressors (yes = 1, no = 0), the multivariate logistic regression analysis was performed, and the forward-stepwise variable selection was used (inclusion criteria:  $p < 0.05$  and exclusion criteria:  $p > 0.1$ ). The results revealed that Cr, arterial partial pressure of oxygen, HCO<sub>3</sub><sup>-</sup>, CK-MB, and the GCS score were the factors that influence the timing of surgical intervention for liver rupture (Table 2).

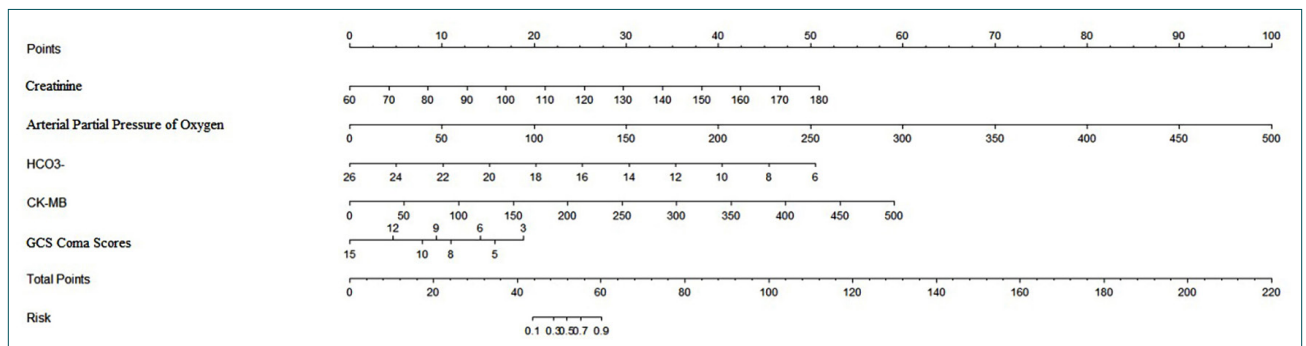
### The Nomogram Prediction Model for Liver Rupture Patients Who Require Surgical Intervention

Influencing factors would affect the treatment of patients

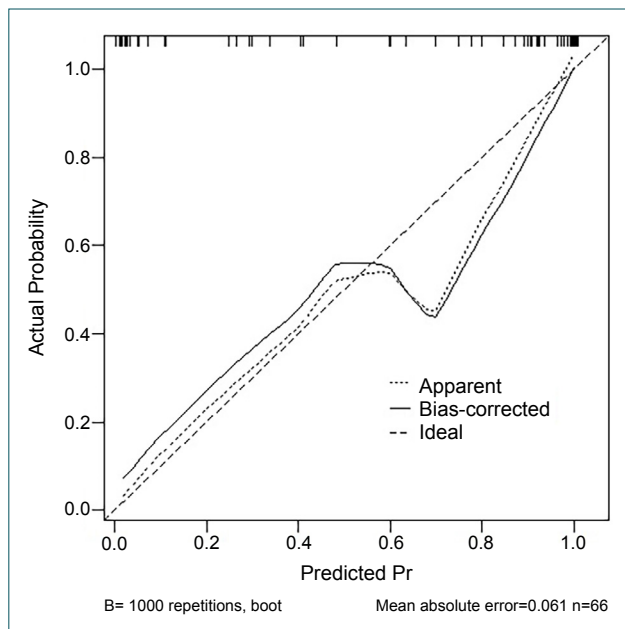
who require surgery, including Cr, arterial partial pressure of oxygen, HCO<sub>3</sub><sup>-</sup>, and CKMB. The GCS score and other indicators were included in the nomogram, and the nomogram for liver rupture patients who underwent surgical treatment was established (Fig. 1). The Bootstrap method was used to internally verify the nomogram. The number of self-sampling B was 1,000, and the calculated C-index was 0.768 (95% CI: 0.699–0.837). The calibration curve revealed that the recurrence-free rate predicted by the nomogram prognostic model was in good agreement with the actual observed recurrence-free rate (Fig. 2). The ROC curve analysis results suggested that the prediction model had better prediction discrimination (AUC=0.971, 95% CI: 0.986–0.997) (Fig. 3).

