

# The combination of serum NLR and D-dimer levels at diagnosis predicts overall survival in metastatic pancreatic cancer

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## Research article

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# Abstract

**Background** Many studies have confirmed that the systemic inflammatory response and hypercoagulable state of the patient are related to the occurrence and development of various tumors, including pancreatic cancer. The aim of this research was to combine blood inflammatory factors and D-dimer into a new prognostic scoring system.

**Methods** We conducted a retrospective cohort study of 73 patients with metastatic pancreatic cancer between January 2015 and December 2018 at our institution. To identify the prognostic predictors, circulating inflammatory cells and D-dimer were analyzed.

**Results** Univariate analysis showed that the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), CA19-9, Eastern Cooperative Oncology Group performance status (ECOG PS) score and D-dimer levels were significantly associated with overall survival in patients with metastatic pancreatic cancer. Multivariate analysis suggested that only the NLR ( $p < 0.026$ ) and D-dimer level ( $p < 0.012$ ) were independent prognostic predictors. Then, we combined the NLR and D-dimer level to divide the cohort into three "NLRD" groups: "NLRD0"= $NLR \leq 3.38$  and  $D\text{-dimer} \leq 1.47$ , "NLRD1"= $\text{either } NLR > 3.38 \text{ or } D\text{-dimer} > 1.47$ , "NLRD2"= $NLR > 3.38$  and  $D\text{-dimer} > 1.47$ . Finally, we found that the NLRD2 group had the worst survival, with a median overall survival (OS) of 2 months (95%CI=1.450-2.550), while the NLRD0 group had the best outcome, with a median OS of 7 months (95%CI=5.897-8.121).

**Conclusions** The scoring system combining the blood NLR with D-dimer levels provides important prognostic information for risk stratification in patients with metastatic pancreatic cancer and may help us identify patients who have a poor prognosis so that clinicians can develop personalized treatment strategies for these patients.

## 1. Introduction

Pancreatic ductal adenocarcinoma cancer (PDAC) is one of the most fatal cancers in the world due to its insidious onset, early metastasis, and chemoresistance. Most patients have developed local invasion or distant metastases at the time of diagnosis (80%-85%), and only a few patients can receive radical surgery (15%-20%)[1]. The 5-year survival rate of patients with pancreatic cancer (PC) is less than 8%, with a median survival duration of 6 months[1]. The prognostic scoring system plays a very important role in guiding individualized treatment, monitoring the treatment response, and alerting patients about changes in their condition. However, the prediction of tumor progression or recurrence is limited due to histopathological and clinical factors, such as tumor size, histological grade, histological subtype or age at diagnosis. In addition, there are no widely used prognostic tools for metastatic pancreatic cancer (MPC) so far. Therefore, it is an urgent need to find a suitable clinical prognostic tool to provide more accurate survival information, especially for patients with highly lethal malignancies, such as PC; this will not only benefit them economically but also enable them to receive personalized treatment.

Blood-based indicators, such as the C-reactive protein level, erythrocyte sedimentation rate, and white blood cell count, may reflect, to some extent, the changes in the inflammatory state in response to tumor invasion. Studies have shown that the prognosis of patients with cancers is associated with not only the characteristics of the tumor itself but also the systemic inflammatory response[2]. For instance, it is reported that a variety of routine inflammation-based prognostic scoring systems, like the NLR, PLR and lymphocyte-monocyte ratio (LMR), have prognostic significance for different tumors[3–6].

