Am J Transl Res 2024;16(5):1701-1710
www.ajtr.org /ISSN:1943-8141/AJTR0151477

*Original Article*

# Risk factors for hemoglobin decline in gastric cancer patients undergoing postoperative chemotherapy: a retrospective analysis

Ruofei Ma[1], Huqin Yuan[1], Yaling Wang[2], Tao Wang[1], Jijun Wang[1]

*[1]Department of Gastric Tumor Surgery, Gansu Provincial Cancer Hospital, Gansu Provincial Academic Institute for Medical Research, No. 2 Xiaoxihu East Street, Qilihe District, Lanzhou 730050, Gansu, China; [2]Department of Respiratory Oncology, Gansu Provincial Cancer Hospital, Gansu Provincial Academic Institute for Medical Research, No. 2 Xiaoxihu East Street, Qilihe District, Lanzhou 730050, Gansu, China*

Received May 28, 2023; Accepted December 6, 2023; Epub May 15, 2024; Published May 30, 2024

**Abstract:** Objective: To investigate the independent risk factors for a decreased hemoglobin level in gastric cancer patients undergoing adjuvant chemotherapy. Methods: A retrospective study was conducted on 142 gastric cancer patients who received chemotherapy between May 2017 and May 2021 at the Gansu Provincial Cancer Hospital. All patients were subjected to the same regimen of adjuvant chemotherapy combining platinum/taxane and fluorouracil. The correlation between patients' clinicopathological features and the decreased hemoglobin during adjuvant chemotherapy was analyzed. Logistic and LASSO regression analyses were employed to screen for independent risk factors for decreased hemoglobin during adjuvant chemotherapy. Results: Univariate analysis revealed that intraoperative bleeding, pre-chemotherapy anemia, and hypoalbuminemia were risk factors for the decreased hemoglobin in patients during adjuvant chemotherapy (all $P < 0.05$). Both logistic and LASSO regression analyses corroborated these factors as influential factors in the decrease of hemoglobin ($P < 0.05$). In addition, both logistic and LASSO regression models demonstrated similar performance in this aspect. The nomogram model was subjected to internal validation, resulting in a C-index of 0.712 (0.629-0.796). The calibration curves exhibited satisfactory alignment with the ideal curve. Conclusion: Intraoperative blood loss, pre-chemotherapy anemia, and hypoalbuminemia are independent risk factors for hemoglobin reduction following chemotherapy. Moreover, both the logistic and LASSO regression models exhibited equivalent performance in this context. These findings bear substantial clinical implications, aiding physicians in the management of anemia in patients undergoing chemotherapy.

**Keywords:** Gastric cancer, postoperative adjuvant chemotherapy, decreased hemoglobin, risk factors, Nomogram

## Introduction

Gastric cancer remains one of the most common and deadly cancers worldwide [1]. Despite significant advancements in treatment strategies, the prognosis for gastric cancer patients, particularly those with advanced stages, remains poor [2]. Postoperative adjuvant chemotherapy is a key treatment strategy used to reduce tumor recurrence and improve survival [3]. However, this approach is often associated with significant side effects and complications, among which anemia is one of the most frequent and troublesome [4].

Anemia, characterized by a decrease in hemoglobin levels, is a common adverse effect during postoperative chemotherapy. It can lead to various symptoms such as fatigue, dizziness, and palpitations, severely affecting a patient's quality of life and even the efficacy of their treatment [5]. Numerous factors have been postulated to influence the occurrence of anemia during chemotherapy, including the cytotoxicity of chemotherapy agents on hematopoietic cells, and the treatment-induced inflammation that disturbs iron metabolism [6]. However, the specific risk factors causing hemoglobin decline after postoperative chemotherapy in gastric cancer patients remain poorly understood [7]. Existing studies investigating the factors influencing hemoglobin decline in gastric cancer patients undergoing chemotherapy have largely been limited by their small sample sizes, single-

https://doi.org/10.62347/CLLZ7409

center designs, and lack of rigorous statistical analyses [8, 9]. In addition, most previous studies have not developed predictive models to help clinicians identify patients at high risk for hemoglobin decline, thus limiting their clinical utility [10, 11].

In the present study, we applied advanced statistical methods including univariate analysis, logistic regression, and LASSO regression to identify and validate independent risk factors for hemoglobin decline. Furthermore, we innovatively constructed and compared the performance of two predictive models for hemoglobin decline, which could assist clinicians in the risk stratification and management of anemia in gastric cancer patients undergoing chemotherapy. These findings are expected to provide new insight into the management of anemia in gastric cancer patients and improve their overall treatment outcome and quality of life.

## Materials and methods

### *General information*

This retrospective study involved 205 gastric cancer patients who underwent chemotherapy between May 2017 and May 2021 at Gansu Provincial Cancer Hospital. All patients were treated with an adjuvant chemotherapy regimen that combined platinum/taxane and fluorouracil. This research was approved by the medical ethics committee of Gansu Provincial Cancer Hospital (P-LW202311210013).

### *Treatment regimen*

Patients included in this study received adjuvant chemotherapy following surgical resection of gastric cancer. The chemotherapy regimen was characterized by the inclusion of fluorouracil-based medications, particularly 5-fluorouracil (5-FU, Chinese Pharmaceutical Criterion H23021711, Heilongjiang Fuhe Pharmaceutical Group Co., Ltd.) and leucovorin (Sinopharmaceutical Criterion H20023636, Jiangsu Hengrui Pharmaceutical Co., Ltd.), in combination with either oxaliplatin (Sinopharmaceutical Criterion H20133094, Harbin Pharmaceutical Group Biological Engineering Co., Ltd.) or cisplatin (Guoyao Zhanzi H20213819, Qilu Pharmaceutical Co., Ltd.). The specific regimen, referred to as either FOLFOX or FOLFIRI, was selected based on the patient's overall health, cancer stage, and the oncologist's evaluation.

