High Postoperative Monocyte Predicts Worse Lung Adenocarcinoma or Squamous Cell Carcinoma Outcomes

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Authors' contribution:

Yang Hai contributed to the conception of the study, data collection and analysis and in writing the manuscript. Nan Chen made the graphics and contributed in writing the manuscript. Jian Zhou reviewed the West China Lung Cancer database and conducted the initial data analysis. Yang Hai and Nan Chen helped with interpretation of the initial data and graphics.

Abstract

Background: Peripheral monocyte count is an assessable parameter. Recently, evidence suggested an elevated preoperative monocyte counts predicting poor prognosis in malignancies. The aim of this study was to determine the prognostic effect of early postoperative (within 4 days) blood monocyte count in patients with lung adenocarcinoma or squamous cell carcinoma following lobectomy.

Methods: We retrospectively reviewed patients with operated lung adenocarcinoma or squamous cell carcinoma from 2006 to 2011 in Western China Lung Cancer database. Both the preoperative and postoperative monocyte counts were divided into two groups. Univariate analysis on disease-free survival (DFS) and overall survival (OS) was performed using the Kaplan-Meier and log-rank tests, and multivariate analysis was conducted using the Cox proportional hazards regression model.

Results: There were 433 patients enrolled in our analysis. The cut-off values were $0.375*10^9$/L and $0.845*10^9$/L for preoperative and early postoperative monocyte count respectively which were calculated by receiver operating characteristic curve. Two-tailed log-rank test indicated patients with an early postoperative elevated monocyte count predicted a poor DFS and OS overall ($P<0.001$, $P<0.001$, respectively) as well as in subgroup analysis. On univariate and multivariate analysis, early postoperative elevated monocyte count presented as a promising independent prognostic factor for both DFS and OS (HR=2.991, 95%CI: 2.243-3.988, $P<0.001$; HR=2.705, 95%CI: 1.977-3.700, $P<0.001$, respectively). However, no significance was detected for preoperative monocyte in multivariate analysis.

Conclusions: Elevated early postoperative peripheral monocyte count is an independent predictor of poor prognosis for patients with operable lung adenocarcinoma or squamous cell carcinoma by lobectomy.

Key words: Lung squamous carcinoma; Lung adenocarcinoma; Peripheral monocyte count; Prognosis

Introduction

Lung cancer is the leading cause of cancer-related death worldwide, with 5-year survival rates of less than 17% (1). Among all types, non-small-cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers. Adenocarcinoma and squamous cell carcinoma account for approximately 40% and 25-30% of lung cancers, respectively (1, 3). In the aspect of treatment, if operable, surgery provides the best chance to cure NSCLC (2), which also calls for a comprehensive perioperative evaluation system.

The hypothesis of the relationship between cancer and inflammation has triggered researcher interests though it is not new. Back to 1863, chronic inflammation was firstly regarded as the origin of tumor cells, and the response of the human body towards malignancies was proven to be closely related with inflammation (3). Examples included tissue necrosis factor (TNF), interleukin (IL)-1, IL-6, matrix metalloproteinases, vascular endothelial growth factor, etc. As for peripheral blood cells, monocytes/macrophages, neutrophils, dendritic cells, and natural killer cells form the first line of immune defense in normal situations (4), and some of them have been regarded as “superstars” for oncologists. Specifically, in real clinical work, elevated preoperative monocyte counts have recently been shown to predict poor prognosis in various types of malignancies, including hepatic cell carcinoma, malignant lymphomas as well as lung adenocarcinoma (5-7). However, it is still unclear if an elevated early postoperative (within 4 days) monocyte count is associated with a poor prognosis in lung adenocarcinoma or squamous cell carcinoma after lobectomy. We focused on the early postoperative period because it is the most turbulent stage of the host immune system which may be caused by the surgical trauma and/or tumor removal effect, and we hypothesized that this change in immune environment related with tumor progression. The aim of this study was to evaluate whether an elevated early postoperative monocyte count predicts a poor prognosis in patients with operable lung adenocarcinoma or squamous cell carcinoma after lobectomy.