Hypercoagulability is another physiological change in cancer patients. A large-scale study involving 83203 patients with malignant tumors revealed that the absolute rate of venous thromboembolism (VTE) reached 13.9 per 1000 person-years, while the risk of VTE was 4.7 times higher than that in the general population[7]. D-dimer, as a product of fibrin deposition and subsequent degradation, can be utilized as an indicator of the hypercoagulable state of blood. It has been confirmed that a high level of D-dimer is frequently found in lung cancer[8], breast cancer[9], ovarian cancer[10] and PC[11] patients due to tumor cell proliferation, adhesion, and angiogenesis, and it is correlated with a poor prognosis and reduced treatment response. As is known, elevated D-dimer levels reflect the dual activation of coagulation and fibrinolysis. Although it also plays an important role in the diagnosis and treatment of thrombi, it has not routinely served as a tumor biomarker in cancer patients. Thus, the predictive and prognostic ability of D-dimer in metastatic MPC requires further verification.

The aims of this research were first to identify the prognostic significance of inflammatory markers and D-dimer in patients with MPC and then to combine these independent predictors of overall survival (OS) into a prognostic scoring system.

## **2. Materials And Methods**

### **2.1. Patients**

This study was a retrospective study approved by the Ethics Committee of Renmin Hospital of Wuhan University (Wuhan, China). Hospitalized patients with PC admitted to our institution from January 2015 to December 2018 were enrolled. The histopathological diagnosis of adenocarcinoma was obtained by biopsy. There was no indication for surgery, as the MPC was diagnosed with imaging data. The patients' clinical pathological parameters and laboratory results were collected from the medical electronic records, including sex, age, tumor location, site of metastasis, blood cell count, CA19-9 and D-dimer levels, treatment regimen, ECOG PS, and OS. The blood cell count, CA19-9 and D-dimer were tested within 48 hours after admission. All patients received conventional chemotherapy or optimal support therapy only based on their performance status scores. Additionally, all patients were followed by telephone, and the follow-up deadline was September 30, 2019. The exclusion criteria were as follows: (a) pathological diagnosis of non-PDAC; (b) dysfunction of important organs or malignant tumors in other areas; (c) received anti-tumor treatment before; (d) suffering from hematology or infectious diseases; (e) suffering from acute or chronic inflammatory diseases or autoimmune diseases; (f) inability to obtain informed consent; and (g) lost to follow-up.

## 2.2. Blood sampling and laboratory analysis

5 ml of fasting venous blood was collected within 48 hours of admission and placed in a yellow cap vacuum collection tube with separation gel. After the blood coagulates naturally, use Baiyang B600A horizontal centrifuge, centrifuge at 3500 r/min for 10 min (centrifugation radius = 16 cm), aspirate the separated serum, and store it in a -80°C refrigerator for testing. The blood cell count was detected by SystemXN-20 (kobe, Japan). D-dimer (reference: 0-0.55 mg/L) was determined by SysmexCA-7000 (kobe, Japan). The level of CA19-9 (reference: 0–37 U/ml) was quantified by the German Siemens CENTAUR XP automatic chemiluminescence immunoassay analyzer. All indicators were tested in accordance with the kit instructions and the standard operating procedures of the instrument. The standard and quality control products used in the detection system are original supporting reagents, and the indoor quality control is in control and the room quality evaluation is qualified.

## 2.3. Statistical analysis

The optimal cut-off values of the NLR, PLR, CA19-9 level, and D-dimer level were decided by receiver operating characteristic (ROC) curve analysis. Patients were divided into two groups according to each cut-off value. The Kaplan-Meier method was used to calculate the estimated median OS (the time from the date of diagnosis to the date of death), and the log-rank test was used for comparisons between groups. To determine the independent prognostic predictors, we conducted univariate and multivariate analyses with the Cox proportional hazard regression model. Then, we combined the independent predictors of OS identified in the multivariate analysis into a prognostic scoring system. SPSS 23.0 software were used to perform all statistical analyses. All tests were two-sided, and statistical significance was set to  $p < 0.05$ .

## 3. Results

### 3.1. Patient general characteristics

This study enrolled 73 patients with MPC, including 43 males and 30 females, with a median age of 63 years at diagnosis. More detailed baseline characteristics are shown in Table 1.

