

Proportions of Beneficial Factors in MLR, NLR, PLR and D-dimer in Preoperative Peripheral Blood of Patients With Early Stage Lung Cancer as Predictors of Patient Survival After Surgery

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Abstract

Objective

The purpose of this paper is to predict the following items. preoperative baseline monocyte-to-lymphocyte ratio (MLR)■neutrophil-to-lymphocyte ratio (NLR) Platatura-to-lymphocyte ratio (PLR) and dimeric fibrin fragment D (D-dimer) associated with clinical outcome in patients with Early Lung Cancer (LC).

Methods

We performed a retrospective analysis of 376 patients with LC. Progression-free survival (PFS) and overall survival (OS) were assessed by Kaplan-Meier, and univariate and multivariate Cox regression analyses were performed to identify prognostic factors. Finally, multivariate Cox regression analysis was used to evaluate the influence of favorable factors on patients' OS and PFS combined with the basic clinical characteristics of the patient

Results

Among the variables screened by univariate Cox regression, MLR < 0.22, NLR < 1.99, PLR < 130.55 and D-Dimer < 70.5 (ng/ml) were significantly associated with both better OS and PFS. In multivariate Cox regression analysis, it was determined that MLR and D-Dimer had a better independent correlation with OS ($p = 0.009$, $p = 0.05$, respectively), while MLR was only better independently associated with PFS ($P = 0.005$). Furthermore, according to the number of favorable factors, patients with none of these factors had a significantly worse prognosis than patients with at least one of these factors.

Conclusion

Baseline characteristics of low MLR, low NLR, low PLR and low D-dimer were associated with better outcomes.

Background

With the increasing morbidity and mortality in China, malignant tumors have become the main cause of death, among which lung cancer is the most common cancer and the main cause of death^{1,2}. With the development of science and technology, the treatment of lung cancer also presents a variety of methods including surgery, chemotherapy and immunotherapy. However, due to the new coronavirus epidemic, some operations cannot be performed in time. Nevertheless, studies have shown that the benefit of delayed surgical treatment for patients with early-stage non-small cell lung cancer is still better than immediate radiotherapy³. Nevertheless, there is still a wide variation in OS and PFS in post-operative patients. Currently, the prediction of survival in postoperative lung cancer patients relies mainly on tumor node metastases (TNM) staging⁴. Although genetic and some molecular tests have shown great promise in predicting patient prognosis⁵, their huge financial burden makes it difficult to be widely available in

most otherwise affluent cancer families. Therefore, we are working to identify novel circulating biomarkers that can successfully predict patient outcomes during routine preoperative testing.

In recent years, many studies have demonstrated the important role of peripheral blood markers in the prognosis of patients with various tumors. Patients with bladder cancer with a low NLR⁶ had significantly better clinical survival outcomes than those with high NLR⁶. In patients with HER2+ breast cancer, lower NLR and lower MLR show longer survival status^{6,7}. It was reported that Plasma D-dimer was regarded as a prognostic marker for various types of malignancies, which included non-small-cell lung carcinoma (NSCLC)⁸. In addition, peripheral blood biomarkers have shown good prognostic ability in a variety of solid tumors including melanoma⁹, colorectal cancer¹⁰, esophageal cancer¹¹ and pancreatic cancer¹². The above studies strongly suggest that single peripheral blood biomarkers have good prognostic ability in patients with malignancies, but whether there is a superimposed effect or whether these peripheral blood parameter indicators interact with each other needs further elucidation.

Methods

Patients

This study retrospectively reviewed the medical records of all LC patients with stage I and stage II that who were treated with standard lobectomy at the Department of Thoracic Surgery, Second Affiliated Hospital of Harbin Medical University, Heilongjiang Province, China, from January 2015 to July 2017. Inclusion criteria: (1) preoperative imaging suggestive of a mass confined to a single lung lobe; (2) no distant metastases; (3) no preoperative adjuvant medication; (4) no hematological malignancies; (5) complete clinical and follow-up information; and (6) survival for at least 30 days postoperatively. Patients were followed up every three months after surgery via outpatient clinics or over the phone, with the last follow-up visit for all patients on June 30, 2020. This paper has been approved by the Ethics Committee of the Second Affiliated Hospital of Harbin Medical University. Because the study was retrospective, informed consent from patients was not required. Patient data confidentiality rules are consistent with the Declaration of Helsinki.