In the FOLFOX regimen, patients were intravenously administered oxaliplatin (85 mg/m$^2$) on the first day, followed by leucovorin (400 mg/m$^2$), then an intravenous bolus of 5-FU (400 mg/m$^2$), and finally a continuous infusion of 5-FU (2400 mg/m$^2$) over 46 hours. This cycle was repeated every two weeks. In the FOLFIRI regimen, patients were given an intravenous dose of irinotecan (180 mg/m$^2$) on the first day, coupled with leucovorin (400 mg/m$^2$), followed by an intravenous bolus of 5-FU (400 mg/m$^2$), and finally a continuous infusion of 5-FU (2400 mg/m$^2$) over 46 hours. This cycle was similarly repeated every two weeks. Patients underwent a total of 8 to 12 cycles of chemotherapy, which were contingent upon their response to treatment and side effects tolerance. Dosage adjustments were made in accordance with the observed toxic effects as per standard guidelines. The response to chemotherapy was evaluated after every two cycles, following the Response Evaluation Criteria in Solid Tumors (RECIST) [12].

### *Inclusion and exclusion criteria*

Inclusion criteria: patients with histologically confirmed gastric cancer [13], those who had successfully completed D2 type surgery and R0 resection, patients who completed a minimum of 4 cycles of adjuvant chemotherapy with platinum/taxane and fluorouracil, patients without secondary malignant tumors, and those with complete clinical data. The study complied with the provisions of the "Declaration of Helsinki of the World Medical Association" [14].

The exclusion criteria: patients with a history of radiotherapy and renal insufficiency, patients with hemorrhagic diseases, autoimmune hemolysis, chronic inflammation, or patients with elevated carcinoembryonic antigen (CEA) and CA199, as well as patients who had received preventative supplemental hematopoietic raw materials.

### *Sample grouping*

As per the grading standards delineated in the NCCN anemia guideline [13] in the United States, anemia is defined as Hb < 110 g/L. Mild anemia is classified as Hb 90-110 g/L, moderate anemia as Hb 60-90 g/L, and severe anemia as Hb < 60 g/L. According to the defined inclusion and exclusion criteria, we initially screened 205 samples, and 142 patients

**Table 1.** Baseline data sheet

| Factor | n |
|---|---|
| Age | |
| ≥ 60 | 55 |
| < 60 | 87 |
| Gender | |
| Male | 88 |
| Female | 54 |
| Tumor location | |
| Pancreatic | 23 |
| Gastric body | 81 |
| Gastric sinus | 44 |
| Differentiation degree | |
| Low | 123 |
| Medium | 19 |
| TNM staging | |
| I-II staging | 43 |
| III staging | 99 |
| Surgical method | |
| Proximal resection | 9 |
| Total gastrectomy | 87 |
| Distal resection | 42 |
| T-staging | |
| T1-T3 | 23 |
| T4 | 119 |
| Deep venous invasion | |
| Yes | 98 |
| No | 44 |
| Lymph node metastasis | |
| Yes | 101 |
| No | 41 |
| Intraoperative blood loss | |
| ≥ 100 mL | 26 |
| < 100 mL | 116 |
| Pre-chemotherapy anemia | |
| Yes | 31 |
| No | 111 |
| Hypoalbuminemia | |
| Yes | 59 |
| No | 83 |
| Smoking history | |
| Yes | 88 |
| No | 54 |
| Alcohol abuse history | |
| Yes | 15 |
| No | 127 |
| Hypertension history | |
| Yes | 31 |
| No | 111 |
| Diabetes history | |
| Yes | 22 |
| No | 120 |

Note: TNM staging: Tumor, nodes, metastasis-classification.

met the requirements finally. Patients were categorized into a decline group (n=84) and a non-decline group (n=58) based on the decline in Hb after chemotherapy.

*Clinical data collection*

We collated data pertaining to patients' age, gender, tumor location, degree of differentiation, TNM stage, surgical method, T stage, deep vein invasion, lymph node metastasis, intraoperative bleeding, among other clinical data.

*Statistical analysis*

The study used R language 4.1.1 software (R Foundation for Statistical Computing, Vienna, Austria) for data cleaning, data analysis, and model building. LASSO regression was used to screen predictive factors with non-zero coefficients, and logistic regression was used to screen influencing factors. R (R3.5.3) software package and rms package were used to create Nomograms, and rms package was used to calculate the concordance index (C-index). The clinical value was verified through the receiver operating characteristic (ROC) curve. Delong's test was used to analyze the difference in the area under the ROC curve. Graph Pad Prism 8.0 was used for data visualization. A $P$ value < 0.05 indicated statistical significance.