### 3.2. ROC curves analysis of NLR, PLR, D-dimer and CA19-9

The median NLR, PLR, D-dimer, and CA19-9 values were 3.65 (1.07–19.96), 164 (4-613), 1.47 mg/L (0.14–17.45 mg/L) and 670 U/ml (34-20000 U/ml), respectively. ROC curves were plotted to determine the optimal cut-off values of NLR, PLR, D-dimer, and CA19-9. As demonstrated in Fig. 1, the optimal values of NLR, PLR, D-dimer, and CA19-9 were 3.38 (AUC = 0.838, 95%CI = 0.739–0.937, Sensitivity: 85%, Specificity: 75.8%), 180 (AUC = 0.686, 95%CI = 0.562–0.810, Sensitivity: 55%, Specificity: 78.8%), 1.47 mg/L (AUC = 0.827, 95%CI = 0.733–0.921, Sensitivity: 77.5%, Specificity: 84.8%) and 780 U/ml (AUC = 0.637, 95%CI = 0.510–0.763, Sensitivity: 55%, Specificity: 77.4%), respectively.

### 3.3. Kaplan-Meier analysis of the NLR and PLR and the D-dimer and CA19-9 levels

As shown in Fig. 2, median survival was significantly different between the groups with high and low levels of NLR (2.5 months vs. 6 months,  $p < 0.0001$ ), PLR (2.5 months vs. 5 months,  $p = 0.004$ ), D-dimer (2 months vs. 6 months,  $p < 0.0001$ ), and CA19-9 (3 months vs. 5 months,  $p = 0.002$ ). In addition, the results of the univariate analysis confirmed the different prognostic values of these indicators, as shown in Table 2.

### 3.4. Univariate and multivariate analysis

The results from univariate analysis indicated that age, sex and tumor location showed no correlation with mortality, whereas site of metastasis ( $p = 0.043$ ), ECOG PS ( $p = 0.017$ ), NLR ( $p < 0.001$ ), PLR ( $p = 0.013$ ), D-dimer ( $p < 0.001$ ), CA19-9 ( $p = 0.042$ ), and chemotherapy ( $p = 0.039$ ) were significantly associated with OS. We employed multivariate analysis to further adjust for standard prognostic predictors and to verify the independent predictors of OS, the NLR ( $p = 0.026$ ) and D-dimer level ( $p = 0.012$ ).

### 3.5. NLRD prognostic score

The independent predictors, the NLR and D-dimer level, were chosen to form a prognostic scoring system. Kaplan-Meier analysis was applied to compare the four groups divided by high or low levels of NLR and D-dimer. Interestingly, significant differences were found among the four groups in terms of OS ( $p < 0.001$ , Fig. 3). The OS rates of the groups with either a high NLR and/or D-dimer levels had similar results; therefore, we created three distinct “NLRD” (NLR & D-dimer) groups: NLRD0 =  $NLR \leq 3.38$  and  $D\text{-dimer} \leq 1.47$ , NLRD1 = either  $NLR > 3.38$  or  $D\text{-dimer} > 1.47$ , NLRD2 =  $NLR > 3.38$  and  $D\text{-dimer} > 1.47$ . The NLRD0, NLRD1 and NLRD2 groups contained 21, 27 and 25 patients, respectively, and had a median OS of 7 months (95%CI = 5.897–8.121), 4 months (95%CI = 3.364–4.636) and 2 months (95%CI = 1.450–2.550), respectively ( $p < 0.001$ , Fig. 3B).