Materials and Methods

Study population

The data were retrieved from Western China Lung Cancer database (WCLC). We enrolled patients with operable lung adenocarcinoma or squamous cell carcinoma treated with lobectomy at West China Hospital, Sichuan University between 2006 and 2011. All patients were >18 years of age, with complete clinicopathological data, and proven to be lung adenocarcinoma or squamous cell carcinoma after surgery. Preoperative evaluation included physical examination, blood routine examination, tumor markers test, chest X-ray and computed tomography, brain magnetic resonance imaging (MRI), bone scintigraphy, and bronchoscopy and integrated positron emission tomography scan and CT (PET/CT) scan when necessary. The eligibility criteria were: 1) lobectomy with no microscopic residual tumor; 2) no preoperative chemotherapy and/or radiotherapy; 3) no previous history of other malignancies; 4) no evidence of infections such as pneumonia; 5) availability of laboratory data and follow-up information. The peripheral venous blood samples were collected from patients within one week before and within 4 days after surgery, the latter meant the first postoperative blood sample taken from the patient must be within 4 days, and only the first sample after surgery was recorded. Absolute peripheral blood count and the percentage were analyzed for each blood sample. Histological classification was made with reference to the latest WHO guideline (8). The stages of lung cancer were confirmed based on the 7th edition of TNM classification of malignant tumors (9). The study approval was granted by the Institutional Review Board at the West China Hospital, Sichuan University.

Evaluation of clinicopathological factors

Baseline characteristics included age, sex, underlying diseases, smoking history, pathological stage, pathological tumor status, pathological lymph node status, and peripheral blood counts and the percentages. Blood samples used for analysis were taken within one week before and within 4 days after surgery performed within the clinical laboratory of our hospital via Cell-Dyn 3700 (Abbott Diagnostics, USA).

Other data included the surgical date and procedures.

Treatment and follow-up

Lobectomy was performed on all patients with intent to cure, and systematic nodal dissection was carried out. The resection was done both macroscopically and histologically completely with a negative tumor margin and no evidence of distant metastasis. Patients were regularly followed up at outpatient department 1 month after surgery, every 3 months for the first year, every 6 months for the next four years, and once annually thereafter. Patients received a physical examination, blood routine examination, Chest and brain and upper abdomen CT scan at each follow-up. Bone scintigraphy was performed every 12 months. Particularly, all the patients treated in our department received phone call following-up regularly, during which we recorded their living status, tumor recurrence/metastasis condition, and sequential treatments such as chemotherapy and/or radiotherapy, etc. The patients were followed until December 31, 2016 or until they died.

Statistical analysis

Receiver operating characteristic (ROC) curve was performed to search the best cut-off value for monocyte count to stratify patients at a high risk of tumor recurrence, distant metastasis, or death. In the ROC curve, the point with the maximum sensitivity and specificity was selected as the best cut-off value. Disease-free survival (DFS) was calculated from the date of surgery to the date of recurrence/metastasis or death with any cause, and overall survival (OS) was presented from the date of surgery to the date of death with any cause. DFS and OS were both censored at the date of the last follow-up. Fisher's exact test or $\chi 2$-test for categorical variables and t-test for continuous variables were used to analyze the clinicopathological features for the two groups divided by the cut-off value of monocyte. Life table method was conducted to calculate 1, 3, 5-year survival rate. Survival curves were plotted using the Kaplan–Meier method and compared using the log-rank test. The prognostic factors of OS and DFS were analyzed by Cox

proportional hazard model with univariate and multivariate analysis. Factors proven significant in the univariate analysis were included in the multivariate analysis. Subgroup analysis was used to further discriminate tumor prognosis between monocyte count and other prognostic factors: pathological stage, histological type, surgical procedure, etc. All *P* values were two-tailed with less than 0.05 considered to be statistically significant. Statistical analysis was performed using SPSS (SPSS version 19.0, Chicago, IL, USA) and STATA 14.0 (STATA Corporation, College Station, TX, USA). Survival curves were drew by GraphPad Prism 5.0 (GraphPad Software, San Diego, CA).

Results

The selection process of patients was showed in Figure A. There were 1665 patients identified totally. 1232 patients were excluded for cancer type, pathological stage, or surgical procedure mismatch, previous history of malignancies or chemotherapy/radiotherapy, and those who combined with infections. Finally, there were 433 patients enrolled in our analysis. Among them, there were 278(64.2%) male and 155(35.8%) female. The average age of year's old and standard difference were 60.6 and 10.0, respectively. Video-assisted thoracic surgery (VATS) was performed in 221(51.0%) patients compared with traditional open thoracic surgery in 212(49.0%) patients. Specimens were histologically proven to be lung adenocarcinoma in 264(61.0%) patients and squamous cell carcinoma in 169(39.0%) patients. The details were presented in Table A.