Data collection

Peripheral blood biomarkers including neutrophil count ($10^9/L$), monocyte count ($10^9/L$), lymphocyte count ($10^9/L$), platelet count ($10^9/L$) and D-dimer (ng/ml) were collected from the electronic medical record within 3 days prior to the procedure, as well as the patient's age, gender, BMI, underlying disease history, pathology profile and ECOG at that time scores and other basic clinical information. NLR and MLR were calculated as follows: NLR equals neutrophil count/lymphocyte count; Second, MLR equals monocyte count/lymphocyte count and PLR equals platelet count/lymphocyte count. Survival rates were analyzed by PFS and OS.

Statistical analysis

According to receiver operating Characteristic (ROC) curve analysis, the critical values of MLR, NLR, PLR and D-dimer can be determined and the highest Yorden index (defined as sensitivity + specificity -1) can be used to predict OS. This study used SPSS version 25.0 (IBM Corp., Armonk, NY, USA) for baseline statistics of patient clinical data. Moreover, OS and PFS were analyzed according to the Kaplan-Meier estimate by the log-rank test. Univariate and multivariate Cox regression were used to determine 95% confidence interval (CI) and risk ratio (HR). Clinical characterizations, including smoking status (former or never), age, multivariate cox regression was used to analyze the performance of patients in the Eastern tumor cooperative group. A P value less than 0.05 was considered statistically significant. $P < 0.05$ on both sides was considered statistically significant.

Results

Patient demographics and clinical characteristics

As shown in Table 1, 376 patients with early LC who underwent surgery were finally screened out. The results showed that there were 218 cases (58%) in males and 158 cases (42%) in females. The median age was 60(53,65) years. In our population, the majority of patients had an ECOG physical status of 0-1 (320/376, 85.1%) and the greatest number of patients had lung adenocarcinoma (n=233/376, 62%).

We identified four preoperative peripheral blood biomarkers by referring to relevant studies and combining them with clinical significance^{13,14}. Some of the peripheral blood biomarkers for all patients are shown in (Table 2). Basis on the best CUT-OFF, low MLR (239/376, 63.6%), high NLR (207/376, 55.1%), low PLR (209/376, 55.6%) and high D-Dimer (263/376, 69.7%) were more predominant.

Univariate and Multivariate Cox Analysis for Survival Outcome

The results of OS and PFS based on cells counts of peripheral blood were shown in Figure 1: pre-treatment NLR < 0.216 (log-rank test $p < 0.0001$), NLR < 1.987 ($p = 0.00016$), PLR < 130.55 ($p = 0.0034$) and D-dimer < 70.5 ml/ng (0.00016). In univariate Cox regressions analysis, sex, smoking, pathology type, MLR, PLR, NLR, D-dimer, and ECOG PS were associated with OS ($p < 0.0001$, 0.0037, 0.00021, 0.00045 and 0.0001, respectively). The above parameters were correlated with PFS ($P < 0.0001$, 0.01429, 0.00025, 0.01265, 0.0001, respectively) (Table 3). In multivariate COX regressions, the preoperative peripheral blood biomarkers MLR and D-Dimer ($p = 0.009145$, 0.005376, respectively), which we observed, maintained their significance for OS. However, D-dimer was not significant in PFS ($p = 0.07662$) (Table 4).

Multivariate Model for Survival of Patients

Then, according to the quantitative analysis results of favorable factors, including MLR<0.22, NLR<1.99, PLR<130.55 and D-DIMER <70.5(ng/ mL). As shown in Figure 2, Sixty-eight patients (18%) showed no significant reduction in PFS and OS compared to those who had 1 and 2(group II, at 71 and 93, respectively) or three and four (group III, at 102 and 42, respectively) (Kaplan Meier analysis and survival rates compared to $P < 0.0001$, respectively). Multivariate COX analysis including clinically important

Covariates (age, gender, BMI, ECOG ps, etc.) confirmed that the number of favorable factors was closely associated to PFS and OS (Table 5).