## Results

*Baseline data*

We obtained a total of 142 samples, including 55 patients aged ≥ 60 and 87 patients aged < 60; among them there were 88 male patients and 54 female patients. **Table 1** shows the clinical characteristics of patients: tumor sites: 23 in pancreatic, 81 in gastric body and 44 in gastric sinus; 123 cases of hypofractionation, 19 cases of intermediate differentiation; 43 cases of TNM stage I-II, 99 cases of stage III; 9 cases of proximal resection, 87 cases of total gastric resection, and 42 cases of distal resection; 23 cases of stage T1-T3, 119 cases of T4 stage; 98 cases of deep venous duct invasion; 101 cases of lymph node metastasis; 26 cases with intraoperative bleeding ≥ 100 mL, 116 cases with < 100 mL; 31 cases with anemia before chemotherapy; 59 cases with hypoproteinemia; 88 cases with a history of smoking; 15 cases

**Table 2.** Univariate analysis of the hemoglobin decline in patients

| Factor | Decrease group (n=84) | Non-decrease group (n=58) | $\chi^2$ value | *P* value |
|---|---|---|---|---|
| Age | | | | |
| ≥ 60 years | 32 | 23 | 0.035 | 0.810 |
| < 60 years | 52 | 35 | | |
| Gender | | | | |
| Male | 55 | 33 | 1.072 | 0.339 |
| Female | 29 | 25 | | |
| Tumor location | | | | |
| Pancreatic | 13 | 10 | 0.328 | 0.848 |
| Gastric body | 49 | 32 | | |
| Gastric sinus | 28 | 16 | | |
| Differentiation degree | | | | |
| Low | 71 | 52 | 0.779 | 0.383 |
| Medium | 13 | 6 | | |
| TNM staging | | | | |
| I-II staging | 29 | 14 | 1.753 | 0.185 |
| III staging | 55 | 44 | | |
| Surgical methods | | | | |
| Proximal resection | 4 | 5 | 3.407 | 0.182 |
| Total gastrectomy | 50 | 37 | | |
| Distal resection | 30 | 12 | | |
| T-staging | | | | |
| T1-T3 | 15 | 8 | 0.417 | 0.518 |
| T4 | 69 | 50 | | |
| Deep venous invasion | | | | |
| Yes | 60 | 38 | 0.560 | 0.454 |
| No | 24 | 20 | | |
| Lymph node metastasis | | | | |
| Yes | 62 | 39 | 0.720 | 0.395 |
| No | 22 | 19 | | |
| Intraoperative blood loss | | | | |
| ≥ 100 mL | 21 | 5 | 6.154 | 0.013 |
| < 100 mL | 63 | 53 | | |
| Pre-chemotherapy anemia | | | | |
| Yes | 25 | 6 | 7.580 | 0.005 |
| No | 59 | 52 | | |
| Hypoalbuminemia | | | | |
| Yes | 43 | 16 | 7.871 | 0.005 |
| No | 41 | 42 | | |
| Smoking history | | | | |
| Yes | 55 | 33 | 1.072 | 0.301 |
| No | 29 | 25 | | |
| Alcohol abuse history | | | | |
| Yes | 10 | 5 | 0.391 | 0.531 |
| No | 74 | 53 | | |
| Hypertension history | | | | |
| Yes | 19 | 12 | 0.074 | 0.784 |
| No | 65 | 46 | | |
| Diabetes history | | | | |
| Yes | 12 | 10 | 0.228 | 0.632 |
| No | 72 | 48 | | |

Note: TNM staging: Tumor, nodes, metastasis-classification.

with a history of alcohol abuse; 31 cases with a history of hypertension; 22 cases with a history of diabetes mellitus.

*Univariate analysis*

Univariate analysis indicated that intraoperative blood loss, pre-chemotherapy anemia, and hypoalbuminemia were risk factors for hemoglobin decline in patients (all P < 0.05, **Table 2**).

*Logistic regression analysis and risk model establishment*

To further identify the risk factors affecting the patient's hemoglobin decline, we used logistic regression for analysis. The results showed that intraoperative blood loss, pre-chemotherapy anemia, and hypoalbuminemia were independent risk factors affecting the decrease of hemoglobin in patients after chemotherapy (all P < 0.05, **Table 3**). Subsequently, we constructed a risk model of logistic regression based on the β coefficients of logistic regression. The risk score of each patient was calculated through the risk scoring formula. Risk formula: intraoperative blood loss * 1.113 + pre-chemotherapy anemia * 1.308 + hypoalbuminemia * 0.940. Based on the risk scoring formula, we obtained the risk score of each sample. By comparison, we found that the risk score of patients in the decline group was significantly higher than that of the non-decline group (P < 0.0001, **Figure 1A**). Through the ROC curve analysis, it was found that the area under the curve of the risk score in predicting patient's lung infection was 0.712 (**Figure 1B**).

**Table 3.** Logistic regression analysis

| Factor | β | Standard error | $\chi^2$ value | *P* value | OR value | 95% CI | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower | Upper |
| Intraoperative blood loss | 1.113 | 0.552 | 4.065 | 0.044 | 3.045 | 1.032 | 8.985 |
| Pre-chemotherapy anemia | 1.308 | 0.509 | 6.595 | 0.010 | 3.697 | 1.363 | 10.028 |
| Hypoalbuminemia | 0.940 | 0.383 | 6.028 | 0.014 | 2.559 | 1.209 | 5.420 |

Note: CI: Confidence interval; OR: Odds ratio.

