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*Retrospective Cohort Study*

# Establishment and evaluation of a prognostic model for patients with unresectable gastric cancer liver metastases

Chang ZY *et al*. Gastric cancer liver metastases

**Abstract**

BACKGROUND

Liver metastases is the primary factor contributing to unfavorable outcomes in patients diagnosed with gastric cancer. The objective of this study is to analyze significant prognostic risk factors for patients with gastric cancer liver metastases (GCLM) and develop a reliable nomogram model that can accurately predict individualized prognosis, thereby enhancing the ability to evaluate patient outcomes.

AIM

To analyze prognostic risk factors for gastric cancer liver metastases and develop a reliable nomogram model to accurately predict individualized prognosis, thereby enhancing patient outcome assessment.

METHODS

Retrospective analysis was conducted on clinical data pertaining to gastric cancer patients with liver metastases (C-GCLM type III), admitted to the Department of General Surgery across multiple centers of the Chinese PLA General Hospital from January 2010 to January 2018. The dataset was divided into a development cohort and validation cohort in a ratio of 2:1. In the development cohort, we utilized univariate and multivariate COX regression analyses to identify independent risk factors associated with overall survival in GCLM patients. Subsequently, we established a prediction model based on these findings and evaluated its performance using ROC curve analysis, calibration curves, and clinical decision curves. A nomogram was created to visually represent the prediction model, which was then externally validated using the validation cohort.

RESULTS

A total of 372 patients were included in this study, comprising 248 individuals in the development cohort and 124 individuals in the validation cohort. Based on COX

analysis results, our final prediction model incorporated five independent risk factors including albumin levels, primary tumor size, presence of extrahepatic metastases, surgical treatment status, and chemotherapy administration. The 1-, 3-, and 5-year Area Under the Curve (AUC) values in the development cohort are 0.753, 0.859, and 0.909, respectively; whereas in the validation cohort, they are observed to be 0.772, 0.848, and 0.923. Furthermore, the calibration curves demonstrated excellent consistency between observed values and actual values. Finally, the DCA curve indicated substantial net clinical benefit.

CONCLUSION

Our study identified significant prognostic risk factors for gastric cancer liver metastases and developed a reliable nomogram model, demonstrating promising predictive accuracy and potential clinical benefit in evaluating patient outcomes.

**Key Words:** Gastric cancer; Liver metastases; Nomogram; Prognostic model; Survival analysis

Chang Z, Gao W, Zhang Y, Zhao W, Wu D, Chen L. Establishment and evaluation of a prognostic model for patients with unresectable gastric cancer liver metastases. *World J Clin Cases* 2024; In press

**Core Tip:** This study identifies pivotal prognostic factors and introduces a nomogram model for predicting individualized prognosis in gastric cancer liver metastases. The developed model, supported by comprehensive validation, showcases substantial potential for improving patient outcome evaluation. Notably, the incorporation of five independent risk factors demonstrates promising predictive accuracy, paving the way for enhanced clinical decision-making in managing gastric cancer liver metastases patients, ultimately offering valuable insights for personalized treatment strategies.

## INTRODUCTION

Among all malignant tumor types, gastric cancer has the highest morbidity and fatality rates. It is one of the most frequent malignant tumors in the world[1]. With the development of treatment technology, the prognosis of patients with gastric cancer continues to improve. However, the 5-year overall survival rate (OS) of gastric cancer is only about 5%-20%[2]. Therefore, many studies have focused on exploring and analyzing the factors affecting the prognosis of GC patients, such as tumor size and distant metastases. liver is the most common distant metastases organ. The incidence of gastric cancer with liver metastases (GCLM) is 5%-34%[3], which is the main cause of poor prognosis of gastric carcinoma (GC) patients[4]. Although the comprehensive treatment technology has made some progress, the prognosis of gastric cancer patients with liver metastases is still not ideal[5]. Therefore, effective individualized treatment and comprehensive prognosis evaluation for GCLM patients are of great significance for the implementation of clinical strategies.

Based on a large number of clinical data, nomogram prediction models are widely used to evaluate the prognosis of patients with various types of cancer by combining multiple independent prognostic evaluation factors and quantifying individual survival risk[6-8]. Previous studies have explored the clinical prognostic factors of GCLM patients, but due to the small case size and incomplete research content, the analysis of the prognosis of patients is limited.