By analyzing the ROC curve, the cut-off value for preoperative monocyte count was $0.375*10^9$/L with the area under the curve (AUC) of 0.566; while for postoperative monocyte count, the cut-off value was $0.845*10^9$/L with AUC of 0.692 (Figure B). The baseline characteristics were stratified by high versus low preoperative monocyte and early postoperative monocyte count (Table A). The preoperative monocyte was detected to be associated with male gender ($P<0.001$), smoking history ($P<0.001$), T stage ($P=0.014$) and histological type ($P<0.001$). For early postoperative group,

compared to the low monocyte count group, male gender (P<0.001), positive smoking history (P=0.005), and higher N stage (P=0.002) and higher tumor stage (P=0.026) were more common found in high monocyte count group. The association between preoperative or postoperative monocyte and clinical characteristics were presented in Table A in details.

We further performed Kaplan-Meier method to identify difference of survival rates between two subgroups stratified by monocyte count (low vs. high) of both preoperative and early postoperative group. For preoperative group, the 1-year OS of low and high subgroups were 95% and 93% (P=0.003), and the 1-year DFS of low and high subgroups were 82% and 85% (P=0.106). The 3-year OS of low and high subgroups were 82% and 74% (P=0.003), and the 3-year DFS of low and high subgroups were 67% and 60% (P=0.106), respectively. Additionally, the 5-year OS of low and high subgroups were 72% and 58% (P=0.003), and the 5-year DFS of low and high subgroups were 62% and 51% (P=0.106). As for the early postoperative group, the 1-year OS of low and high subgroups were 96% and 90% (P=0.004), and the 1-year DFS of low and high subgroups were 90% and 71% (P<0.001). The 3-year OS of low and high subgroups were 89% and 62% (P<0.001), and the 3-year DFS of low subgroup was 78% compared to 41% in high group (P<0.001). In addition, the 5-year OS of low and high subgroups were 79% and 46% (P<0.001), and the 5-year DFS of low and high subgroups were 72% and 33% (P<0.001). Overall, an early postoperative elevated monocyte count was significantly associated with poor OS (P<0.001) and DFS (P<0.001) (Figure C). In further analysis, high level postoperative monocyte count was associated with poor OS and DFS in both adenocarcinoma and squamous carcinoma subgroups (Figure D). These differences were also significant in subgroup analysis when stratified by gender, age, smoking history, stage, T stage, N stage and surgical procedure in postoperative group (Figure E, Figure F). On the contrary, no statistical significance was seen in subgroup analysis of preoperative group.

Univariate prognostic analysis was performed to detect the prognositic significance of clinicopathological factors, and preoperative and early postoperative blood monocyte count (Table B). N stage (P<0.001), tumor stage (P<0.001)), histological type (P=0.014), preoperative (P=0.023) and postoperative monocyte count level (P<0.001) were significantly associated with DFS, while age (P=0.017), surgery procedure (P=0.002), T stage (P=0.003), N stage (P<0.001), tumor stage (P<0.001), preoperative(P=0.024) and postoperative monocyte count level (P<0.001) showed significant relationships with OS. The clinicopathological factors proved to be prognostic predictors in univariate analysis were included as covariates in further multivariate analysis (Table C). Finally, open surgery (HR=1.520, 95%CI: 1.117-2.069, P=0.008), positive N status (HR=2.506, 95%CI: 1.625-3.864, P<0.001), squamous cell carcinoma (HR=0.633, 95%CI: 0.468-0.856, P=0.003) and high postoperative monocyte count (HR=2.991, 95%CI: 2.243-3.988, P<0.001) were risk factors with statistical significance for DFS. Correspondingly, age (HR=1.022, 95%CI: 1.005-1.038, P=0.009), open surgery (HR=1.700, 95%CI: 1.163-2.486, P=0.006), advanced tumor stage (HR=2.253, 95%CI: 1.178-4.309, P<0.001), and high postoperative monocyte count (HR=2.705, 95%CI: 1.977-3.700, P<0.001) were observed as risk factors for OS. However, preoperative monocyte was no more associated with either DFS or OS within multivariate analysis.