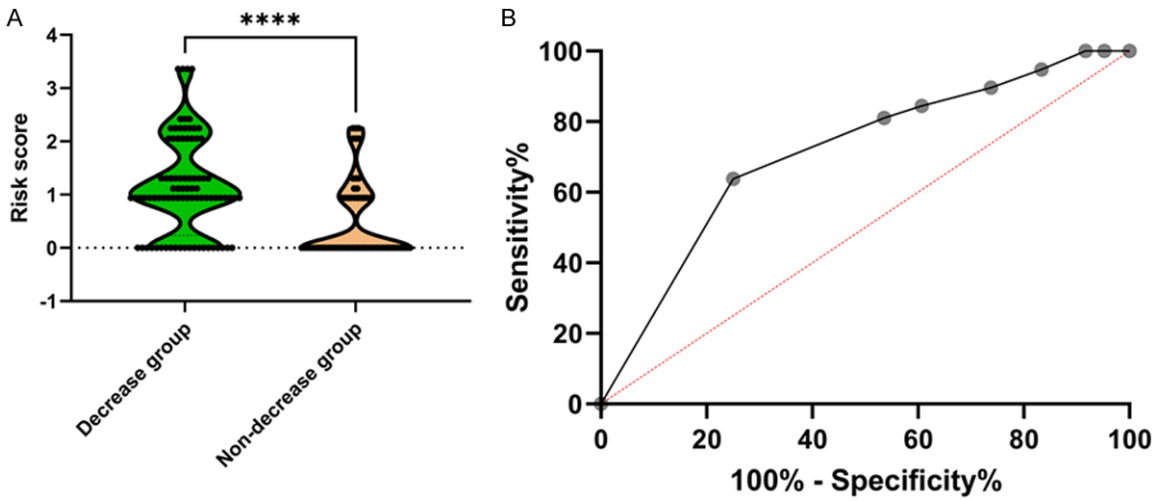


**Figure 1.** Logistic risk model in predicting patient hemoglobin decline. A. Logistic regression risk model score in each patient. B. ROC curve of the logistics regression risk model. Note: ROC curve: Receiver operating characteristic curve; ****P < 0.0001.

*LASSO regression analysis and risk model establishment*

We performed LASSO regression analysis on the obtained data again and found that intraoperative blood loss, pre-chemotherapy anemia, and hypoalbuminemia were all significant (all P < 0.05), and 3 indicators were acceptable for lambda selection in both 1se and min, so we chose lambda.1se (0.07714) for analysis (**Figure 2A**, **2B**). Based on lambda.1se, we built the risk scoring formula: intraoperative blood loss * 0.04616139 + pre-chemotherapy anemia * 0.08243276 + hypoalbuminemia * 0.07001516. Based on the risk scoring formula, we obtained the risk score of each sample. By comparison, we found that the risk score of patients in the decline group was significantly higher than that of the non-decline group (P < 0.0001, **Figure 2C**). Through the ROC curve analysis, it was found that the area under the curve of the risk score for predicting hemoglobin levels in patients undergoing postoperative chemotherapy for gastric cancer was 0.707 (**Figure 2D**).

*Predictive performance comparison*

To compare the predictive performance of the two models in predicting hemoglobin decline, we used Delong's test to compare the area under the curve of the two models. The results showed no difference in the area under the curve of the two models (P > 0.05, **Table 4**; **Figure 3**), and through the ROC parameters (**Table 5**), the specificity and sensitivity of the two models were consistent. This indicates that the predictive performances of the two models in predicting the hemoglobin decline in patients are comparable.

*Establishment of nomogram risk model*

Based on 3 independent prediction factors, a risk nomogram model was established to predict the risk of hemoglobin decline in patients. Each score line's left end corresponds to 0 points, and the right end starts from the intraoperative blood loss indicator, in turn, 85, 100, 72 with a total score of 280 points (**Figure 4A**). For example, for a patient with intraoperative