Discussion

To date, biomarkers remain a major focus of research in the field of Oncology, whether in the diagnosis of disease, the assessment of efficacy of treatment or the prognosis of patients. The connection between inflammation and cancer was first explored in 1863 by Rudolf Virchow et al.¹⁵. Since then, more and more studies have further confirmed the value of inflammatory markers in the diagnosis and prognosis evaluation of various malignant tumors. The inflammatory response is an organism's antagonistic response to noxious stimuli, both exogenous and endogenous^{16,17}. Inflammation associated with cancer has a dramatic impact on the tumor microenvironment, which consists of tumor cells and inflammatory cells that release various cytokines and chemotactic factors¹⁸. Among them, NLR, PLR, MLR and D-dimer are closely related to inflammation and immune status of cancer patients, and have been applied to predict the prognosis of patients with various solid tumors^{9–12}. NLR, PLR and MLR, as indicators of inflammation, are obtained from peripheral blood neutrophilic granulocyte, platelets and monocytes compared to lymphocytes, respectively. Therefore, the ratios between them can similarly indicate the role of inflammatory mediators in tumors.

The function of inflammatory mediators in the tumor microenvironment is not fully understood, but there are several potential mechanisms that could provide a simple explanation for their role. (1) Lymphocytes are an important component of an organism's immune system, playing a major role in the body's immune surveillance and serving as a protective prognostic factor for patients with malignancies¹⁹. CD8 cytotoxic T lymphocytes (CTL) are the primary immune cells that target tumors. During cancer progression, CTL become dysfunctional and suppressed due to immune-related tolerance and immunosuppression within the tumor microenvironment (TME)²⁰. (2) The role of neutrophilic granulocyte in the body is to regulate immunity by producing tumor necrosis factor (TNF)-α, a cytokine that impairs CD8T cell activity and increases vascular permeability, thus suppressing the immune system by inhibiting the immune activity of lymphocytes and ultimately leading to progression and metastasis^{21,22}. (3) Monocytes play an important role as a protective immune factor in suppressing tumor growth by inducing the recruitment and function of lymphocytes in TME and interacting with adaptive immunity, especially in peripheral blood where monocytes are involved in paracrine signaling and produce many inflammatory cytokines and chemokines, including tumor necrosis factor α²³. (4) Platelets in plasma play a vital part in tumor hematogenous metastasis and are a prerequisite for it. The mechanism of action may be that platelets protect tumor cells from shear and NK cell attack²⁴. (5) Although the mechanism of plasma D-Dimer in tumor development is still unclear, some studies have reported that elevated plasma D-Dimer levels in breast cancer patients are associated with progesterone receptor expression, TNM staging and metastasis in breast cancer²⁵.

Although a number of studies have demonstrated that NLR, PLR, MLR and D-Dimer can be used as potential prognostic biomarkers in patients with a variety of solid tumors, these studies have more or less analyzed only one or two of these inflammatory indicators as markers. MLR and D-dimer were also proposed in our study as independent predictive markers of prognosis in patients with surgically treated lung cancer. However, we are not aware of any studies that have examined whether there is superposition between these markers or whether there is an interaction between them. For this reason, we divided these markers into three groups according to the number of beneficial factors, and the results of a multifactorial COX regression show that patients in the group without a single beneficial factor had the worst prognosis compared to the other two groups, while patients in the group with the most beneficial factors had the best prognosis. It is reasonable to believe that the number of beneficial peripheral blood biomarkers described above could be a valid predictor of the prognostic status of patients. There are some shortcomings in our study, as a retrospective study, selection bias may occur in the investigation and therefore the results need to be further clarified in a multicenter prospective study. In addition, only patients with operable early-stage lung cancer were selected, while it is unknown whether patients with inoperable advanced lung cancer have a superimposed effect in these tumor markers, and further studies are needed.

Conclusion

MLR and D-Dimer can be inexpensive and convenient independent predictors of prognosis in patients with surgically treatable early-stage lung cancer, and their predictive superposition can play a greater role in individualizing patient treatment.