Discussion

Immune response is an essential component of tumor progression. Studying these responses within tumor microenvironment via several immune factors can further stratify the prognosis of cancer (10). Back to the last century, Negus et al. had demonstrated a number of cells expressed chemokine receptors could infiltrate to tumor areas (11). Later on, an increasing number of experimental studies found that inflammation played a crucial role in tumor progression. Inflammatory markers such as C-reactive protein in esophageal squamous cancer (12), Colony-stimulating factor-1 in mammary tumor (13), and inhibitors of metalloproteinases in NSCLC (14), all have been suggested as alternative markers for tumor progression (8).

Likewise, as easy assessable parameters, peripheral blood cell counts have also been regarded as predictors of tumor prognosis. An elevated neutrophil, monocyte and leukocyte counts were proven to be associated with poor survival in patients with metastatic melanoma (15).

Monocytes belong to circulating peripheral blood cells that play the crucial role in immune response with the capability of differentiating into macrophages and antigen-presenting cells (APCs). Thus, they form the first line of innate immune defense (16). In addition, monocytes could activate T and B lymphocytes and further produce cytokines such as IL-12 and TNF-α to stimulate the immune response (17). However, either overstimulation or immunosuppression of monocytes caused by surgical procedure and/or other external factors could disrupt the immune system (18, 19). Previous studies have found an elevated preoperative monocyte count demonstrated a poor prognostic factor in esophageal squamous cell carcinoma, mantle cell lymphoma, follicular lymphoma, and classical Hodgkin lymphoma, respectively (20-23). Also, for the early postoperative period, Franke et al. discovered an increase in the absolute monocyte count but an impairment of monocyte function, indicating a decreased ability to synthesize IL-12 and TNF-α, to express HLA-DR, and to act as the APC (24). To the best of our knowledge, this is the first study showing the prognostic significance of the early postoperative monocyte count in patients with lung adenocarcinoma or squamous cell carcinoma after lobectomy.

The mechanisms of elevated monocyte count relates with poor prognosis of several kinds of tumors are still not clearly elucidated. There are several possible explanations. First, it is hypothesized that monocytes are attracted by several cytokines or chemokines to the tumor site and then differentiate into tumor-associated macrophages (TAMs), which further promote those invading leukocytes to bring out potentials of angiogenesis, motility, and invasion (25, 26). Angiogenic signals from surrounding cells result in vasodilatation and increased

vascular permeability (27, 28), forming a vicious cycle for tumor progression. Second, human monocyte subsets were differentiated according to their surface CD14/CD16 expression as “majority/classical” (CD14++CD16-), “minority/non-classical” (CD14+CD16+) and the subset with pro-angiogenic feature (CD14++CD16+CCR2+) (29, 30). Among all subsets of the monocytes, the “majority/classical” accounts for approximately 90% of monocytes in healthy people (31). However, Schauer et al. found that along with the increased number of monocytes, the major subsets shifted from CD16- to CD16+ after liver resection, showing a stronger potential of angiogenesis (32). Correspondingly, while the classical monocytes are recruited to tumor sites, contributing to tumor macrophage content and promote tumor growth and metastasis, Richard N. Hanna et al. also found out the potential protective role of nonclassical “patrolling” monocytes tumor growth and metastasis (33). This is also our next step to find out whether it will happen after lobectomy of lung cancer and what the exact type is and the alternatives of the function in immunity. Third, peripheral monocytes grow into TAMs when entering tumor areas. TAMs are classified into two phenotypes: M1 and M2. Activated M1 macrophages have the anti-tumor response, while M2 macrophages, activated by tumor-derived cytokines, are suitable for tumor development (34, 35). A previous study has reported that circulating macrophages predict tumor recurrence after surgery in patients with NSCLC (36), while in this study, an elevated early postoperative peripheral monocyte count is significantly associated with a poor prognosis in patients with lung adenocarcinoma or squamous cell carcinoma after lobectomy. These results might suggest a complex association between peripheral TAMs (M2 type) and monocytes, which still calls further studies to verify. Moreover, the reason why we focused on the early postoperative period--the most turbulent stage of host immune system caused by surgical trauma and/or tumor removal effect probably was that we hypothesized that change in this period of immune environment might relate with tumor progression more closely than that of the preoperative data.

In the present study, an elevated early postoperative monocyte count was shown to predict a poor DFS and OS both in the univariate and multivariate analysis. In addition, as shown in the subgroup analysis, the monocyte count was found to be significantly associated with poor prognosis when stratified by gender, age, smoking history, TNM stage, surgical procedure and histological type. All of the above indicated that an elevated early postoperative blood monocyte count to be a very strong prognostic factor in tumor progression.