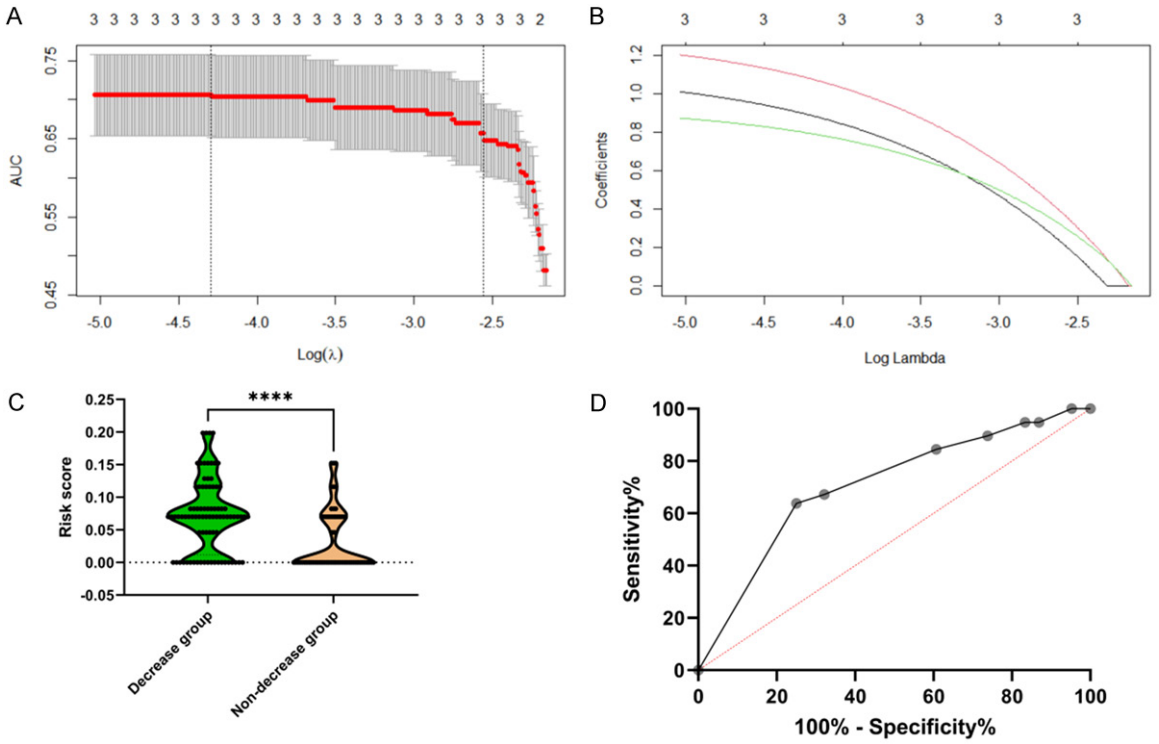


**Figure 2.** LASSO risk model for predicting patient hemoglobin decline. A, B. LASSO coefficient distribution of regression analysis and the level of adjusted parameter (lambda) based on 10-fold cross-validation. C. LASSO regression risk model score per patient. D. ROC curve of LASSO regression risk model. Note: LASSO: Least absolute contraction and selection operator; ROC curve: Receiver operating characteristic curve; ****P < 0.0001.

**Table 4.** Delong test

| | Z value | *P* value | AUC difference | Standard error difference | 95% CI | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| Logistic vs LASSO | 0.439 | 0.66 | 0.004 | 0.285 | -0.015 | 0.024 |

Note: CI: confidence interval; AUC: area under the curve.

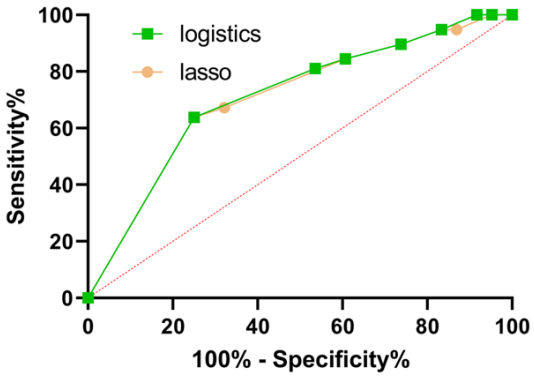


**Figure 3.** Comparison of ROC curves in predicting the decrease of hemoglobin between logistic and LASSO prediction models. Note: LASSO: Least absolute shrinkage and selection operator; ROC curve: Receiver operating characteristic curve.

blood loss ≥ 100 mL, existed pre-chemotherapy anemia, and no hypoalbuminemia, the score shown by the nomogram model is 85 + 100 + 0=185 points. The corresponding probability of hemoglobin decline is about 65%. The nomogram model was internally validated using the Bootstrap method (after 1,000 times of resampling the original data), and the results showed that the internal validation C-index was 0.712 (0.629-0.796), and the calibration curve was in good agreement with the ideal curve (**Figure 4B**).

## Discussion

After surgical resection, postoperative adjuvant chemotherapy has become one of the routine

**Table 5.** ROC parameters

| Predictive variable | AUC | 95% CI | Cut-off value | Sensitivity | Specificity | Youden index |
|---|---|---|---|---|---|---|
| Logistic | 0.712 | 0.630-0.795 | 0.470 | 0.637 | 0.750 | 0.387 |
| LASSO | 0.708 | 0.624-0.791 | 0.023 | 0.637 | 0.750 | 0.387 |

Note: AUC: Area under the Curve; CI: confidence interval.

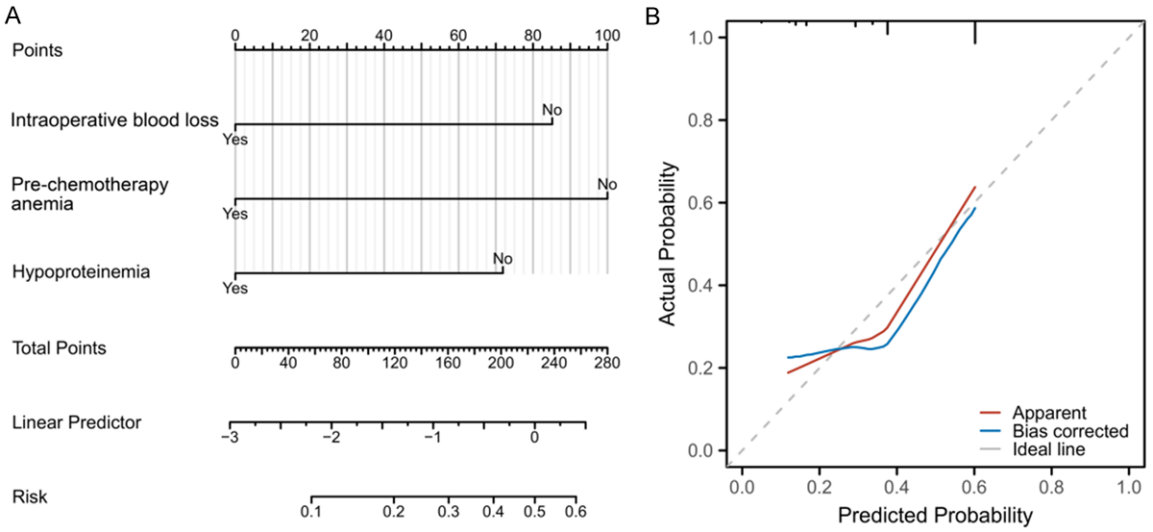


**Figure 4.** Nomogram risk model and internal validation. A. Nomogram for predicting hemoglobin decline. B. Bootstrap method for internal validation of the nomogram model.