## 4. Discussion

Although tumor-specific therapies and surgery have continued to advance in the majority of malignancies, the median survival for pancreatic cancer remains unsatisfactory[1]. A suitable prognostic tool can help clinicians identify patients who have a poor prognosis and then develop a personalized treatment plan for these patients. The progression and prognosis of cancer depends on individual factors as well as the characteristics of the tumor itself. A growing body of evidence suggests that inflammation plays a crucial role in the development of tumors, such as invasion and metastasis[12–16]. The NLR is an indicator of the balance between pro-inflammatory and anti-inflammatory responses disturbed by tumor progression, and its prognostic value has been widely explored[12]. The correlation between an

elevated NLR and a poor prognosis has been confirmed in many tumors, such as lung[14], colorectal[13], stomach[15] and liver[16]. However, whether the NLR can be applied as an independent prognostic predictors in PC has remained controversial up to now[17]. Clark et al. and Sanjay et al. found no prognostic value of an elevated NLR in patients with PC who had primary tumor resection[18, 19], while in contrast, more studies have shown that an increased NLR may be utilized as a predictor of survival in patients with PC[20–22]. According to a recent meta-analysis that included 11 prospective studies focusing on PDAC specifically, a high level of NLR at diagnosis is related to a worse overall survival and negatively affects the outcomes of surgery or conventional palliative chemotherapy[21]. However, most studies were limited to patients with resectable tumors, which accounted for only a small fraction of patients with PC. Therefore, our study focused on the prognostic role of the NLR in patients with local or distant metastasis before treatment. Multivariate analysis showed that the NLR was also an independent prognostic factor for OS in MPC, which was consistent with most previous studies.

In addition, increasingly more studies in recent years have demonstrated that coagulation dysfunction is associated with tumor progression[8, 9, 11, 23–25]. Malignancies are often accompanied by the activation of coagulation and the fibrinolysis system. Approximately 50% of patients and up to 95% of metastatic tumors have coagulation dysfunction[23, 26–28]. Abnormal elevation of the D-dimer level usually indicates the overall activation of hemostasis and fibrinolysis, which is associated with poor prognosis in several cancers, such as lung cancer[8], breast cancer[9], ovarian cancer[10] and PC[11].

To obtain more prognostic information in PC, we designed this study and hoped to develop a new prognostic tool. We compared the prognostic value of a series of serum indicators, including the NLR, PLR, D-dimer level, and CA19-9 level, and then combined these predictors identified as independent prognostic value of survival, the NLR and D-dimer level, into a scoring system, the NLRD. The result indicates that high levels of the NLR and D-dimer at diagnosis are considered useful prognostic markers in MPC. As shown in Fig. 3B, the group NLRD2 (high NLR and high D-dimer) had the worst survival, with a median OS of 2 months, while the group NLRD0 (low NLR and low D-dimer) had the best outcomes, with a median OS of 7 months. The scoring system improves the accuracy of the prognostic prediction, which can help clinicians better determine treatment plans and provide patients with more accurate survival estimates.

There are also a number of shortcomings that should be noted. First, this research is a retrospective analysis of a single institution, and thus, bias in population selection cannot be avoided. Leucocyte counts and D-dimer are not specific to any one disease and are affected by a number of variables. Since there is no international standard for D-dimer and each method uses different subsets of D-dimer containing proteins, the results may not necessarily be applicable at other centers using a different reagent and analyzer. However, undeniably, these results still have important reference value in assessing the patient's condition during clinical work. Second, the number of patients involved is relatively small. Therefore, future work with a larger population is needed to further validate the findings of this study. Additionally, whether anticoagulation and anti-inflammatory treatments can be used to increase the

sensitivity of pancreatic cancer to chemotherapy drugs and prolong the survival of patients is a subject worthy of further exploration.

## 5. Conclusions

This research identified the independent prognostic indicators of survival in patients with MPC, namely, the NLR and D-dimer level, and then combined them into a scoring system, which was found to be a useful prognostic tool for MPC. However, further research is needed to verify these meaningful outcomes.

## Declarations

### Acknowledgements

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### Funding

Not applicable.

### Conflict of interests

The authors declare no conflict of interests regarding the publication of this paper.

### Author contribution

PM, QG, QF and JT retrospectively collected and analyzed the data. PM, JT and JC wrote, reviewed and revised the literature, and participated in the writing of the paper. All authors read and approved the final manuscript to be published.