Limitations of the current study are inherent to its design, including the retrospective data collection and several confounding factors when comparing postoperatively. Moreover, the small number of patients, especially the cases with endpoints, also limits the conclusion of the current study.

Conclusion

The present study supports the prognostic significance of early postoperative peripheral blood monocyte count in patients with operable lung adenocarcinoma or squamous cell carcinoma after lobectomy in both OS and DFS. We found that the tumor recurrence/metastasis and death rates were significantly higher in the high monocyte group compared with the low monocyte group. This easily measured blood parameter may provide useful information for the clinicians to consider when prescribing the adjuvant therapy. Further investigations are still needed to figure out the oncological significance of monocyte and its subsets, the association with host inflammatory microenvironment.

Abbreviations

OS: overall survival

DFS: disease-free survival

NSCLC: non-small cell lung cancer

TNF: tissue necrosis factor

IL: interleukin

MRI: magnetic resonance imaging

PET-CT: positron emission tomography scan and CT

ROC: receiver operating characteristic

VATS: video-assisted thoracic surgery

AUC: area under the curve

APCs: antigen-presenting cells

TAMs: tumor-associated macrophages

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Yang Hai contributed to the conception of the study, data collection and analysis and in writing the manuscript. Nan Chen made the graphics and contributed in writing the manuscript. Zi-huai Wang, Cheng-lin Guo and Feng Lin reviewed the West China Lung Cancer database and conducted the initial data analysis. Cheng-wu Liu helped with interpretation of the initial data and graphics. Wei-min Li and Lun-xu Liu contributed with the study design, the interpretation of the result and critical revision of the manuscript. All authors approved the paper to be published. All authors have no conflict of interest or financial ties to disclose. This work was supported by Key Science and Technology Program of Sichuan Province, China (2014SZ0148 to Dr. Weimin Li; 2016FZ0118 to Dr. Lunxu Liu).

Disclosure

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Conflict of Interest: Yang Hai declares that she has no conflict of interest. Nan Chen declares that he has no conflict of interest. Jian Zhou declares that he has no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were inaccordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study

Foot Notes

Fig. A Flow chart of patient selection

Table A. Basic characteristics of clinicopathological features of patients with different monocyte counts

Fig. B Receiver operating characteristic curve for determination of the cut-off value for monocyte. The cut-off value for preoperative monocyte count was $0.375*10^9$/L with area under the curve (AUC) of 0.566; while $0.845*10^9$/L with AUC of 0.692 for postoperative monocyte count.

Fig. C 1 Disease-free survival of high and low postoperative monocyte level; **2** overall survival of high and low postoperative monocyte level.

Fig. D Disease-free survival and overall survival of 433 lung cancer patients with different monocyte stratified by histological type. **1** Disease-free survival of patients with adenocarcinoma; **2** Disease-free survival of patients with squamous cell carcinoma; **3** Overall survival of patients with adenocarcinoma; **4** Overall survival of patients with squamous cell carcinoma.

Fig. E Disease-free survival and overall survival of 433 lung cancer patients with different monocyte stratified by tumor stage. **1** Disease-free survival of patients with stage I disease; **2** Disease-free survival of patients with stage II disease; **3** Disease-free survival of patients with stage IIIA disease; **4** Overall survival of patients with stage I disease; **5** Overall survival of patients with stage II disease; **6** Overall survival of patient with stage IIIA disease

Fig. F Disease-free survival and overall survival of 433 lung cancer patients with different monocyte stratified by N stage. **1** Disease-free survival of patients with N0 stage; **2** Disease-free survival of patients with N1 stage; **3** Disease-free survival of patients with N2 stage; **4** Overall survival of patients with N0 stage; **5** Overall survival of patients with N1 stage; **6** Overall survival of patients with N2 stage

Table B. Univariate analysis of clinicopathological parameters and inflammatory

biomarkers influencing prognosis

Table C. Multivariate analysis of clinicopathological parameters and inflammatory biomarkers influencing prognosis

(Color used in Figure B-F)

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Fig. A Flow chart of patient selection

