The Value of Complete Blood Count For The Prognosis Analysis of Esophageal Squamous Cell Carcinoma

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Research Article

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Abstract

Objective

To investigate the value of complete blood count in predicting the survival rate of patients with esophageal squamous cell carcinoma.

Methods

A total of 3587 patients with esophageal squamous cell carcinoma who were initially admitted to the Affiliated Cancer Hospital of Xinjiang Medical University from January 2010 to December 2017 were collected by retrospective study. The relevant clinical data were collected by the medical record system, and the patients were followed up by the hospital medical record follow-up system. The follow-up outcome was death. The survival time of all patients was obtained. The survival curve was established using the cut-off value of each index obtained by ROC curve. The Cox proportional hazards regression analysis model and nomogram were established to predict the survival prognosis of esophageal squamous cell carcinoma. The role of each index in the prognosis of patients with esophageal squamous cell carcinoma was studied

Results

The cut-off values of NLR, NMR, LMR, RDW and PDW in blood routine were 3.52, 10.22, 2.25, 13.85% and 12.05%, respectively. Survival curve analysis showed that patients aged < 60 years and NLR < 3.52 had survival. All indicators were divided into high and low groups according to ROC curve. Univariate Cox regression analysis model showed that RDW (≥ 13.85) and NLR (≥ 3.52) groups were risk factors for the prognosis of ESCC, with HR values of 1.099 (1.015–1.191; $p = 0.020$) and 1.340 (1.231–1.458; $p < 0.001$) compared with RDW (< 13.85) and NLR (< 3.52), respectively; multivariate Cox regression analysis model showed that NLR was significantly associated with the prognosis of ESCC, with HR of 1.342 (1.232–1.461; $p < 0.001$) for NLR (≥ 3.52) NLR (< 3.52).

Conclusion

NLR results in blood count can be used to predict the survival of patients with esophageal squamous cell carcinoma.

Background

Malignancy is a major public health problem in the world. According to the 2019 global cancer data report, esophageal cancer incidence and mortality rank the 7th and 6th in all cancer incidence and mortality worldwide, respectively ^[1]. According to the histological type, esophageal cancer can be divided

into two categories: Esophageal Squamous Cell Carcinoma (ESCC), Esophageal Adenocarcinoma (EAC), ESCC is mainly seen in Asia, accounting for about 90%, EAC is mainly seen in Europe, accounting for about 70% -80% [2] [3], esophageal cancer is mainly in middle-aged and elderly people, the early clinical manifestations are mainly dysphagia, burning sensation under the sword, weight loss and other atypical symptoms, the later can be manifested as progressive dysphagia, so the early symptoms are easy to miss the diagnosis, most of the diagnosis is advanced, the five-year survival rate is only 10–20%^{[4][5]}, although its surgical methods and management have great progress, but the prognosis of patients has no significant change, how to evaluate the prognosis of patients has important clinical significance for clinicians and patients, can help clinicians to change the treatment plan, and improve the survival confidence of patients.

Over the past few decades, it has been confirmed that depth of invasion, lymph node metastasis, TNM stage, and various other factors^[6] are important factors affecting the prognosis of esophageal cancer, and an increasing number of experiments in recent years have demonstrated that inflammation is associated with the survival of malignant tumors. Complete blood count (CBC) is one of the most common clinical laboratory tests, and absolute counts of neutrophils, lymphocytes, and monocytes reflect the inflammatory response and the overall immune status of the body. Peripheral blood prognostic inflammatory markers include Neutrophil to Lymphocyte ratio (NLR), Neutrophil to Monocyte ratio (NMR), Lymphocyte to Lymphocyte ratio (LMR), Red blood cell distribution width (RDW) and Blood cell distribution width (PDW), which have been demonstrated to be closely related to the prognosis of various cancers^{[6][7]}. In clinical laboratory, because blood routine examination is mandatory for patients, and the cost is low, experimental data is relatively easy to obtain. Therefore, it is of great clinical significance to predict and analyze the prognosis of patients with esophageal cancer by using the results of routine blood tests.