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## Tables

**TABLE 1** Characteristics of patients with metastatic pancreatic cancer.

Characteristics	Values/Counts
Age, years, median(range)	63(41-87)
Gender(male/female)	43/30
Tumor location(head/body/tail)	31/25/17
Metastatic site(liver/other)	46/27
AJCC Stage (Stage III/Stage IV)	6/67
ECOG PS ( $\leq 2$ / $> 2$ )	41/32
CA19-9, U/ml, median(range)	670(34-20000)
D-dimer, mg/L, median(range)	1.47(0.14-17.45)
NLR, median(range)	3.65(1.07-19.96)
PLR, median(range)	164(4-613)
Treatment(chemotherapy/other)	20/53
Survival time, months, median(range)	4(0.5-10)

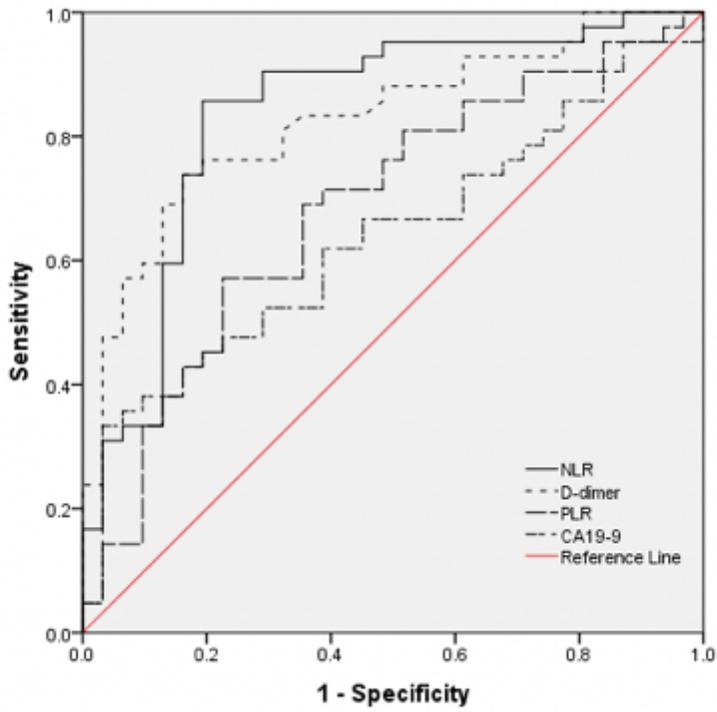
*Note:* AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NLR=neutrophil-to-lymphocyte ratio. PLR=platelet-lymphocyte ratio.

**TABLE 2** Univariate and multivariate analysis of parameters used to predict overall survival in patients with metastatic pancreatic cancer.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
<b>Age, years</b>						
≤63	1 (referent)					
>63	1.036	0.648-1.655	.884			
<b>Gender</b>						
Male	1 (referent)					
Female	1.346	0.829-2.185	.230			
<b>Tumor location</b>						
Head	1 (referent)					
Body	1.160	0.680-1.979	.507			
Tail	0.831	0.457-1.512	.575			
<b>Site of metastasis</b>						
Liver	1 (referent)			1 (referent)		
Other	.595	0.360-0.985	.043	0.716	0.405-1.265	.250
<b>ECOG PS</b>						
≤2	1 (referent)			1 (referent)		
>2	0.527	0.311-0.893	.017	0.542	0.307-0.957	.055
<b>CA19-9</b>						
≤780	1 (referent)			1 (referent)		
>780	1.885	1.152-3.085	.042	1.013	0.569-1.805	.765
<b>NLR</b>						
≤3.38	1 (referent)			1 (referent)		
>3.38	4.239	2.441-7.361	<.001	2.034	3.058-5.962	.026
<b>PLR</b>						
≤180	1 (referent)			1 (referent)		
>180	1.796	1.108-2.912	.048	0.760	0.429-1.348	.169
<b>D-dimer</b>						
≤1.47	1 (referent)			1 (referent)		
>1.47	5.515	2.149-9.659	<.001	2.392	2.436-7.067	.012
<b>Treatment</b>						
No chemotherapy	1 (referent)			1 (referent)		
Chemotherapy	1.696	2.326-4.311	.039	0.842	1.421-3.272	.083