Abbreviations

MLR: monocyte-to-lymphocyte ratio

NLR: neutrophil-to-lymphocyte ratio

PLR: Platura-to-lymphocyte ratio

D-dimer: dimeric fibrin fragment D

LC: Lung Cancer

PFS: Progression-free survival

OS: overall survival

TNM: tumor node metastases

NSCLC: non-small-cell lung cancer

ROC: receiver operating Characteristic

CI: confidence interval

HR: risk ratio

CTL: cytotoxic T lymphocytes

Declarations

Ethics approval and consent to participate

For this study, the IRB approved our application for waiver of informed consent. Because of our IRB regulations, informed consent can be exempted as long as all the following conditions are met:

1. The risk to the subjects in this study is not greater than the minimum risk. (Minimum risk refers to the possibility and degree of the expected risk in the research is not greater than the risk of daily life, or routine physical examination or psychological test.)
2. Exemption of informed consent will not adversely affect the rights and health of subjects. Note: The patient only needs to accept the normal diagnosis and treatment process of the disease, and any medical treatment and rights will not be affected.
3. The subjects' privacy and personally identifiable information are protected. Note: The personal information of patients in the study is confidential. Information that can identify patients will not be disclosed to members other than the research team. All study members and study sponsors are required to keep patient identities confidential. The patient file will only be available to researchers. In order to ensure that the research is carried out in accordance with regulations, when necessary, the government management department or the members of the ethics committee can review the patient data in the research unit according to the regulations. When the results of this research are published, no personal information about the patients will be disclosed.
4. If informed consent is required, the research will not be possible (patients have the right to know that their medical records/specimen may be used for research, and their refusal or disagreement to participate in the research is not the reason why the research cannot be implemented or the informed consent is exempted). Note: Patients have the right to know that their tissue samples may be used for research and have the right to refuse to participate in the research.
5. This study does not use medical records and specimens that patients/subjects have specifically refused to use in the past.
6. Research using human body materials or data with identifiable information has failed to find the subject, and the research project does not involve personal privacy or commercial interests.

We believe that our research meets the above conditions.

This study has been reviewed by the Ethics Committee of the Second Affiliated Hospital of Harbin Medical University, with approval number:KY2021-254.

Consent for publication

This study is a retrospective study, and the ethics committee's exemption consent application has been passed, and the relevant data is only used in this study

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due [Our ethics committee stipulates that the information that can identify patients will not be disclosed to members other than the research team] but are available from the corresponding author on reasonable request. **Competing interests**

The authors declare that they have no competing interests

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Authors' contributions

WJ and LHW wrote the main manuscript text .

XR prepared figures 1.

LT prepared figures 2.

ZJY>ZPF>QLD>ZSQ and GJD prepared table 1-5

All authors reviewed the manuscript.

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Tables

Tab 1. Patients' characteristics at baseline

Characteristic	Total N=376	Median (25%,75%) or mean±SD
Age		60±53±65
Sex	Female	158 (42%)
	Male	218 (58%)
BMI		23.86 ± 3.2
Address	Country	155 (41.2%)
	Town	221 (58.8%)
Smoking status	Former	164 (43.6%)
	Never	43.6 (56.4%)
Tumor site	RUL	81 (21.5%)
	LUL	103 (27.4%)
	RLL	82 (21.8%)
	LLL	83 (22.1%)
	RML	27 (7.2%)
Histologic subtype	Adeno.	233 (62%)
	Squamous.	90 (23.9%)
	SCLC	25 (6.6%)
	Another	28 (7.4%)
Differentiation	Well	66 (17.6%)
	Moderately	90 (23.9%)
	Poorly	220 (58.5%)
PIS	Yes	94 (25%)
	No	282 (75%)
TNM staging	I	205 (54.5%)
	II	171 (45.5%)
ECOG PS	0-1	320 (85.1%)
	2-4	56 (14.9%)
Basic illness	Hypertension	59 (15.7%)
	Diabetes	20 (5.3%)
Tumor Size		32.68±16.62

Lung function	FEV1	2.37±0.63
	FEV1%	78.65±9.84
	DLCO	6.74±1.91

BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; TNM staging, tumor, nodes, metastasis-classification staging; PIS=Pleural invasion status; HOM=History of malignancy; RUL=Right upper lobe; RML=Right middle lobe; RLL=Right lower lobe; LUL=Left upper lobe; LLL=Left lower lobe.