Due to the great differences in pathological types, clinical manifestations, tumor size and clinical stage among different types of GCLM patients, the prediction of disease prognosis and the selection of diagnosis and treatment methods are still controversial in clinical practice. C-GCLM (Chinese Type for Gastric Cancer Liver Metastases)[9] is a new clinical classification standard proposed by Chinese experts, which has a high reference value for clinical diagnosis and treatment decisions. This study focused on patients with C-GCLM type III, namely unresectable patients, and developed a prediction model to improve the ability to evaluate the individualized prognosis of patients.

## MATERIALS AND METHODS

*Study population*

A total of 761 individuals diagnosed with gastric cancer liver metastases were selected for this study from January 2010 to January 2018 at multiple centers within the Chinese PLA General Hospital's General Surgery Department. Following the exclusion of participants who were lost during follow-up, GCLM TypeI & TypeII, or lacking essential clinical data, a final cohort of 372 patients was included (Figure 1). The Ethics Committee of the Chinese PLA General Hospital approved this study (S2023-724-02), and all participant information was anonymized prior to analysis.

*Data collection*

Obtaining demographic information and clinical data from electronic medical record systems, Age, gender, height, weight, drinking habits, tumor size, tumor location, metastases size, metastases location, aspartate aminotransferase (AST), alanine aminotransferase (ALT), hemoglobin, albumin, γ-glutamyl transferase (γ-GGT), chemotherapy, surgery, *etc.* All the above data were collected and reviewed by uniformly trained professionals.

*Definition*

The classification of liver metastases of gastric cancer was formulated by the consensus of Chinese experts[9], and the specific classification criteria were as follows: (1) Type I : 1) the invasion depth of the primary tumor of gastric cancer was ≤T4a, and the lymph node metastases was within the D2 dissection range (Bully N2 was not included); Bulky N2 -- presence of at least one lymph node ≥3 cm in diameter or at least three adjacent lymph nodes ≥1.5 cm in diameter along the hepatic, celiac, or splenic arteries. 2) 1-3 Liver metastases; The maximum diameter of the metastatic lesions was ≤4 cm or they were confined to one lobe of the liver and did not involve important blood vessels or bile ducts. (2) Type II : 1) The invasion depth of the primary tumor was T4b, or Bulky N2, or Bulky No.16a2, b1 -- abdominal aortic lymph nodes. 2) The number and size of

liver metastases were beyond the scope of TypeI , but with potential surgical technical resectability. (3) Type III : 1) primary gastric cancer significantly invaded adjacent tissues or organs; Regional lymph nodes such as mesenteric or paraaortic lymph nodes were fixed, fused, or unresectable and confirmed by imaging studies or biopsy. 2) Liver metastases were divided into type IIIa, bilobar multiple diffuse metastases without extrahepatic metastases, and type IIIb, liver metastases with one or more extrahepatic organs with or without peritoneal metastases. The difference between the date of GCLM diagnosis and the date of death or the final follow-up was known as overall survival.

*Statistical analysis*

There were two cohorts created: one for derivation and the other for validation, with a 2:1 ratio. Utilizing chi-square analyses, categorical variables were compared and are shown as percentages (%). Continuous variable data were presented as the median and interquartile range (25th, 75th). Mann-Whitney U test were applied for comparing differences between groups for continuous variables. Following thte univariate and multivariate cox regression analysis, independent risk variables linked to the GCLM were found. A nomogram was created to visualize the model and calculate 1-, 3-, and 5-year overall survival rates. The predictive accuracy of the prediction model was evaluated using ROC curves in both development and validation cohorts. Calibration curves were employed to assess agreement between predicted results and actual outcomes, while Hosmer-Lemeshow statistics determined goodness-of-fit for the model. Survival curves for each major variable were generated using Cox hazard models. *P* values with two sides less than 0.05 were considered statistically significant. Software versions 22.0 and 4.0 of SPSS and R were used for all statistical analyses.

