Am J Transl Res 2023;15(6):4155-4163
www.ajtr.org /ISSN:1943-8141/AJTR0149387

Original Article

Construction of an auxiliary scoring model for myelosuppression in patients with lung cancer chemotherapy based on random forest algorithm

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Received January 29, 2023; Accepted May 22, 2023; Epub June 15, 2023; Published June 30, 2023

Abstract: Objective: To construct an auxiliary scoring model for myelosuppression in patients with lung cancer undergoing chemotherapy based on a random forest algorithm, and to evaluate the predictive performance of the model. Methods: Patients with lung cancer who received chemotherapy in Shanxi Province Cancer Hospital from January 2019 to January 2022 were retrospectively selected as research subjects, and their general demographic information, disease-related indicators, and laboratory test results before chemotherapy were collected. Patients were divided into a training set (136 cases) and a validation set (68 cases) in a ratio of 2:1. R software was used to establish a scoring model of myelosuppression in lung cancer patients in the training set, and the receiver operating characteristic curve, accuracy, sensitivity, and balanced F-score were used in the two data sets to evaluate the predictive performance of the model. Results: Among the 204 lung cancer patients enrolled, 75 patients developed myelosuppression during the follow-up period after chemotherapy, with an incidence of 36.76%. The factors in the constructed random forest model were ranked in order of age (23.233), bone metastasis (21.704), chemotherapy course (19.259), Alb (13.833), and gender (11.471) according to the mean decrease accuracy. The areas under the curve of the model in the training and validation sets were 0.878 and 0.885, respectively (all $P < 0.05$). The predictive accuracy of the validated model was 82.35%, the sensitivity and specificity were 84.00% and 81.40%, respectively, and the balanced F-score was 77.78% (all $P < 0.05$). Conclusion: The risk assessment model for the occurrence of myelosuppression in patients with lung cancer chemotherapy based on a random forest algorithm can provide a reference for the accurate identification of high-risk patients.

Keywords: Lung cancer, chemotherapy, myelosuppression, random forest, prediction model

Introduction

Chemotherapy is the main treatment method for lung cancer, but chemotherapy drugs have different degrees of toxicity and side effects while prolonging the survival period of patients [1]. As a common toxic side effect of chemotherapy, bone marrow suppression not only greatly reduces the effect of chemotherapy, but also increases the risk of visceral bleeding in patients and can even cause death in severe cases [2, 3]. If the risk of bone marrow suppression can be reduced during chemotherapy, it will help to improve the effect of chemotherapy, prolong the survival time of patients, and improve quality of life. The mechanism of bone marrow suppression is complex and can be affected by multi-dimensional indicators. Most of the existing studies use logistic regression analysis to screen the influencing factors and build prediction equations. These models are prone to over-fitting, which leads to lower prediction accuracy [4, 5].

In recent years, the application of random forests algorithm in the medical field has improved the effectiveness of multidimensional clinical data statistics and analysis. Many studies have confirmed that its prediction accuracy is higher than that of conventional multi-factor analysis

[6-8]. For example, Watanabe et al. [9] proved in their study that for thromboembolisms, the C-statistic of the random forest model was significantly higher than that of the Logistic model (0.66 vs. 0.59, P = 0.03). However, at present, there are few studies on the application of a random forest algorithms in the risk prediction of bone marrow suppression in patients with lung cancer. Therefore, this study established a random forest model to predict the risk of bone marrow suppression by collecting multidimensional clinical indicators of lung cancer patients. The purpose of this study was to predict the risk of bone marrow suppression in lung cancer patients undergoing chemotherapy and provide a reference for the selection and adjustment of clinical treatment plans.

Data and methods

Data source

Lung cancer patients who received chemotherapy in Shanxi Provincial Cancer Hospital from January 2019 to January 2022 were selected as the study subjects. The clinical data of 204 patients were retrospectively collected and analyzed in this study. Inclusion criteria: (1) The patients were diagnosed with lung cancer by biopsy; (2) The patient's treatment plan included chemotherapy, and the course of chemotherapy was ≥ 1; (3) The estimated survival time of the patient was no less than 3 months; (4) The patients had not received any intervention related to bone marrow suppression; (5) The patient's clinical data was complete. Exclusion criteria: (1) Patients with other malignant tumors; (2) Those with insufficiency of heart, liver, kidney, brain, and othervital organs; (3) Patients with incomplete follow-up data. This study was approved by the Ethics Committee of Shanxi Provincial Cancer Hospital.