Table 2. Patient's peripheral blood data

Characteristic	Median (25%,75%)	Total(n=376)	
		High%¶	low%¶
Neutrophil count	4.07±3.13±5.04±(10^9/L)		
Lymphocyte count	1.87±1.5±2.34±(10^9/L)		
Monocyte count	0.36±0.25±0.46±(10^9/L)		
Platelet count	237±196±285±(10^9/L)		
D-Dimer	110.5±62.25±168±(ng/ml)	263±69.7±	113±30.3±
MLR	0.22±0.14±0.25±	137±36.4±	239±63.6±
NLR	2.61±1.58±2.94±	207±55.1±	169±44.9±
PLR	137.6±96.73±162.73±	167±44.4±	209±55.6±

MLR, monocyte to lymphocyte ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio

Table3. Univariate analyses of biomarkers for OS and PFS.

Characteristic	Reference	OS			PFS		
		HR	95% CI	p-value	HR	95% CI	p-value
sex	female	2.44	1.59-3.75	0.000048	2.26	1.51-3.40	0.000081
age		1.01	0.99-1.03	0.241034	1.01	0.99-1.03	0.257189
smoking	no	1.69	1.16-2.46	0.006738	1.53	1.07-2.20	0.021356
pathology	adeno.						
another		1.73	0.85-3.51	0.128456	1.70	0.87-3.32	0.121719
SCLC		2.86	1.49-5.47	0.001567	2.53	1.33-4.81	0.004787
squama.		1.96	1.29-3.00	0.001793	1.82	1.21-2.75	0.004036
size		1.01	0.99-1.02	0.326866	1.01	1.00-1.02	0.262015
PIS	no	1.78	1.20-2.64	0.003969	1.96	1.35-2.85	0.000426
TNM	□	1.25	0.86-1.83	0.238301	1.32	0.92-1.89	0.133186
BMI		0.97	0.92-1.03	0.369197	0.98	0.93-1.04	0.527315
MLR	high	0.39	0.27-0.57	0.000001	0.43	0.30-0.61	<0.0001
NLR	high	0.46	0.31-0.70	0.00021	0.49	0.33-0.72	0.000252
PLR	high	0.57	0.39-0.83	0.003706	0.64	0.44-0.91	0.014286
D-Dimer	high	0.40	0.24-0.67	0.000453	0.57	0.37-0.89	0.012654
ECGO PS	2-4	0.26	0.18-0.39	<0.0001	0.21	0.14-0.31	<0.0001

Table4. multivariate analyses of biomarkers for OS and PFS.

Characteristic	Reference	OS			PFS		
		HR	95% CI	p-value	HR	95% CI	p-value
sex	female	1.72	1.06-2.80	0.02843	1.51	0.96-2.39	0.077308
Pathology	adeno.						
another		1.41	0.69-2.90	0.344902	1.47	0.75-2.91	0.265219
SCLC		2.25	1.14-4.44	0.018932	2.44	1.26-4.72	0.008322
squama.		1.56	0.98-2.46	0.05821	1.61	1.03-2.51	0.037925
PIS	no	1.48	0.97-2.28	0.069652	1.61	1.07-2.40	0.021767
MLR	high	0.56	0.37-0.87	0.009145	0.57	0.39-0.85	0.005487
PLR	high	0.74	0.49-1.12	0.157511			
D-Dimer	high	0.48	0.29-0.80	0.005376	0.67	0.43-1.04	0.076619
ECGO PS	2-4	0.28	0.18-0.42	<0.0001	0.23	0.15-0.34	<0.0001

Table5. Multivariate COX regression analysis of OS and PFS grouped by beneficial factors

group	Total n=376	OS			PFS		
		HR	95% CI	p-value	HR	95% CI	p-value
0(0)	68	Reference			Reference		
1(1-2)	164	0.40	0.26-0.62	<0.0001	0.48	0.31-0.74	0.00083
3(3-4)	144	0.29	0.17-0.48	<0.0001	0.37	0.23-0.59	<0.0001