## RESULTS

*Baseline characteristics of the study participants*

This study analyzed 372 individuals diagnosed with gastric cancer liver metastases, with an average age of 60 years. The group consisted of 306 males and 66 females. Table 1 displays the patients' fundamental characteristics. 96 (25.8%) patients underwent surgery, 72 (19.4%) patients had concurrent extrahepatic metastases, and 60 (16.1%) patients received chemotherapy. All participants were assigned randomly to the development group ($n$ = 248) and the validation group ($n$ = 124) , as a ratio of 2:1, prior to further analysis. According to the results, there were no appreciable variations based on gender, age, tumor site, primary tumor dimensions, surgical procedures, radiotherapy or chemotherapy between the modeling and validation groups (all $P$>0.05).

*Construction of nomogram*

In the development cohort, univariate COX regression analysis identified BMI, albumin levels, primary tumor size, presence of extrahepatic metastases, surgical intervention, and chemotherapy as significant factors influencing patients' OS. Multivariate Cox regression analysis revealed that Albumin [$P$ = 0.021, HR (95%CI) = 0.96 (0.92, 0.99)], primary tumor size [$P$ = 0.025, HR (95%CI) = 1.10 (1.03, 1.21)], surgical intervention [$P$ = 0.002, HR (95%CI) = 0.34 ( 0.17, 0.67)], presence of extrahepatic metastases [$P$ = 0.002, HR (95 %CI) =2.21 (1.32, 3.69)] and administration of chemotherapy [$P$ = 0.009, HR (95%CI) = 0.46, 0.25, 0.82)] were identified as independent prognostic factors for patients diagnosed with GCLM (Table2). Based on the above results, a nomogram was drawn using five variables. By utilizing the respective scale associated with every risk factor on the nomogram, we derived individual scores for each factor and obtained a cumulative score by summing them up. By further comparing the percentage at the bottom, the predictive value of the 1-, 3-, and 5-year OS of C-GCLM type III patients could be obtained (Figure 2).

*Assessment of nomogram*

The nomogram in the development cohort correctly predicted overall survival after 1-, 3-, and 5-years, with area under the curve (AUC) values of 0.753, 0.859, and 0.909, respectively, according to the receiver operating characteristic curve (ROC). In the validation cohort, the values of 0.772, 0.848, and 0.923 were observed, all exceeding the threshold of 0.7 (Figure 3), suggesting a favorable predictive capacity of the nomogram. Patient overall survival rates from the development and validation cohorts were used to create the calibration curve at1,3, and 5 years. The findings indicated a strong concordance between the OS predicted by the nomogram model and the actual observation, as evidenced by the close alignment of their prediction curve with the 45° diagonal. This indicated that the constructed model had good discrimination ability and accuracy (Figure 4). Decision curve analysis was conducted in both the development and validation cohorts, revealing favorable net benefits for 1-, 3-, and 5-year overall survival rates. These findings indicate that the predictive model holds certain clinical value when it comes to forecasting OS in patients with unresectable GCLM (Figure 5).

*K-M survival curve analysis*

The impact of each individual factor on overall survival was further examined. Patients in the low-risk group had a significantly higher OS than those in the high-risk group, according to the Kaplan-Meier curve survival analysis ($P < 0.05$) (Figure 6).

## DISCUSSION

In this study, a cohort of 372 individuals diagnosed with C-GCLM type III were assigned to two groups in a random manner, maintaining a ratio of 2:1. The development group was utilized to assess the correlation between potential factors that may pose risks and outcomes related to survival, as well as build a prognostic model. On the other hand, the validation group served to confirm the effectiveness of the developed model in predicting future events. Independent prognostic factors influencing the overall survival rate of patients with GCLM were identified through multivariate Cox regression analysis, including albumin levels, size of the primary

tumor, presence of extrahepatic metastases, utilization of surgical treatment and administration of chemotherapy. Additionally,a nomogram model was developed to assess the survival rates at 1-, 3-, and 5-year intervals for patients with C-GCLM type III. The findings demonstrated that the proposed model exhibited satisfactory prognostic discrimination ability and survival prediction capability, indicating its potential in facilitating clinical decision-making.