According to the value of each variable, the vertical projection to the score axis corresponds to the score. In this manner, the total scores correspond to all variables, and the critical illness risk axis can be projected through the corresponding total score axis, allowing for the prediction of the risk probability of surgery after admission for patients with liver rupture.

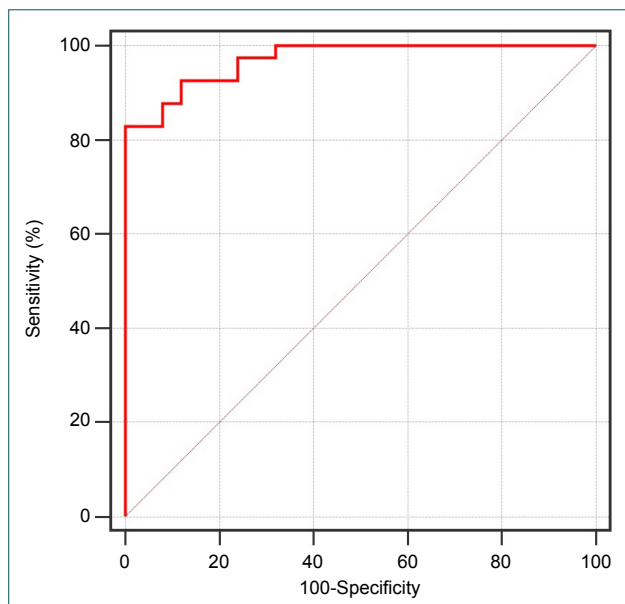
The calibration curve presents the agreement between the predicted value of the model and the actual occurrence rate: the 45° thick gray line represents the ideal predictive performance, the non-45° dashed line represents the prediction performance of the nomogram model, and the solid line represents the correction of the model prediction performance deviation.



**Figure 1.** The nomogram for liver rupture patients who underwent surgical treatment.



**Figure 2.** Calibration curve for the model.



**Figure 3.** The receiver operating characteristic curve for the predictive model for liver rupture patients who require surgery.

## DISCUSSION

The liver is located under the diaphragm and the deep side of the ribs. Since it is protected by the thoracic cage and diaphragm, it generally cannot be easily damaged. However, due to its fragile texture and rich blood vessels, when external violence or sharp object stabbing causes rupture and bleeding, this has become one of the most commonly damaged organs in abdominal injuries.

The clinical manifestations of liver rupture greatly vary, including those with stable hemodynamics that only require

conservative treatment and those who require surgical treatment. Since the 1990s, the concept of surgical treatment for liver rupture has undergone significant changes.<sup>[12]</sup> If the patient's hemodynamics is stable or there is no obvious peritoneal irritation sign, conservative treatment is often recommended.<sup>[13]</sup> However, the judgment of different doctors on hemodynamics, peritoneal irritation sign, and other intra-abdominal injuries is closely correlated to the doctor's experience.<sup>[14]</sup> In addition, although most blunt liver trauma can be cured by conservative treatment, serious complications, such as re-bleeding or hemorrhagic shock caused by delayed bleeding, are prone to occur after conservative treatment, and emergency surgery has to be taken. Therefore, the establishment of a model that can predict the timing of surgical intervention for liver rupture is very important for clinical decision-making. That is, if the intervention too late, the liver rupture may easily lead to hemorrhagic shock, while if the intervention is too early or inappropriate surgical intervention is given early, this often causes aggravated shock, and can even lead to the "lethal triad" of coagulopathy, hypothermia, and acidosis, which is difficult to correct, ultimately threatening the patient's life.<sup>[15]</sup>