treatment plans for gastric cancer patients to reduce postoperative tumor recurrence and mortality [15-18]. However, the adverse reactions of postoperative chemotherapy are inevitable, including nausea, vomiting, diarrhea, and fatigue, among which anemia is the most common [19-21]. Anemia is also common during postoperative chemotherapy. Its main manifestation is a decline in hemoglobin, leading to symptoms such as fatigue, dizziness, and palpitations in patients, which may seriously affect the patient's quality of life and treatment effect [22-24]. Therefore, exploring the risk factors causing the decline of hemoglobin after postoperative chemotherapy is of great significance for guiding clinical doctors' treatment strategies and improving quality of life.

In gastric cancer patients undergoing chemotherapy after surgery, the etiology of anemia can be multifactorial. Extensive clinical discussions have highlighted various factors contributing to decreased hemoglobin levels after postoperative chemotherapy, such as chemotherapy drugs irreversibly damaging hematopoietic cells alongside tumor cells [25]. Additionally, studies have demonstrated that chemotherapy-induced inflammation plays a significant role in anemia development. Overexpression of inflammatory cell factors such as γ-interferon (IFN-γ), interleukin (IL-1), and tumor necrosis factor (TNF) leads to increased hepcidin levels, which subsequently diminish the direct utilization of iron by red blood cells, thereby causing disruptions in red blood cell production [26]. However, the consistency of these findings remains unclear. In this retrospective analysis, we investigated the influence of various factors on hemoglobin reduction in patients. Univariate analysis revealed that intraoperative blood loss, pre-chemotherapy anemia, and hypoalbuminemia could significantly impact hemoglobin levels. Logistic regression and LASSO regression analyses confirmed the independent association of intraoperative blood loss, pre-chemotherapy anemia, and hypoalbuminemia with hemoglobin decline. Notably, intraoperative blood loss exceeding 100 mL indicates substantial bleeding during surgery, which can lead to postoperative anemia. Insufficient blood volume resulting from significant blood loss, relative to red blood

cell count reduction, also contributes to this anemia [27]. Furthermore, the administration of hemostatic drugs and blood transfusions during surgery may also influence anemia development. Pre-existing anemia exacerbates the decline in hemoglobin levels caused by chemotherapy due to the reduced number of red blood cells in the patient's body [28]. Anemia-induced oxygen deficiency further diminishes the patient's tolerance to chemotherapy drugs, ultimately affecting the treatment outcome [29]. Hypoalbuminemia, characterized by below-normal levels of plasma protein, adversely impacts various physiologic activities. Its correlation with postoperative anemia is due to insufficient blood volume, resulting in a relative reduction in red blood cell count [30]. Additionally, hypoalbuminemia may compromise the patient's immune function and reduce their tolerance to chemotherapy drugs, thereby influencing the treatment outcome [31].

In medical diagnosis and prediction, predictive models play a vital role in assisting doctors with patient assessment and disease trend forecasting [32-34]. Two commonly used predictive models are logistic regression and LASSO regression. Logistic regression is well-suited for binary classification tasks, enabling clinicians to make judgments regarding the presence or absence of a particular disease by constructing an appropriate model [35]. On the other hand, LASSO regression is a linear regression technique that incorporates feature selection, making it effective for handling high-dimensional data and enhancing the accuracy of predictive models [36]. In our study, we developed predictive models using both logistic regression and LASSO regression. Interestingly, we observed comparable performance between the two models, with no significant difference in the area under the curve (AUC) and consistent specificity and sensitivity. These findings indicate that the selected features in our models were reasonable, accurately reflecting the patients' actual conditions, and both algorithms demonstrated robust performance. We considered the sample size and distribution in our study, implementing measures such as cross-validation to ensure the reliability and stability of the models. Additionally, we employed a nomogram risk model to predict the risk of anemia following chemotherapy. This model integrated three key factors: intraoperative blood loss, pre-chemotherapy anemia, and hypoalbuminemia. By considering these variables, the nomogram effectively predicted the likelihood of anemia development after chemotherapy. The model demonstrated good predictive performance, as evidenced by a C-index of 0.712 (95% CI: 0.629-0.796), further supporting its reliability and clinical utility.

In this study, we analyzed the risk factors for the decline in hemoglobin after gastric cancer chemotherapy through two models and determined that intraoperative blood loss, pre-chemotherapy anemia, and hypoalbuminemia are related to the decline in hemoglobin in patients. However, this study still has certain limitations. First, the study is a single-center study with a small sample size, which may result in bias in the results. Second, due to the small sample size, we did not perform external validation in this study. The generalizability of the model still needs to be further empirically verified. Therefore, we hope to carry out more experiments in subsequent research to improve our results.

In summary, intraoperative blood loss, pre-chemotherapy anemia, and hypoalbuminemia are independent risk factors affecting the decrease of hemoglobin in patients after chemotherapy. Moreover, logistic regression and LASSO regression models perform similarly in this regard. These results have some clinical significance for doctors to guide the management of anemia in patients after chemotherapy.

## Acknowledgements

Gansu Provincial Science and Technology Support Plan (No. 1504FKCA049).