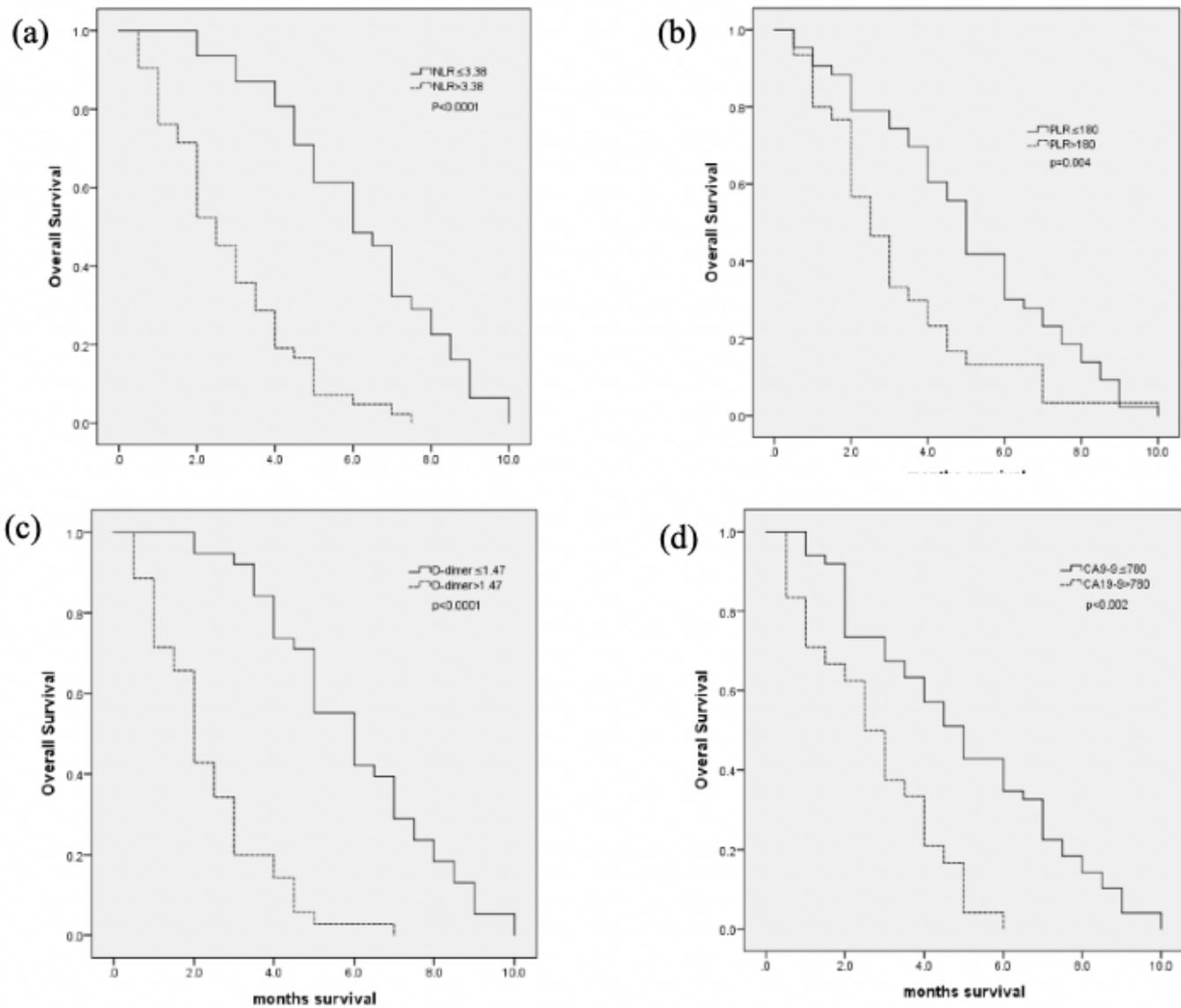
Note: CI=confidence interval; HR=hazard; AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NLR=neutrophil-to-lymphocyte Ratio; PLR=platelet-lymphocyte ratio.