Method

Source of data

This retrospective study was approved by the Ethics Committee of Cancer Hospital Affiliated to Xinjiang Medical University. All cases of esophageal cancer were diagnosed by pathological results. A total of 3587 cases of ESCC were initially admitted and diagnosed in Cancer Hospital Affiliated to Xinjiang Medical University from January 2010 to December 2017. All patients with ESCC were staged according to the 8th edition of TNM staging issued by the American Joint Committee on Cancer (AJCC). Experienced oncologists performed pathological TNM staging according to pathological diagnosis. In order to exclude potential bias such as infection and infectious disease, we excluded white blood cell count $\geq 20 \times 10^9/L$. Of these, 2503 were male and 1084 were female. The mean age was 63.4 years for men and 64.3 years for women. The results of the first routine blood test performed on their initial admission were also collected, all tests were performed in the same institutional laboratory, assessed and

the patients were followed up by the hospital case follow-up system, and the follow-up outcome was patient death to obtain the survival time of all patients.

Statistical Analysis

The area under the curve (AUC) was calculated by receiver operating characteristic curve (ROC) and the optimal cut-off value for continuous variables was calculated. Survival curves were compared using the Kaplan-Meier method and the Log-Rank test. In addition, univariate and multivariate analyses were performed using Cox proportional hazards regression analysis models to assess the impact of multiple covariates on survival outcomes, and nomograms were generated with Cox regression coefficients and validated. For all analyses, $P < 0.05$ was defined as significant. Statistical analysis was performed using SPSS version 26.0 (SPSS, Chicago, IL) and the RMS package in R language.

Results

1. The Critical Value of Each Detection Index

The ROC curve was used to find out whether each test item has a suitable critical value to predict the death outcome of patients, and then to demonstrate the significance of each index in the prognosis. NLR, NMR, LMR and PDW were the quantitative indexes related to death outcome. The ROC curve and related statistical results of each index are shown in Fig. 1 and Table 1.

Table 1
ROC Analysis Results of Significant
Quantitative

Index	AUC	P value	Cut-off value
NLR	0.700	< 0.001	3.52
NMR	0.650	< 0.001	10.22
LMR	0.617	< 0.001	2.25
PDW	0.496	0.438	12.05
RDW	0.563	0.027	13.85

2.the General Clinical Features Of 3587 Escc Patients

From Table 2,we can see that Age > 60 (65.69%)and tumor location in the middle 66.68%was significantly higher than < 60 34.31%and tumor location in the upper and lower segments. In the pathological stage, T357.37% was the most depth of tumor invasion group, which was related to the diagnosis of advanced ESCC patients. Only 29.89% of ESCC patients had no lymph node metastasis. In clinical classification, stage II21.86% and III57.34% patients accounted for the vast majority

Table 2
The baseline characteristics in patients with escc

	Number of subjects	Composition ratio (%)
Sex		
Male	2503	69.78%
Female	1084	30.22%
Age		
< 60 years	1231	34.31%
≥ 60 years	2356	65.69%
NLR		
< 3.52	2722	75.89%
≥ 3.52	865	24.11%
NMR		
< 10.22	2277	63.48%
≥ 10.22	1310	36.51%
LMR		
< 2.25	2491	69.46%
≥ 2.25	1096	30.54%
RDW		
< 13.85	2519	70.23%
≥ 13.85	1068	29.77%
PDW		
< 12.05	2169	60.47%
≥ 12.05	1418	39.53%
Tumor location		
Upper	397	11.07%
Middle	2392	66.68%
Lower	798	22.25%
Stage		

	Number of subjects	Composition ratio (%)
□	185	5.16%
□	1128	31.45%
□	1859	51.82%
□	415	11.57%
Depth of tumor invasion		
T1	213	5.94%
T2	784	21.86%
T3	2058	57.37%
T4	532	14.83%
Lymph node metastasis		
N0	1072	29.89%
N1	1463	40.78%
N2	782	21.80%
N3	270	7.53%

3. Survival Analysis Results Of Significance Test Indicators

The survival curve was used to analyze the significance of gender, age and five quantitative indicators related to the death outcome of patients with esophageal cancer in judging the prognosis of patients with esophageal squamous cell carcinoma. The results are shown in Fig. 2. From Fig. 2, it can be seen that there was no significant difference in gender, NMR, LMR, RDW and PDW survival ($P > 0.05$); the survival time of age < 60 years group and NLR < 3.52 group was significantly higher than that of age ≥ 60 years group and NLR ≥ 3.52 group ($P < 0.05$), and the diagnostic efficacy of NLR (ACU: 0.700) was significantly higher than other items.