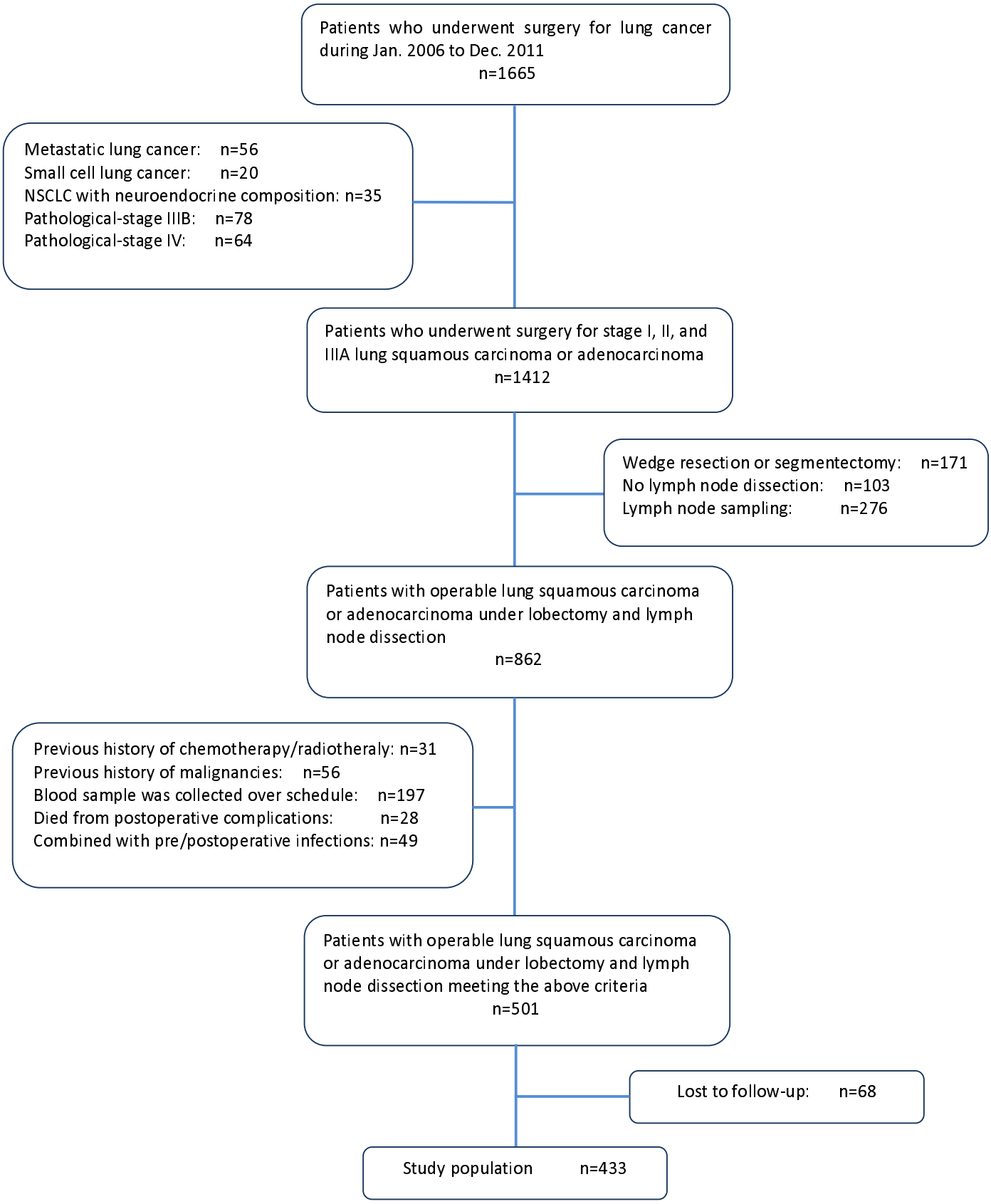


Table. A Basic characteristics of clinicopathological features of patients with different monocyte counts