Gastric cancer is a highly invasive cancer, and liver metastases is the most common distant metastases mode[10], and the prognosis is poor. Multidisciplinary comprehensive treatment has become the main treatment mode of GCLM. However, the prognosis and treatment effect of patients with unresectable gastric cancer liver metastases are still controversial. Therefore, it is essential to construct a reliable, efficient and easy to generalize prognostic model to improve the survival rate of GCLM patients. Most of the previous studies that proposed survival prediction models for gastric cancer have limited samples, limited predictors, or difficult to obtain evaluation indicators, which greatly limits the clinical application of these models. Chau *et al*[11] established a four-factor prognostic model including performance status, liver metastases, peritoneal metastases and alkaline phosphatase level. A meta study involving 1304 GCLM patients found that surgical resection of gastric cancer liver metastases had better 5-year overall survival (5yOS) and 10-year overall survival (10yOS) than medical control alone[12]. In addition, Ma T *et al*[13] developed and verified a nomogram prognostic scoring model including 9 variables, and simplified metastatic or recurrent gastric cancer into low, medium and high risk subgroups according to the survival rate to evaluate the prognosis. However, the applicability or reliability of these models in GCLM patients are limited. This study attempts to construct a clinical prediction model with good prediction ability and convenience, so that clinicians can make appropriate treatment according to individualized prediction and achieve better prognosis of patients.

The influence of the independent risk factors included in this study on the prognosis of patients with GCLM has also been confirmed in other studies. Nationwide retrospective studies from the United Kingdom have shown that gastrectomy and hepatectomy for

GCLM may confer a survival advantage for selected patients[14]. A systematic review showed that the median OS of patients who underwent gastrectomy combined with liver resection was significantly longer than that of patients who received palliative care (23.7 vs. 7.6 months)[15]. Similar to the findings of our investigation, surgical intervention demonstrates a beneficial impact on patient prognosis. This could be attributed to the presence of primary lesions, which potentially stimulate para-cancerous tissues surrounding metastatic lesions to create a tumor microenvironment that facilitates the infiltration, spread, and proliferation of cancer cells[16]. Albumin is often used as an indicator of clinical nutritional status, and low albumin is an indication of cachexia, which is usually associated with poor prognosis of cancer patients[17, 18]. A cohort study involving 147 patients with metastatic gastric cancer found that the score of hemoglobin, albumin, lymphocyte and platelet composition had good prognostic value in advanced gastric cancer[19]. In the prediction model of recurrent or metastatic gastric cancer established by Ma *et al*, albumin is also a risk factor affecting the prognosis[13]. Tumor size directly affects the survival of gastric cancer patients [20-22]. In this study, we found that tumor size was an independent prognostic factor in patients with unresectable liver metastases from gastric cancer and was inversely associated with OS in our model. Chemotherapy is one of the main treatment methods for patients with GCLM. With the wide application of new chemotherapeutic drugs in recent years, preoperative neoadjuvant chemotherapy has been increasingly used in advanced or metastatic gastric cancer, which provides support for reducing postoperative recurrence and prolonging survival time for patients with multiple GCLM. A Japanese study showed that chemotherapy can be applied to patients who underwent R2 resection of liver metastases (macroscopic residual tumor after resection), and the general condition and major organ function of these patients should be ensured before receiving chemotherapy[23]. For GCLM patients who cannot undergo radical resection at the time of initial diagnosis, preoperative chemotherapy can reduce the stage of the primary tumor, so as to obtain a high R0 resection rate (R0) resection refers to the absence of cancer cells at the surgical margin under the microscope)[24]. The metastases of GCLM

outside the liver indicates that the patient has entered a more advanced stage of the tumor, suggesting a worse prognosis. Liver metastases of gastric cancer is usually multifocal, and can be accompanied by extrahepatic metastases (peritoneum, lymph node, *etc.*). Yamaue *et al*[25] showed that peritoneal metastases and lymph node metastases were independent risk and prognostic factors of GCLM. The outcomes of advanced GC patients with distant metastases were poor, with lung, bone, and brain metastases being 4 months, 3 months, 4 months, and 3 months, respectively[26]. This study found that the survival time of patients with extrahepatic metastases was significantly reduced, and simultaneous hepatectomy can be attempted in GCLM patients without extrahepatic metastases.

At present, with the promotion of multidisciplinary treatment (MDT) mode, GCLM has gradually changed from a single-discipline treatment mode to a multidisciplinary treatment mode[9]. In addition to surgery, the treatment of unresectable gastric cancer also includes chemotherapy, immunosuppressant (ICI), molecular targeted drugs and so on[27]. In the process of treatment, we should correctly evaluate the patient's condition and take the patient as the center. According to the individual differences of patients, we should study and formulate an individualized treatment plan of "one person, one policy", so as to improve the quality of life of patients and prolong the survival time of patients as far as possible.