4.univariate And Multivariate Cox Regression Analysis Of Various Indicators

Using univariate Cox regression analysis to calculate the value of gender, age, each quantitative index, tumor location, depth of invasion, lymph node metastasis and stage for the prognosis of ESCC patients(Table 3), respectively, it could be found that age (< 0.001), NLR (< 0.001), RDW ($= 0.020$), depth of invasion (< 0.001), lymph node metastasis (< 0.001) and stage (< 0.001) were prognostic factors for

esophageal cancer; using multivariate Cox regression analysis, it could be found that age (< 0.001), NLR (< 0.001), depth of invasion (< 0.001), lymph node metastasis (< 0.001) and stage < 0.001 were independent risk factors for the prognosis of esophageal cancer; in the group aged ≥ 60 years, the risk of death increased 1.263-fold (1.168–1.367) compared with the group aged < 60 years; in the group NLR ≥ 3.52 , the group ratio < 3.52 The risk of death increased by 1.355-fold (1.245–1.465); depth of invasion: T3 + T4 group had a 1.322 fold (1.187–1.471) increased risk of death compared with T1 + T2 group; lymph node metastasis: N1 + N2 + N3 group had a 1.221 (fold (1.168–1.367) (1.079–1.382) increased risk of death compared with N0 group; stage: III + IV group had a 1.675 fold (1.467–1.912) increased risk of death compared with I + II group.

Table 3
Univariate and multivariate Cox proportional hazards regression models in patients with ESCC

	β	Univariate analysis HR (95% CI)	P- value	β	Multivariate analysis HR (95% CI)	P- value
Age (years)	0.245		< 0.001	0.234		< 0.001
< 60 years		1.000			1.000	
$\geq$ 60 years		1.278(1.182–1.383)			1.263(1.168–1.367)	
Gender	−0.021		0.614	-		-
Male		1.000			-	
Female		0.980(0.904–1.061)			-	
Tumor location	0.098		0.061	-		-
Upper/Middle		1.000				
Lower		0.907(0.830–0.991)			-	
Depth of invasion	0.608		< 0.001	0.279		< 0.001
T1–2		1.000			1.000	
T3–4		1.836(1.679–2.007)			1.322(1.187–1.471)	
Lymph node metastasis	0.641		< 0.001	0.200		< 0.001
N0		1.000			1.000	
N1–N3		1.898(1.742–2.069)			1.221(1.079–1.382)	
Stage	0.782		< 0.001	0.516		< 0.001
I–II		1.000			1.000	
III–IV		2.186(2.016–2.370)			1.675(1.467–1.912)	
NLR	0.304		< 0.001	0.294		< 0.001
< 3.52		1.000			1.000	

	β	Univariate analysis	P-value	β	Multivariate analysis	P-value
		HR (95% CI)			HR (95% CI)	
≥ 3.52		1.340 (1.231–1.458)			1.355(1.245–1.465)	
NMR	0.040		0.308	-		-
< 10.22		1.000			-	

To predict the survival risk (CSS) for patients with ESCC,a novel model (nomogram) was established by prognostic factors combined with age,NLR and Pathological results (Fig. 3). It can predict the probability of death for patients with ESCC.

Discussion

The incidence of esophageal cancer is high in the world. Each year, there are about 580,000 new cases diagnosed worldwide, and about 510,000 people die of esophageal cancer every year. In China, nearly 300,000 patients with esophageal cancer die each year, accounting for more than 50% of the global deaths of esophageal cancer [8]. Now it is generally recognized that inflammation plays an increasingly important role in the development of tumors, and its mechanism may be: inflammation releases cytokines and upregulates transcription factors, leading to the generation and accumulation of a large number of oxygen free radicals, which can cause DNA damage and breakage in parenchymal cells, including stem cells, overexpression of proto-oncogenes, loss of function of tumor suppressor genes and upregulation of genes that promote the cell cycle, leading to abnormal cell proliferation, thereby interfering with the stability of the body's microenvironment, thereby accelerating tumor growth, invasion, metastasis and other processes, affecting the prognosis of tumors [9] [10]. Many reports have shown that LMR, NLR and NMR, PDW, RDW as inflammatory indicators, are closely related to the prognosis of a variety of diseases and can be used as prognostic factors in a variety of malignant tumors^{[7] [11] [12]}.