Method of multi-dimensional indicator collection

A self-made questionnaire was used to collect the data of the patients and the patients were followed up. (1) General demographic information: gender, age, years of education, smoking history, drinking history, hypertension, diabetes, coronary heart disease, and body mass index (BMI). (2) Disease-related indicators: lung cancer type, disease stage, chemotherapy program, course of treatment, bone metastasis status, adverse reactions. (3) Laboratory examination results before chemotherapy: glutamyltransferase (GGT), serum creatinine (Scr), albumin (Alb), neutrophil count (NEUT), blood platelet count (PLT), hemoglobin count (Hb), white blood cell count (WBC), mean corpuscular volume (MCV), lymphocyte percentage (LYMPH%), and urea.

Patients who met one of the following conditions were judged as having bone marrow suppression [10]: ① WBC < 4×10^9/L; ② Hb < 100 g/L; ③ NEUT < 2×10^9/L; ④ PLT < 100×10^9/L. Blood indicators were collected at the end of the last treatment session.

Method of model construction

The ultimate purpose of this study was to determine whether lung cancer patients with chemotherapy have risks of bone marrow suppression, and the explanatory variables were a series of factors that may cause bone marrow suppression (the flow chart of this study is shown in **Figure 1**). The random forest program package in R studio software was used to randomly divide the research objects into training sets and verification sets according to the ratio of 2:1, and the random forest model was built on the training set data. The specific construction method of the random forest model is as follows: ① 500 samples from the training set were taken through the bootstrap self-help method (including samples that were put back) to build 500 trees; ② In the process of generating the decision tree, the number of variables extracted from each node was the quadratic root of the number of variables in the training set by default; ③ Each node was split according to the second step until all nodes could not split, and a large number of decision trees obtained were random forests.

Methods of statistical analysis

SPSS 25.0 and R studio software were used to analyze the data. Counted data were expressed in frequency and percentage and compared between groups using χ^2 test. The quantitative data conforming to the normal distribution were expressed as Mean ± standard deviation ($x \pm s$) and compared between the two groups using t-test. $P < 0.05$ was regarded as a significant difference.

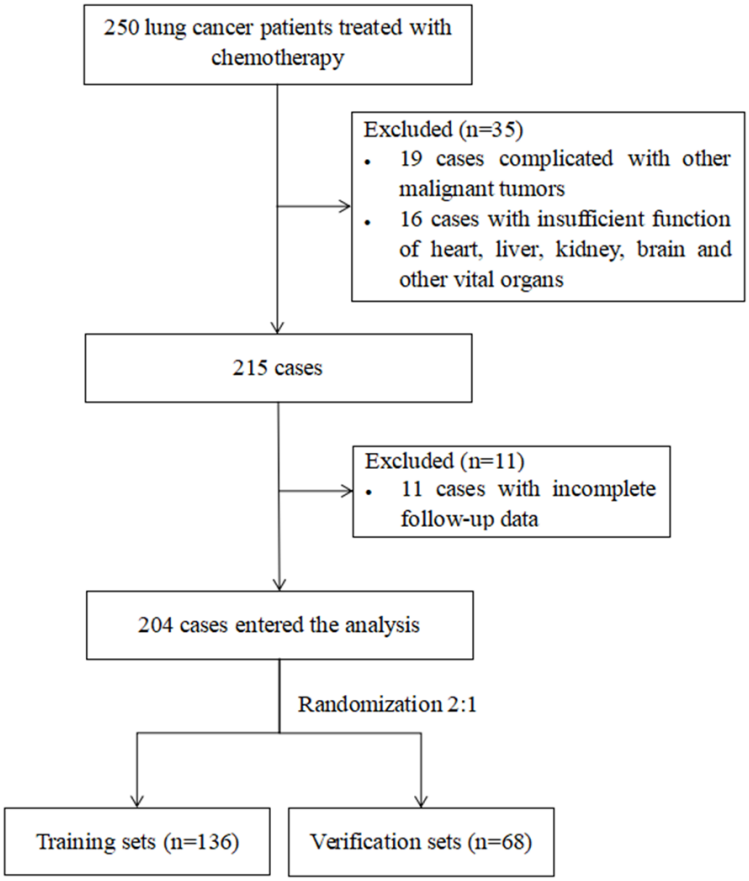

Figure 1. Research flow chart.