Covariates included age, Eastern Cooperative Oncology Group performance status (0-1 or 2-4), smoking status (former or never). I group: with no beneficial factors II group: There are 1-2 beneficial factors III group: There are 3-4 beneficial factors

Figures

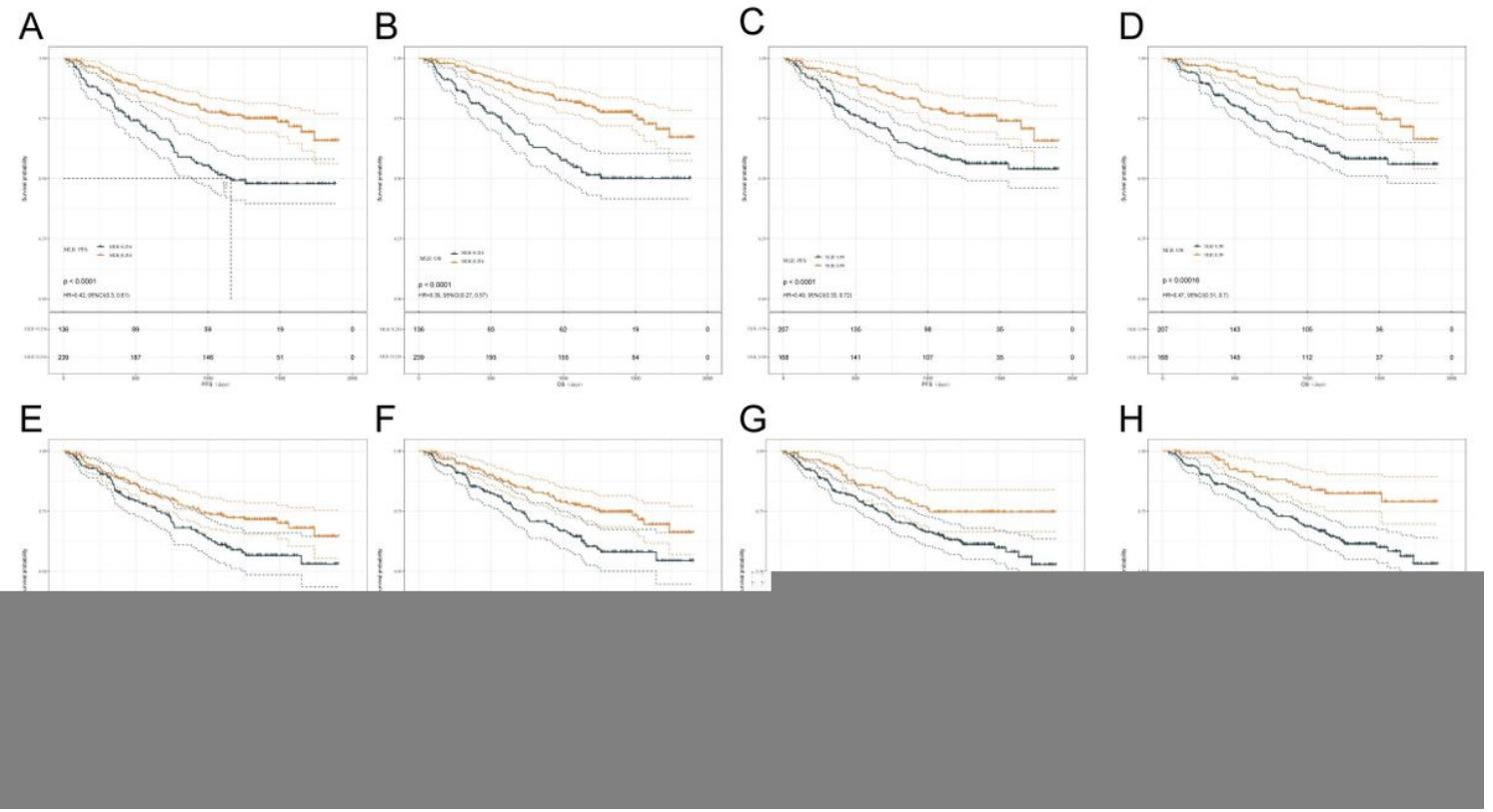


Figure 1

PFS (a, c, e, g) and OS (b, d, f, h) curves of patients stratified according to peripheral blood markers (MLR, NLR, PLR and D-dimer). p Values were calculated with the log-rank test