In this study, we investigated the prognosis of inflammatory indicators in blood routine for esophageal squamous cell carcinoma. Survival curve analysis showed that age < 60 years and NLR < 3.52 patients had survival; univariate Cox regression analysis model showed that RDW ($\geq 13.85\%$) and NLR (≥ 3.52) groups were risk factors for the prognosis of esophageal squamous cell carcinoma, which was the same as most studies; compared with NLR (≥ 3.52), HR was 1.340 (1.231–1.458; $p < 0.001$), which was consistent with Arigami T^[13], Gao GD [14] studies, NLR > 3.0 and NLR > 2.83 were considered to be effective predictors of esophageal cancer; RDW ($\geq 13.85\%$) had HR 1.099 (1.015–1.191; $p = 0.020$) compared with RDW (< 13.85), which was consistent with Chen GP^[15] et al. It can effectively predict the prognosis of esophageal squamous cell carcinoma. Among other relevant blood routine test indicators, PDW has distinct conclusions. Kawakita Y^[16] et al. believed that PDW $< 12.5\text{fl}$ could predict the poor prognosis of esophageal cancer, consistent with this study. However, in contrast to Song Q^[17] et al., he

believed that high PDW could predict the poor prognosis of esophageal cancer. In predicting the prognosis of esophageal cancer, due to inconsistent results, the role of LMR in the prognosis of esophageal cancer was very different. Huang Y ^[18] et al. believed that preoperative LMR < 2.93 predicted the poor prognosis of patients with esophageal squamous cell carcinoma. Hu G ^[19] et al. also did a meta-analysis and concluded that low LMR could predict the poor prognosis of esophageal cancer. In this study, PDW and LMR were not considered to be related to the prognosis of esophageal cancer ($P > 0.05$), which may be different from the cut-off values of LMR and PDW in the included studies. The criteria and methods for determining cut-off values vary among institutions; a suitable cut-off value cannot be proposed by statistical analysis. This may affect the results and lead to an inevitable potential bias. This may limit the use of NLR, LMR, RDW, PDW in clinical practice and even lead to distinct conclusions, therefore, defining NLR, LMR, RDW, PDW requires a standard, uniform cutoff. In the present study, we attempted to establish a predictive nomogram based on prognostic factors of blood routine to predict survival prediction. We believe that our model is a simple and easy tool for both physicians and patients and can be used to estimate the survival rate of esophageal cancer patients in the case of initial diagnosis.

Several limitations should be acknowledged in the current study. First, the current study is a retrospective study, although it is a large sample, but other potential diseases affecting inflammatory cannot be completely ruled out; second, excessive uncontrollable factors of laboratory test results of blood cell count-related indicators and excessive variation of indicators lead to its limited role in the judgment of clinical prognosis. Therefore, this study aimed at the expression level of peripheral blood cells in patients with esophageal cancer and explored the relationship between a variety of inflammatory indicators and the prognosis of esophageal cancer, in order to provide new ideas for the prognosis of esophageal cancer. Similarly, we also expect to have a more scientific and rigorous prospective study to verify in the future.

Declarations

Authors'contributions

The author read and approved the final manuscript.

Competing interests

The author declares that he has no conflict of interests.

Ethics approval and consent to participate

The study was approved by Ethics Committee of Xinjiang Medical University.

The study confirming that informed consent was obtained from all subjects or, if subjects are under 16, from a parent and/or legal guardian.

Consent for publication

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due requirements of Xinjiang Medical University but are available from the corresponding author on reasonable request.

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Authors' contributions

Lv Xiang;Feng YangchunSongtao Han;Bin Xu:manuscript.

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Confirmation of all documents.

The study confirm that all methods were carried out in accordance with relevant guidelines and regulations.

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Figures

Figure 1

ROC analysis diagram of meaningful quantitative indicators.

Figure 2

Survival Curve Analysis for Gender and Meaningful Clinical Indicators

Figure 3

Nomograph