Results

Baseline data

After the screening, 204 patients were finally enrolled in the study. Among the 204 patients, 141 were male and 63 were female. There were 150 cases aged > 60 and 54 cases aged ≤ 60; There were 133 cases of adenocarcinoma or squamous cell carcinoma and 71 cases of other types. The basic information of patients as shown in **Table 1**.

The incidence of bone marrow suppression and the establishment of random forest

204 patients with lung cancer in this study were followed up for 1 to 3 months after chemotherapy. During the follow-up period, 75 cases (36.76%) had bone marrow suppression. Among the 204 lung cancer patients included, 2/3 of the data were extracted by bootstrap to establish a training set, and 1/3 of the data was used as a validation set. The areas under the curve (AUCs) of the constructed random forest in the training set and the validation set were 0.878 and 0.885, respectively (all $P < 0.05$), but there was no significant difference between the two AUCs ($P > 0.05$) (**Figure 2**). After verification, the predictive accuracy of the random model was 82.35%, the sensitivity and specificity were 84.00% and 81.40% respectively, and the equilibrium F score was 77.78% (all $P < 0.05$, **Table 2**).

Ranking of predictive accuracy of variables in random forest model

The average decline of prediction accuracy was used as the basis for evaluating the contribution of each variable in the random forest model. It can be seen from **Figure 3** and **Table 3** that the top five variables affecting the occurrence of bone marrow suppression in patients with lung cancer undergoing chemotherapy were age, bone metastasis, chemotherapy course, Alb, and gender.

Discussion

For many years, lung cancer has ranked first in global malignant tumor mortality. According to the latest cancer survey data in 2020, lung cancer contributes to 18% of all cancer deaths, while the second-ranked colon cancer accounts for only 9.4% [11]. Because the early symptoms of lung cancer are relatively hidden, most patients have been in stage III-IV at the time of diagnosis and have lost the opportunity of radical treatment. Although with the development and progress of genetics, there have been new programs for the treatment of lung cancer such as targeted therapy and immunotherapy. However, platinum-based chemotherapy still plays an important role in the treatment of lung cancer, and most patients still need to undergo standardized chemotherapy to prolong their

Table 1. Baseline data of enrolled patients

Baseline data	N (%)	Baseline data	N (%)
Gender		Lung cancer type	
Male	141 (69.12)	Adenocarcinoma	133 (65.20)
Female	63 (30.88)	Squamous carcinoma or other	71 (34.80)
Age (years)		Disease stage	
> 60	150 (73.53)	III~IV	153 (75.00)
≤ 60	54 (26.47)	I~II	51 (25.00)
Years of education		Chemotherapy program	
> 12	174 (85.29)	Platinum drugs	157 (76.96)
≤ 12	30 (14.71)	N-platinum drugs	47 (23.04)
Smoking		Bone metastasis	
Yes	110 (53.92)	Yes	72 (35.29)
No	94 (46.08)	No	132 (64.71)
Drinking		Chemotherapy treatment course	
Yes	46 (22.55)	Re-chemotherapy	55 (26.96)
No	158 (77.45)	First chemotherapy	149 (73.04)
Hypertension		Adverse reactions	
Yes	81 (39.71)	Yes	39 (19.12)
No	123 (60.29)	No	165 (80.88)
Diabetes		GGT (U/L)	43.78±6.07
Yes	76 (37.25)	Scr (μmom/L)	84.25±7.91
No	128 (62.75)	Alb (g/L)	43.85±4.88
Coronary heart disease		NEUT (× 10^9/L)	3.93±0.51
Yes	22 (10.78)	PLT (× 10^9/L)	162.22±24.84
No	182 (89.22)	Hb (g/L)	128.21±12.55
BMI		WBC (g/L)	6.96±0.89
Abnormal	95 (46.57)	MCV (fL)	89.88±3.82
Normal	109 (53.43)	LYMPH% (%)	29.53±3.98
		Urea (mmol/L)	3.44±0.56