In addition to the "Consensus on circulatory shock and hemodynamic monitoring by the task force of the European Society of Intensive Care Medicine, which include the APACHE II classification system,<sup>[16]</sup> the injury severity assessment (ISS),<sup>[17]</sup> blood transfusion volume,<sup>[18]</sup> and others are also commonly used to evaluate the hemodynamic status of the injury. However, these scoring systems are applied to various injuries, and the consensus is relatively broad. Furthermore, few studies have been conducted on the hemodynamic evaluation of liver ruptures. Nishida et al.<sup>[19]</sup> reported that the shock index, pre-operative SBP, pre-operative ALT, the number of related organ injuries, the GCS, and blood transfusion and urea nitrogen (BUN) are independent prognostic factors for survival after liver trauma. McVay et al.<sup>[20]</sup> reported that the injury mechanism, the related damaged organs, the trauma severity score, HCT value, blood transfusion volume, imaging results, and the solid organ damage grades can affect the prognosis of patients with liver injury. The present study revealed that Cr, arterial partial pressure of oxygen, HCO<sub>3</sub><sup>-</sup>, CK-MB, and the GCS score are influencing factors for surgical intervention in liver rupture.

Cr is a common indicator of renal damage, and CK-MB is a biomarker of myocardial damage. At present, there are few reports on the changes of serum Cr after traumatic liver rupture. It was speculated that the increase in Cr and CK-MB in patients who require surgery after liver rupture may be due to the large extent of liver rupture in some patients, which exceeds the ability of the liver to compensate, inducing liver failure within a short period of time. In addition, the increase in blood loss after liver rupture, the severe arterial hypoperfusion in the systemic blood circulation, the induced acute kidney injury, and the reduction in blood flow to the kidneys



and heart can cause a compensatory increase in CK-MB and Cr.<sup>[21–23]</sup> The GCS is a scale used to assess the degree of consciousness disorder in patients. After liver rupture, patients often lose consciousness and present with coma and other manifestations due to large amount of blood loss. Hence, the GCS score significantly drops. In the present study, the multivariate analysis revealed that the GCS score is a risk factor for liver rupture patients who requiring surgery. A retrospective study collected the medical records of 293 patients with multiple liver injuries, who were admitted to a level I trauma center from 1996 to 2008. During the initial visit, there are 34 cases of hemodynamic instability. The GCS score significantly dropped, and early surgical intervention was needed.<sup>[24]</sup> This is consistent with the results of the present study. The kidney and liver are the main regulators of acid–base balance. The acidosis caused by liver and kidney dysfunction can increase the mortality.<sup>[25]</sup> In the present study, the HCO<sub>3</sub><sup>-</sup> and arterial blood pH of patients who required surgery were significantly lower, when compared to those in the non-surgical group. Furthermore, there was an obvious manifestation of metabolic acidosis. This suggests that such patients need to receive surgical treatment as soon as possible. At the same time, the acid–base imbalance in the body needs to be corrected, to reduce the mortality of patients.<sup>[26]</sup>

At present, in the development of scoring tools, clinical prediction rules (CPRs) are common methods. CPRs are often referred to as predictive models or risk scores. These provide an evaluation strategy for estimating the risk of a disease, the prognosis of the disease, and even the benefit of the diagnosis or treatment plan.<sup>[27]</sup> Based on these CPRs, the present study explored the establishment of a clinical prediction model for liver rupture patients who require surgical treatment, and drew a nomogram using the R software, which had the advantages of simplicity, intuitiveness, and strong practicability in the clinic. In the ROC curve analysis, the predictive value of this model was relatively high (AUC: 0.971, 95% CI: 0.986–0.997). The use of this tool would make it easier for clinicians to accurately determine the timing of surgical intervention for patients with liver rupture.

There were limitations in the present study. First, no external verification was carried out. Hence, further follow-up studies are needed. Second, the construction of a good predictive model often requires the support of a large sample size. In the present study, the sample size was small. Therefore, the sample size would be expanded in future studies. At the same time, a multi-center joint study and external verification would be conducted.

## Conclusion

The nomogram model established based on Cr, arterial partial pressure of oxygen, HCO<sub>3</sub><sup>-</sup>, CK-MB, the Glasgow coma score, and other parameters could accurately predict the surgical treatment of patients with liver rupture.

**Ethics Committee Approval:** This study was approved by the Affiliated Xiaoshan Hospital, Hangzhou Normal University Ethics Committee (Date: 04.09.2020, Decision No: 2020-007).