Category	N(%)	Preoperation monocyte (10^9/L)		P value [a]	Postoperation monocyte (10^9/L)		P value [a]
		<0.375	≥0.375		<0.845	≥0.845	
Gender				**<0.001**			**<0.001**
Male	278(64.2%)	122	156		155	123	
Female	155(35.8%)	128	27		116	39	
Age	433(100%)	61.08±9.74	59.95±10.47	0.247	60.24±10.05	61.21±10.08	0.334
Smoking history				**<0.001**			**0.005**
Yes	258(59.7%)	115	143		148	110	
No	174(40.3%)	135	39		123	51	
Location				0.341			0.789
Left superior	128(29.6%)	74	54		80	48	
Left inferior	62(14.3)	39	23		40	22	
Right superior	128(29.6%)	79	49		80	48	
Right middle	44(10.2)	24	20		24	20	
Right inferior	71(16.4%)	34	37		47	24	
Procedure				**0.026**			0.054
VATS	221(515%)	139	82		148	73	
Open	212(49%)	111	101		123	89	
T stage				**0.014**			0.351
T1	84(19.4%)	58	26		50	34	
T2	279(64.4%)	161	118		178	101	
T3	55(12.7%)	26	29		31	24	
T4	15(3.5%)	5	10		12	3	
N stage				0.291			**0.002**
N0	268(62.0%)	158	110		184	84	
N1	71(16.4%)	35	36		42	29	
N2	93(21.5%)	56	37		45	48	
Stage				0.323			**0.026**
I	205(47.3%)	126	79		139	66	
II	107(24.7%)	59	48		68	39	
IIIA	121(27.9%)	65	56		64	57	
Histological type				**<0.001**			0.232

Adenocarcinoma	259(59.8%)	181	78		168	91	
Squamous carcinoma	174(40.2%)	69	105		103	71	
Differentiation				0.277			0.320
Well	11(2.6%)	8	3		9	2	
Moderate	261(61.7%)	155	106		159	102	
Poor	151(35.7%)	80	71		98	53	

T stage, tumour; N stage, node; VATS, Video-assistant thoracoscopic surgery; N, cases sample size

[a] Significance of Fisher's exact test, X^2-test or t-test. $P < 0.05$ was considered statistically significant.

Table. B Univariate analysis of clinicopathological parameters and inflammatory biomarkers influencing prognosis

Category	Variables	Disease-free survival		Overall survival	
		HR (95% CI)	P[a]	HR (95% CI)	P[a]
Gender	Male	Reference		Reference	
	Female	0.963(0.716-1.295)	0.801	0.841(0.581-1.216)	0.358
Age	Per year	1.008(0.993-1.022)	0.311	1.023(1.004-1.042)	**0.017**
Smoking history	Yes	Reference		Reference	
	No	1.009(0.756-1.348)	0.950	0.838(0.585-1.202)	0.337
Location	Left superior	Reference		Reference	
	Left inferior	0.989(0.634-1.545)	0.962	1.492(0.870-2.560)	0.146
	Right superior	0.875(0.604-1.267)	0.479	1.205(0.758-1.916)	0.431
	Right middle	1.263(0.785-2.031)	0.335	1.486(0.817-2.700)	0.194
	Right inferior	0.655(0.410-1.047)	0.077	0.899(0.506-1.596)	0.715
Procedure	VATS	Reference		Reference	
	Open	1.455(1.093-1.937)	**0.010**	1.760(1.236-2.505)	**0.002**
T stage	T1	Reference		Reference	
	T2	1.219(0.833-1.783)	0.309	1.268(0.775-2.072)	0.344
	T3	1.559(0.945-2.573)	0.082	2.453(1.361-4.421)	**0.003**
	T4	1.376(0.609-3.111)	0.443	1.602(0.601-4.271)	0.346
N stage	N0	Reference		Reference	

	N1	2.467(1.695-3.592)	**<0.001**	2.869(1.833-4.491)	**<0.001**
	N2	3.349(2.414-4.647)	**<0.001**	3.442(2.306-5.139)	**<0.001**
Stage	I	Reference		Reference	
	II	1.847(1.273-2.679)	**0.001**	2.342(1.460-3.757)	**<0.001**
	IIIA	3.163(2.260-4.428)	**<0.001**	4.078(2.658-6.258)	**<0.001**
Histological type	Adenocarcinoma	Reference		Reference	
	Squamous carcinoma	0.687(0.508-0.928)	**0.014**	1.117(0.787-1.587)	0.535
Differentiation	Well	Reference		Reference	
	Moderate	6.446(0.899-46.191)	0.064	3.869(0.538-27.831)	0.179
	Poor	7.172(0.996-51.643)	0.050	4.340(0.599-31.455)	0.146
Preoperation monocyte	<0.375	Reference		Reference	
	≥0.375	1.391(1.047-1.849)	**0.023**	1.490(1.053-2.109)	**0.024**
Postoperation monocyte	< 0.845	Reference		Reference	
	≥0.845	3.974(2.956-5.342)	**<0.001**	3.826(2.662-5.499)	**<0.001**

T stage, tumour; N stage, node; VATS, Video-assistant thoracoscopic surgery; HR, hazard ratio; CI, confidence interval.