Notes: GGT: Glutamyltransferase, Scr: serum creatinine, Alb: albumin, NEUT: neutrophil count, PLT: blood platelet count, Hb: hemoglobin count, WBC: white blood cell count, MCV: mean corpuscular volume, LYMPH%: lymphocyte percentage, BMI: body mass index.

survival [12, 13]. Chemotherapy drugs are not targeted, so they can kill tumor cells and normal cells indiscriminately. Bone marrow hematopoietic stem cells are more vulnerable to the damage by chemotherapy drugs because of their growth activity, which makes bone marrow suppression the most common toxic side effect of chemotherapy patients [14]. Although the incidence of severe myelosuppression has decreased with the use of granulocyte colony-stimulating factors, mild and moderate myelosuppression still has a serious impact on the treatment effect and quality of life of patients [15].

To evaluate the risk and related influencing factors for bone marrow suppression in patients with lung cancer undergoing chemotherapy is the basis and key to taking targeted measures for intervention. The construction of a prediction model is an important method to evaluate the risk of patients. Under the existing research background and medical conditions, there is still a lack of models that can effectively predict the occurrence of bone marrow suppression in chemotherapy patients. With the development of diagnostic and treatment technology, the role of traditional prognostic risk factors of chemotherapy in clinical practice has weakened. It is not difficult to find that the accuracy of most current models is low, and it is also unreasonable to apply them directly to lung cancer patients. Therefore, it is necessary to analyze

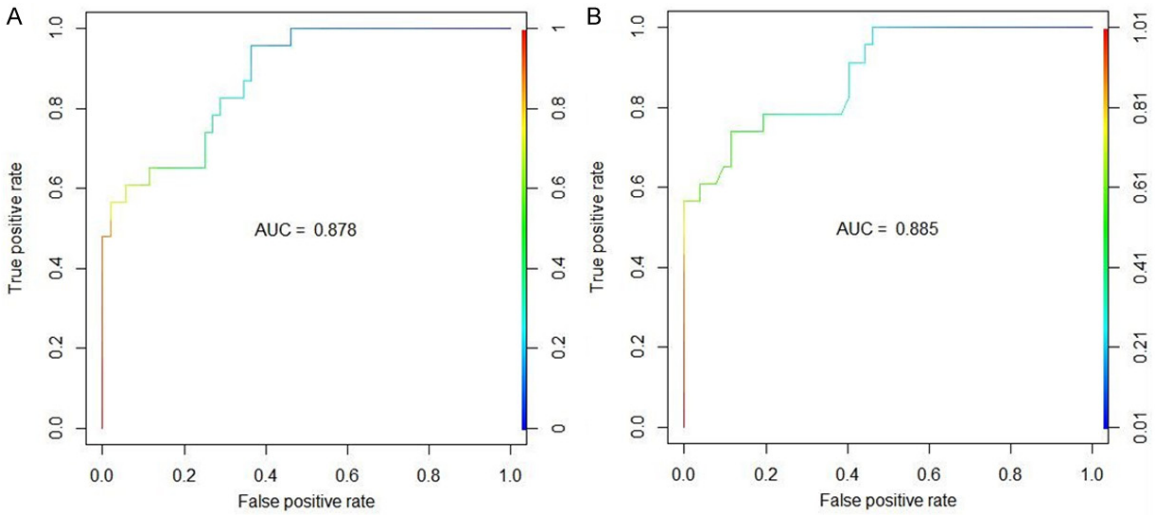

Figure 2. AUCs of the random forest algorithm model for marrow suppression in lung cancer patients underwent chemotherapy. (A) Training set, (B) Verification set. Note: AUC: Area under the receiver operating characteristic curve.