**Peer-review:** Externally peer-reviewed.

**Authorship Contributions:** Concept: F.J.; Design: F.J.; Supervision: F.J.; Resource: G.F.Z.; Materials: G.F.Z.; Data: Z.Q.W.; Analysis: Y.C.; Literature search: G.F.Z.; Writing: G.F.Z.; Critical revision: X.Q.W.

**Conflict of Interest:** None declared.

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## ORİJİNAL ÇALIŞMA - ÖZ

### Cerrahi müdahale geçiren karaciğer rüptürü olan hastalar için bir nomogram öngörü modelinin oluşturulması

Dr. Gen-Fei Zhu,<sup>1</sup> Dr. Xiao-Qing Wu,<sup>1</sup> Dr. Yang Chen,<sup>2</sup> Dr. Feng Jiang<sup>2</sup>

<sup>1</sup>Zhejiang Hastanesi, Genel Cerrahi Bölümü, Zhejiang Eyaleti-Çin

<sup>2</sup>Hangzhou Normal Üniversitesi, Xiaoshan Hastanesi, Genel Cerrahi Bölümü, Zhejiang Eyaleti-Çin

**AMAÇ:** Künt abdominal travma insidansı önemli ölçüde artmıştır ve karaciğer, en sık hasar gören organlardan biridir. Bu çalışmada, cerrahi tedavi gören karaciğer rüptürü olan hastalar için bir nomogram modeli araştırdık ve geliştirdik.

**GEREÇ VE YÖNTEM:** Ocak 2011 ile Ekim 2018 tarihleri arasında hastanemize karaciğer rüptürü ile başvuran 66 erişkin hasta geriye dönük olarak incelendi. Bu hastalar, cerrahi geçirip geçirilmemelerine göre cerrahi uygulanan grup (41 olgu) ve cerrahi uygulanmayan grup (25 olgu) olarak iki gruba ayrıldı. Bu iki hasta grubundan aşağıdaki veriler toplandı: cinsiyet, yaş, yaralanma mekanizması, karaciğer hasarı, laboratuvar test sonuçları ve hastaneye yatış bilgisi. Cerrahi tedavi gerektiren hastaların risk faktörlerini taramak, seçilen göstergelere dayalı bir öngörü modeli oluşturmak ve nomogramı çizmek için çok değişkenli lojistik regresyon analizi yapıldı. Modelin öngörü değerini değerlendirmek için alıcı işletim karakteristiği (ROC) eğrileri ve kalibrasyon eğrisi kullanıldı.

**BULGULAR:** Cerrahi uygulanmayan gruba göre vücut ısısında düşüş, kalp atış hızında artış, yaralanma ciddiyet skorunda (Injury Severity Score-ISS) yükselme, kan üre nitrojeni, kan ürik asit, kreatinin, arteriyel parsiyel oksijen basıncı, alkali fazlalığı, kan laktik asit ve kreatin kinaz izoenzimlerinde (CK-MB) artış ve HCO<sub>3</sub><sup>-</sup> ve Glasgow Koma Skalası (GCS) skorlarında düşüş saptanmıştır (tümü, p<0.05). Lojistik regresyon analizi, kreatinin, arteriyel kısmi oksijen basıncı, HCO<sub>3</sub><sup>-</sup>, CK-MB ve GCS'nin karaciğer rüptürüne yönelik cerrahi müdahale için etkili faktörler olduğunu ortaya koymuştur. Bu beş göstergeye dayalı olarak geliştirilen nomogram modeli, iyi derecede diskriminatifi (AUC=0.971, %95 GA: 0.896–0.997) ve iyi derecede doğruluğa sahipti.

**TARTIŞMA:** Kreatinin, arteriyel kısmi oksijen basıncı, HCO<sub>3</sub><sup>-</sup>, CK-MB, Glasgow koma skoru ve diğer parametrelere dayalı olarak oluşturulan bir nomogram modeli, karaciğer rüptürü olan hastaların cerrahi tedavisinin doğru bir şekilde öngörülebilmesini sağlayabilir.

**Anahtar sözcükler:** Cerrahi tedavi; geriye dönük analiz; karaciğer rüptürü; lojistik model; nomogram.

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