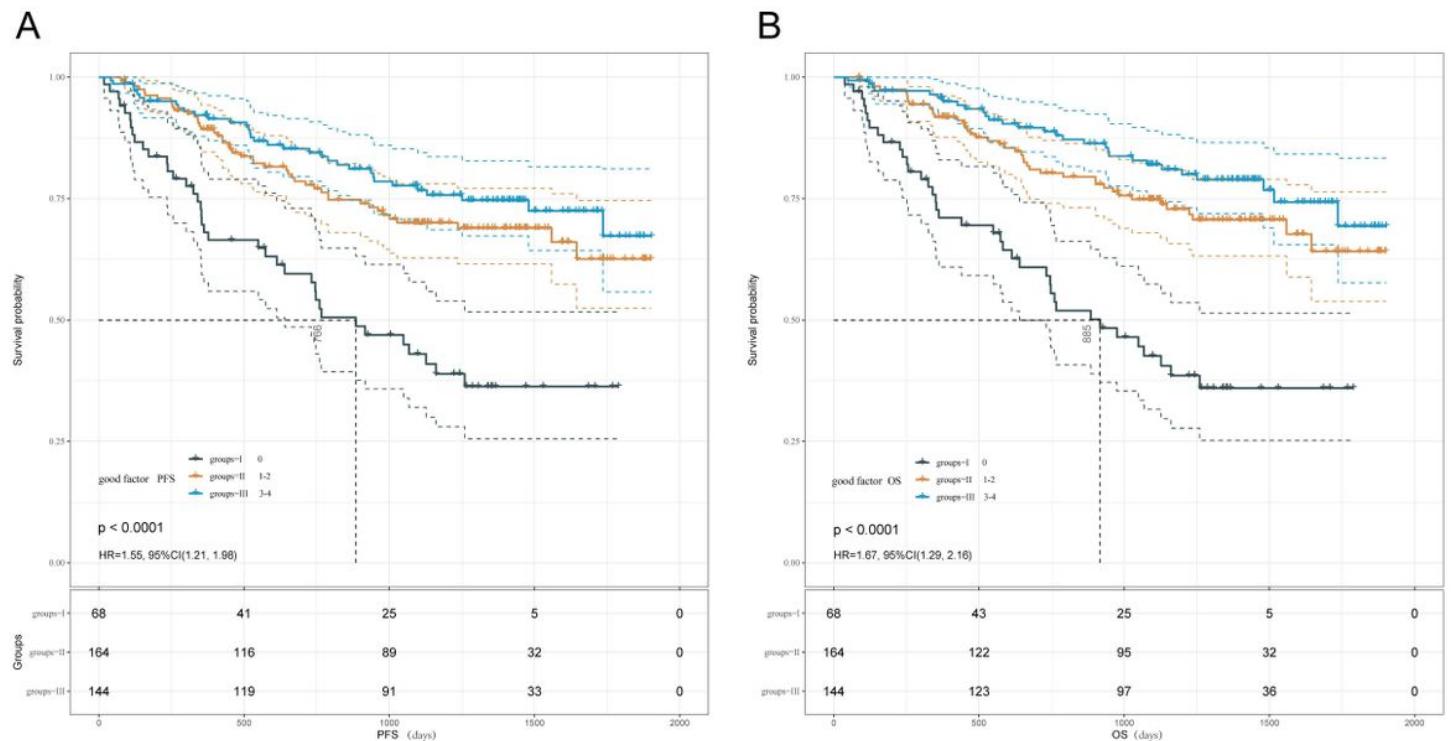


Figure 2

PFS rate (A),and OS rate (B) were determined for patients in groups I, II, and III (non one,one and two ,three and four factors, respectively). p Values were calculated with the log-rank test