Table 2. Prediction results of random forest in validation set

Predictive results of random forest model	Actual results		Total
	Myelosuppression	Non-Myelosuppression	
Myelosuppression	21	8	29
N-Myelosuppression	4	35	39
Total	25	43	68

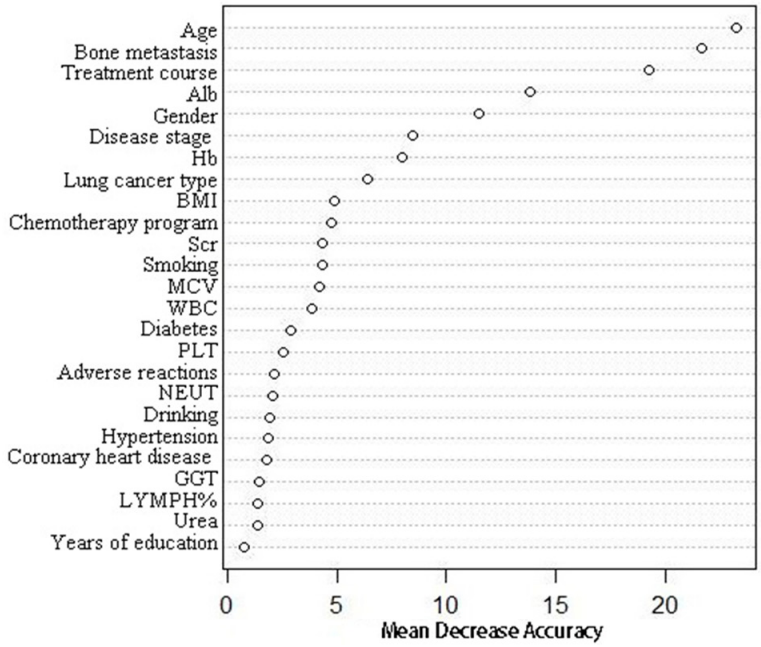

Figure 3. Sorting of prediction accuracy of each variable. Note: The abscissa is mean decrease accuracy, and the ordinate is the variable name of each variable. The dots indicate the mean decrease accuracy of each variable. GGT: Glutamyltransferase, Scr: serum creatinine, Alb: albumin, NEUT: neutrophil count, PLT: blood platelet count, Hb: hemoglobin count, WBC: white blood cell count, MCV: mean corpuscular volume, LYMPH%: lymphocyte percentage, BMI: body mass index.

more factors affecting bone marrow suppression in lung cancer patients with chemotherapy through a predictive model algorithm to achieve the purpose of accurate prediction of bone marrow suppression in lung cancer patients. At present, machine learning algorithms including random forest are widely used in the field of medical and health care. The stochastic forest algorithm has been recognized by many scholars for its powerful data processing ability. Many studies have reported that its prediction accuracy of disease prognosis is higher than that of conventional logistic regression [16-18]. In this study, a random forest algorithm was used to predict the risk of bone marrow suppression in 204 patients with lung cancer undergoing chemotherapy within one year. The 25 variables included in the study are all clinically accessible indicators, that will not increase the additional cost of patient treatment. The results showed that the ROC of the model was 0.885, and the predictive accuracy was 82.35%. The

Table 3. Sorting of predictive accuracy of each variable

Variable	Predictive accuracy	Rank	Variable	Prediction accuracy	Rank
Age	23.233	1	WBC	3.854	14
Bone metastasis	21.704	2	Diabetes	2.911	15
Chemotherapy treatment course	19.259	3	PLT	2.525	16
Alb	13.833	4	Adverse reactions	2.164	17
Gender	11.471	5	NEUT	2.079	18
Disease stage	8.445	6	Drinking	1.913	19
Hb	8.001	7	Hypertension	1.896	20
Lung cancer type	6.404	8	Coronary heart disease	1.763	21
BMI	4.899	9	GGT	1.420	22
Chemotherapy program	4.744	10	LYMPH%	1.382	23
Scr	4.374	11	Urea	0.925	24
Smoking	4.335	12	Years of education	0.735	25
MCV	4.195	13			

Notes: Alb: Albumin, PLT: blood platelet count, MCV: mean corpuscular volume, BMI: body mass index.

results suggest that the model has a high recognition ability for high-risk patients with bone marrow suppression after chemotherapy for lung cancer. The random forest model could not quantify the influence of characteristic attributes on bone marrow suppression, but only judge the importance of attributes. This study is in the preliminary stage and has not yet reached the stage where online tools or additional model packages can be developed. However, the results of this study can provide a reference for the development of online tools or additional model packages.