## Disclosure of conflict of interest

None.

**Address correspondence to:** Jijun Wang, Department of Gastric Tumor Surgery, Gansu Provincial Cancer Hospital, Gansu Provincial Academic Institute for Medical Research, No. 2 Xiaoxihu East Street, Qilihe District, Lanzhou 730050, Gansu, China. E-mail: 18993030306@189.cn

## References

[1] Siegel RL, Miller KD and Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020; 70: 7-30.

[2] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021; 71: 209-249.

[3] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424.

[4] Zhou M, Wang H, Zeng X, Yin P, Zhu J, Chen W, Li X, Wang L, Wang L, Liu Y, Liu J, Zhang M, Qi J, Yu S, Afshin A, Gakidou E, Glenn S, Krish VS, Miller-Petrie MK, Mountjoy-Venning WC, Mullany EC, Redford SB, Liu H, Naghavi M, Hay SI, Wang L, Murray CJL and Liang X. Mortality, morbidity, and risk factors in China and its provinces, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2019; 394: 1145-1158.

[5] Wu C, Li M, Meng H, Liu Y, Niu W, Zhou Y, Zhao R, Duan Y, Zeng Z, Li X, Li G, Xiong W and Zhou M. Analysis of status and countermeasures of cancer incidence and mortality in China. Sci China Life Sci 2019; 62: 640-647.

[6] Feng RM, Zong YN, Cao SM and Xu RH. Current cancer situation in China: good or bad news from the 2018 global cancer statistics? Cancer Commun (Lond) 2019; 39: 22.

[7] Tan Z. Recent advances in the surgical treatment of advanced gastric cancer: a review. Med Sci Monit 2019; 25: 3537-3541.

[8] Khorobrykh T, Nemtsova M, Kytko O, Agadzhanov V, Patalova A, Gogokhiya T, Andriyanov A and Spartak A. Surgical treatment of complicated gastric cancer in young and middle-aged patients. Georgian Med News 2022; 76-84.

[9] Tokunaga M, Sato Y, Nakagawa M, Aburatani T, Matsuyama T, Nakajima Y and Kinugasa Y. Perioperative chemotherapy for locally advanced gastric cancer in Japan: current and future perspectives. Surg Today 2020; 50: 30-37.

[10] Li L, Song X, Liu R, Li N, Zhang Y, Cheng Y, Chao H and Wang L. Chemotherapy versus radiotherapy for FIGO stages IB1 and IIA1 cervical carcinoma patients with postoperative isolated deep stromal invasion: a retrospective study. BMC Cancer 2016; 16: 403.

[11] Lethaby A, Puscasiu L and Vollenhoven B. Preoperative medical therapy before surgery for uterine fibroids. Cochrane Database Syst Rev 2017; 11: CD000547.

[12] Schwartz LH, Litiere S, de Vries E, Ford R, Gwyther S, Mandrekar S, Shankar L, Bogaerts J, Chen A, Dancey J, Hayes W, Hodi FS, Hoekstra OS, Huang EP, Lin N, Liu Y, Therasse P, Wolchok JD and Seymour L. RECIST 1.1-Update and clarification: from the RECIST committee. Eur J Cancer 2016; 62: 132-137.

[13] Ajani JA, D'Amico TA, Bentrem DJ, Chao J, Cooke D, Corvera C, Das P, Enzinger PC, Enzler T, Fanta P, Farjah F, Gerdes H, Gibson MK, Hochwald S, Hofstetter WL, Ilson DH, Keswani RN, Kim S, Kleinberg LR, Klempner SJ, Lacy J, Ly QP, Matkowskyj KA, McNamara M, Mulcahy MF, Outlaw D, Park H, Perry KA, Pimiento J, Poultsides GA, Reznik S, Roses RE, Strong VE, Su S, Wang HL, Wiesner G, Willett CG, Yakoub D, Yoon H, McMillian N and Pluchino LA. Gastric cancer, version 2.2022, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2022; 20: 167-192.

[14] Ballantyne A and Eriksson S. Research ethics revised: the new CIOMS guidelines and the World Medical Association Declaration of Helsinki in context. Bioethics 2019; 33: 310-311.

[15] Hufnagel DH, Mehta ST, Ezekwe C, Brown AJ, Beeghly-Fadiel A and Prescott LS. Prevalence of anemia and compliance with NCCN Guidelines for evaluation and treatment of anemia in patients with gynecologic cancer. J Natl Compr Canc Netw 2021; 19: 513-520.

[16] Ding D, Feng Y, Song B, Gao S and Zhao J. Effects of preoperative and postoperative enteral nutrition on postoperative nutritional status and immune function of gastric cancer patients. Turk J Gastroenterol 2015; 26: 181-185.

[17] Li Z, Shan F, Ying X, Zhang Y, E JY, Wang Y, Ren H, Su X and Ji J. Assessment of laparoscopic distal gastrectomy after neoadjuvant chemotherapy for locally advanced gastric cancer: a randomized clinical trial. JAMA Surg 2019; 154: 1093-1101.

[18] de Steur WO, van Amelsfoort RM, Hartgrink HH, Putter H, Meershoek-Klein Kranenbarg E, van Grieken NCT, van Sandick JW, Claassen YHM, Braak JPBM, Jansen EPM, Sikorska K, van Tinteren H, Walraven I, Lind P, Nordsmark M, van Berge Henegouwen MI, van Laarhoven HWM, Cats A, Verheij M and van de Velde CJH; CRITICS investigators. Adjuvant chemotherapy is superior to chemoradiation after D2 surgery for gastric cancer in the per-protocol analysis of the randomized CRITICS trial. Ann Oncol 2021; 32: 360-367.