The strength of this study is that it is the first prediction model for OS in patients with GCLM type III, which has multi-center and large sample data, and has been internally and externally validated, reflecting good performance. However, it has the following limitations: (1) as a retrospective cohort study, selection bias is inevitable; (2) The data came from Chinese patients, and there may be limitations in generalization to other countries and ethnic groups; (3) With the in-depth study of tumor biological behavior and invasion mechanism, a variety of new tumor treatment methods have emerged, such as immunotherapy, targeted drugs and targeted gene therapy, and have achieved good results. However, the collection of relevant data in this study was not complete, which may cause certain bias.

## CONCLUSION

In conclusion, it is significant for clinicians to conduct precision medicine and individualized medicine by evaluating the prognosis of patients with unresectable GCLM and constructing the corresponding prognostic model. The nomogram model developed in this study offers a convenient, accurate, and user-friendly tool for clinicians to predict and evaluate the prognosis of GCLM patients.

## ARTICLE HIGHLIGHTS

### *Research background*

Liver metastases play a pivotal role in determining poor prognosis for individuals with gastric cancer. This study aims to investigate key prognostic factors influencing outcomes in patients with gastric cancer liver metastases (GCLM) and construct a dependable nomogram model that can effectively forecast personalized prognosis, thereby improving the evaluation of patient outcomes.

### *Research motivation*

This study centers on refining prognostic tools for gastric cancer liver metastases, aiming to address the impact of liver metastases on poor outcomes and enhance individualized prognosis prediction accuracy. By tackling the challenges related to diverse clinical characteristics and treatment uncertainties in GCLM patients, this research seeks to optimize clinical strategies, offering a pathway for improving patient outcomes and guiding future research endeavors in the field.

### *Research objectives*

The primary research objective is to develop a reliable nomogram model for predicting individualized prognosis in gastric cancer liver metastases patients, aiming to improve prognostic accuracy and optimize clinical strategies based on key prognostic factors. By successfully constructing and validating the nomogram model, this study achieved the

goal of enhancing prognostic evaluations for unresectable GCLM patients, offering a valuable tool for personalized treatment decisions and paving the way for future research aimed at refining patient outcomes in this field.

***Research methods***

This study conducted a retrospective analysis involving 372 gastric cancer liver metastases patients to develop a nomogram predictive model for individualized prognosis assessments. By utilizing a multidimensional data collection approach involving demographic and clinical variables, combined with advanced statistical analyses including univariate and multivariate cox regression, nomogram creation, the receiver operating characteristic curve (ROC) curve assessment, calibration curves, and survival analysis, this research showcases an innovative method aimed at improving prognostic evaluations in unresectable GCLM cases, emphasizing accuracy and personalized predictive capabilities. The unique approach of comparing derivation and validation cohorts, alongside the utilization of sophisticated statistical tools such as chi-square analyses, Mann-Whitney U test, and Cox hazard models, reflects the comprehensive nature and robustness of the developed nomogram model, offering valuable insights for enhancing clinical strategies and future research directions in managing gastric cancer liver metastases.

***Research results***

The study of 372 patients with gastric cancer liver metastases revealed key prognostic factors such as Albumin levels, primary tumor size, surgical intervention, presence of extrahepatic metastases, and administration of chemotherapy, which significantly influenced patients' overall survival. The developed nomogram model exhibited satisfactory predictive accuracy for 1-, 3-, and 5-year overall survival rates in both the development and validation cohorts, indicating its potential clinical utility in guiding treatment decisions for unresectable GCLM patients. These results contribute to enhancing personalized prognosis assessments and optimizing clinical strategies.

*Research conclusions*

This study underscores the importance of precision and individualized medicine for patients with unresectable gastric cancer liver metastases (GCLM) through prognosis evaluation and nomogram model development, facilitating tailored clinical decisions. The novel nomogram model presented serves as a practical and precise tool for clinicians to predict and assess GCLM patient prognoses effectively, promoting personalized treatment strategies and optimal patient care in this challenging clinical setting.

*Research perspectives*

Future research endeavors in the field of gastric cancer liver metastases could focus on expanding the nomogram model by incorporating additional prognostic factors and exploring novel therapeutic interventions to further enhance personalized patient care and treatment outcomes.

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