The important predictors of the model obtained in this study were age, bone metastasis, chemotherapy, low albumin level before chemotherapy, and female gender. Age has always been the most common factor in the prognosis of lung cancer patients. Due to physical function and nutritional factors, the hematopoietic function of the elderly patients' own bone marrow is weaker than that of young people, and it is difficult to balance the newborn hematopoietic cells and peripheral blood cells after chemotherapy [2, 19]. Therefore, elderly patients are more prone to bone marrow suppression. In addition, the tolerance of elderly patients to chemotherapy drugs is decreased, and liver and kidney function damage or digestive tract reaction may occur when receiving chemotherapy, affecting the metabolism of chemotherapy drugs and causing bone marrow suppression [20]. Some research results show that with rising age, the hematopoietic function of the body's bone marrow also decreases significantly and is usually accompanied by the decline of the liver and kidney detoxification function [21]. Therefore, when elderly patients are undergoing chemotherapy, chemotherapy drugs are easy to accumulate in the body, causing toxic side effects. In this study, the contribution value of age in all predictors ranked first. This suggests that medical staff should not ignore the influence of age on the treatment effect and adverse reactions during treatment and can adjust the chemotherapy plan according to the patient's physical function and tolerance. Patients with bone metastasis of lung cancer are in the advanced stage, and systemic chemotherapy combined with local chemotherapy can only prolong the survival period. Ribs, vertebrae, and pelvis are the most severelyaffectedsites in patients with lung cancer bone metastasis. These bone tissues are rich in red bone marrow, and the microenvironment of these bone tissues is damaged under the influence of cancer cells. This affects the function of hematopoietic hepatocytes in the bone marrow to a certain extent, and greatly increases the risk of bone marrow suppression [22, 23].

The occurrence of bone marrow suppression is related to the toxic side effects of the accumulation of chemotherapy drugs in the body. With the increase in chemotherapy times, the amount of drugs accumulated in the patient's body increases, and the damage to the body's

bone marrow stem cells also increases [24-26]. Serum albumin is regarded as an indicator that can reflect the nutritional status of the body and has the characteristics of easy measurement [27]. In this study, patients with low serum albumin levels are more prone to bone marrow suppression after chemotherapy. It is speculated that such patients are in poor health status and may be associated with other basic diseases, which limits the use of multiple adjuvant treatment schemes, so bone marrow suppression is more likely to occur at the same dose. Some studies have shown that there are differences in the location, expression, and signal transduction of estrogen receptor and androgen receptors in lung cancer cells, which may be one of the reasons affecting the prognosis of lung cancer patients of different sexes [28, 29]. In this study, female lung cancer patients are more prone to bone marrow suppression after chemotherapy. We speculate that this is related not only to estrogen but also related to the menstrual period, perinatal period, menopause, and other special physiological periods. These factors have certain adverse effects on the biologic effects and metabolism of chemotherapy drugs and are more likely to cause the accumulation of chemotherapy drugs in patients. In addition, the chemotherapy regimen, chemotherapy rounds, and nutritional status of patients may be related to myelosuppression. However, this study was a retrospective study and failed to collect such data, so it failed to make a detailed analysis of these factors.

Limitations

This study confirmed that the random forest model has a high value in identifying the risk of bone marrow suppression in patients with lung cancer after chemotherapy. However, this study has some shortcomings. First, the subjects in this study were from the same center, which has slightly insufficient representation. Secondly, this study was retrospectively conducted and the data were limited. Thirdly, the sample size of this study was small. In addition, this study mainly contrasted the random forest prediction results with the real situation of patients, without contrasting them by constructing logistic regression models. We hope to conduct multicenter, large sample, and prospective research in the future to further improve the reliability of research results.

Conclusion

In the random forest model, the top five variables affecting the occurrence of bone marrow suppression in patients with lung cancer undergoing chemotherapy are age, bone metastasis, chemotherapy course, Alb, and gender. The model has high accuracy in predicting marrow suppression in lung cancer patients undergoing chemotherapy. The results of this study provide a reference for identifying lung cancer patients with myelosuppression after chemotherapy more quickly and accurately.

Disclosure of conflict of interest

None.

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