## Figures



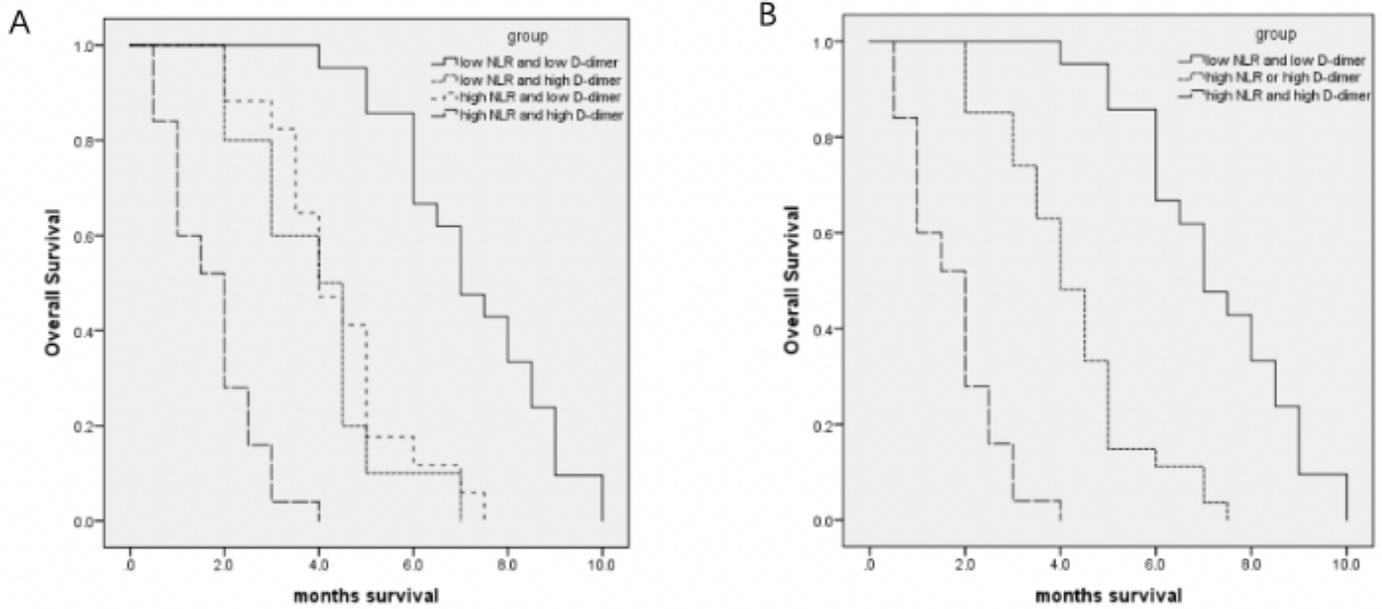
**Figure 1**

The receiver operating characteristic (ROC) curves for neutrophil-to-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), D-dimer, and CA19-9.



**Figure 2**

Kaplan-Meier analysis for (a) neutrophil-to-lymphocyte ratio (NLR), (b) platelet-lymphocyte ratio (PLR), (c) D-dimer and (d) CA19-9, respectively.



**Figure 3**

Kaplan-Meier curves showing differences in estimated median survival when combining neutrophil-to-lymphocyte ratio (NLR) and D-dimer. A. patients were divided into four groups ( $p < 0.001$ ). B. patients were divided into three groups using the NLRD prognosis score ( $p < 0.001$ ).