[19] Liu C, Cheng B, Zhao G and Yuan H. Process analysis of anthracycline adverse reactions in breast cancer patients with postoperative chemotherapy. J Investig Med 2022; 70: 1352-1357.

[20] Liu W, Chen W, Zhang X, Zhao P, Fan Z, Bi L, Wu D, Li S, Yang M, Fu T, Song D, Han B, Zhao G, Du Y and Shi A. Higher efficacy and reduced adverse reactions in neoadjuvant chemothera-

py for breast cancer by using pegylated liposomal doxorubicin compared with pirarubicin. Sci Rep 2021; 11: 199.
[21] Sandrowski K, Edelman D, Rivlin M, Jones C, Wang M, Gallant G and Beredjiklian PK. A prospective evaluation of adverse reactions to single-dose intravenous antibiotic prophylaxis during outpatient hand surgery. Hand (N Y) 2020; 15: 41-44.
[22] Kanemitsu Y, Shitara K, Mizusawa J, Hamaguchi T, Shida D, Komori K, Ikeda S, Ojima H, Ike H, Shiomi A, Watanabe J, Takii Y, Yamaguchi T, Katsumata K, Ito M, Okuda J, Hyakudomi R, Shimada Y, Katayama H and Fukuda H; JCOG Colorectal Cancer Study Group. Primary tumor resection plus chemotherapy versus chemotherapy alone for colorectal cancer patients with asymptomatic, synchronous unresectable metastases (JCOG1007; iPACS): a randomized clinical trial. J Clin Oncol 2021; 39: 1098-1107.
[23] Steuber TD, Howard ML and Nisly SA. Strategies for the management of postoperative anemia in elective orthopedic surgery. Ann Pharmacother 2016; 50: 578-585.
[24] He S, Lingyun Z and Yunpeng L. Analysis of postoperative chemotherapy-related anemia in elderly cancer patients. Zhonghua Zhong Liu Za Zhi 2015; 37: 290-292.
[25] Weiss JM, Csoszi T, Maglakelidze M, Hoyer RJ, Beck JT, Domine Gomez M, Lowczak A, Aljumaily R, Rocha Lima CM, Boccia RV, Hanna W, Nikolinakos P, Chiu VK, Owonikoko TK, Schuster SR, Hussein MA, Richards DA, Sawrycki P, Bulat I, Hamm JT, Hart LL, Adler S, Antal JM, Lai AY, Sorrentino JA, Yang Z, Malik RK, Morris SR, Roberts PJ and Dragnev KH; G1T28-02 Study Group. Myelopreservation with the CDK4/6 inhibitor trilaciclib in patients with small-cell lung cancer receiving first-line chemotherapy: a phase Ib/randomized phase II trial. Ann Oncol 2019; 30: 1613-1621.
[26] Jeney V. Pro-inflammatory actions of red blood cell-derived DAMPs. Exp Suppl 2018; 108: 211-233.
[27] Nyflot LT, Sandven I, Stray-Pedersen B, Pettersen S, Al-Zirqi I, Rosenberg M, Jacobsen AF and Vangen S. Risk factors for severe postpartum hemorrhage: a case-control study. BMC Pregnancy Childbirth 2017; 17: 17.
[28] Newhall DA, Oliver R and Lugthart S. Anaemia: a disease or symptom. Neth J Med 2020; 78: 104-110.
[29] Chaparro CM and Suchdev PS. Anemia epidemiology, pathophysiology, and etiology in low- and middle-income countries. Ann N Y Acad Sci 2019; 1450: 15-31.
[30] Garcia-Bello JA, Ortiz-Flores J, Torres de la Riva FE, Mendoza-Moreno GK and Gomez-Tenorio C. Anemia and hypoalbuminemia as risk factors for left ventricular diastolic dysfunction in children with chronic kidney disease on peritoneal dialysis. Nefrologia (Engl Ed) 2018; 38: 414-419.
[31] Tsuji H, Hashimoto M, Harada T, Tanaka M, Ito H, Murakami K, Ohmura K, Fujii T and Mimori T. Persistent anemia and hypoalbuminemia in rheumatoid arthritis patients with low serum triiodothyronine level. Mod Rheumatol 2020; 30: 640-647.
[32] Kitamura R, Kawabe T, Kajiro T and Yonemochi E. The development of retention time prediction model using multilinear gradient profiles of seven pharmaceuticals. J Pharm Biomed Anal 2021; 198: 114024.
[33] Song J, Wang Y, Tang S, Zhang Y, Chen Z, Zhang Z, Zhang T and Wu F. Local-global memory neural network for medication prediction. IEEE Trans Neural Netw Learn Syst 2021; 32: 1723-1736.
[34] Jiang H and Huang Y. An effective drug-disease associations prediction model based on graphic representation learning over multi-biomolecular network. BMC Bioinformatics 2022; 23: 9.
[35] Barenji AV and Montreuil B. Open logistics: blockchain-enabled trusted hyperconnected logistics platform. Sensors (Basel) 2022; 22: 4699.
[36] Lu J, Wang X, Sun K and Lan X. Chrom-Lasso: a lasso regression-based model to detect functional interactions using Hi-C data. Brief Bioinform 2021; 22: bbab181.