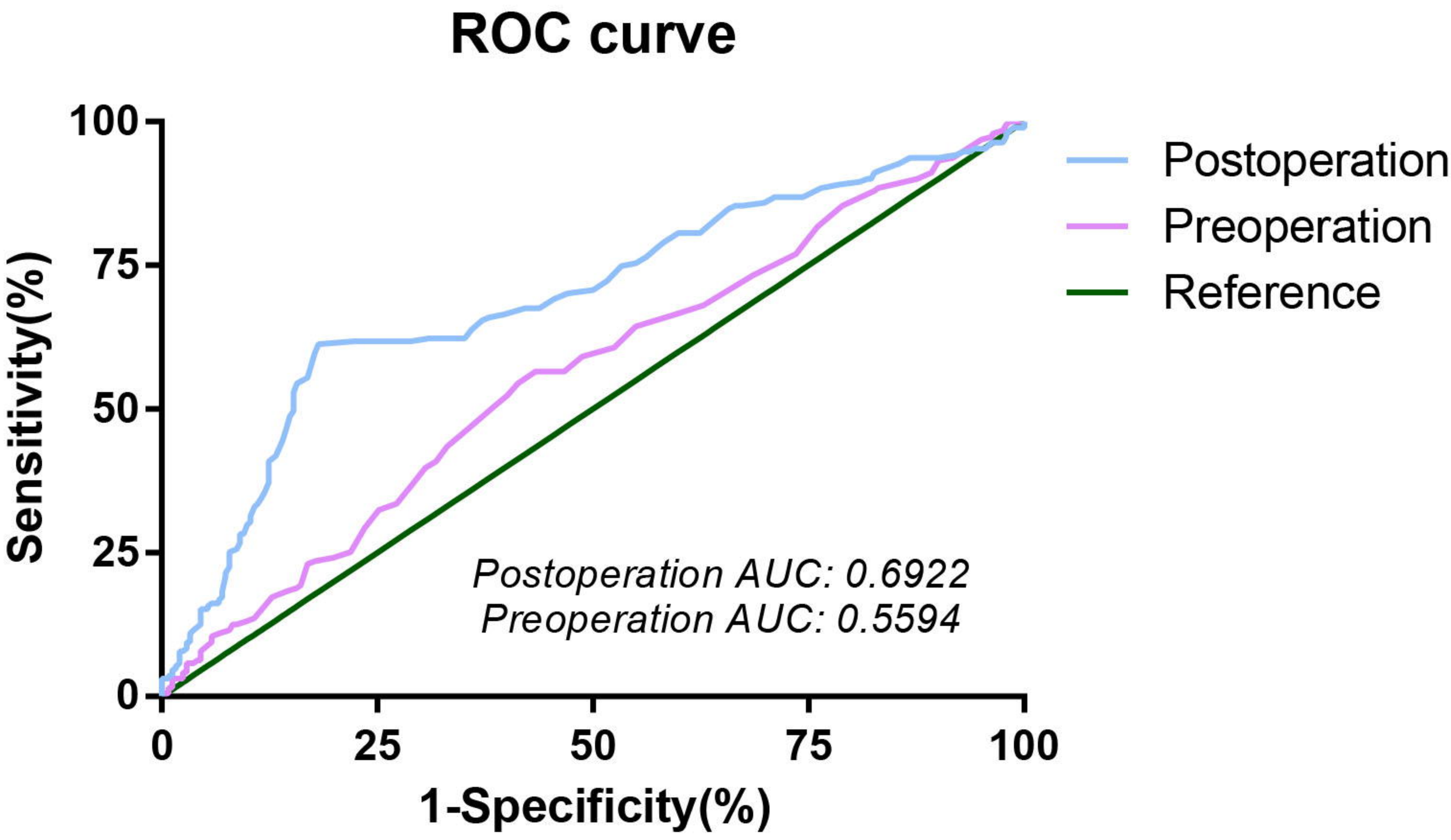
[a] P value of univariate analysis. P < 0.05 was considered statistically significant.

Table. C Multivariate analysis of clinicopathological parameters and inflammatory biomarkers influencing prognosis

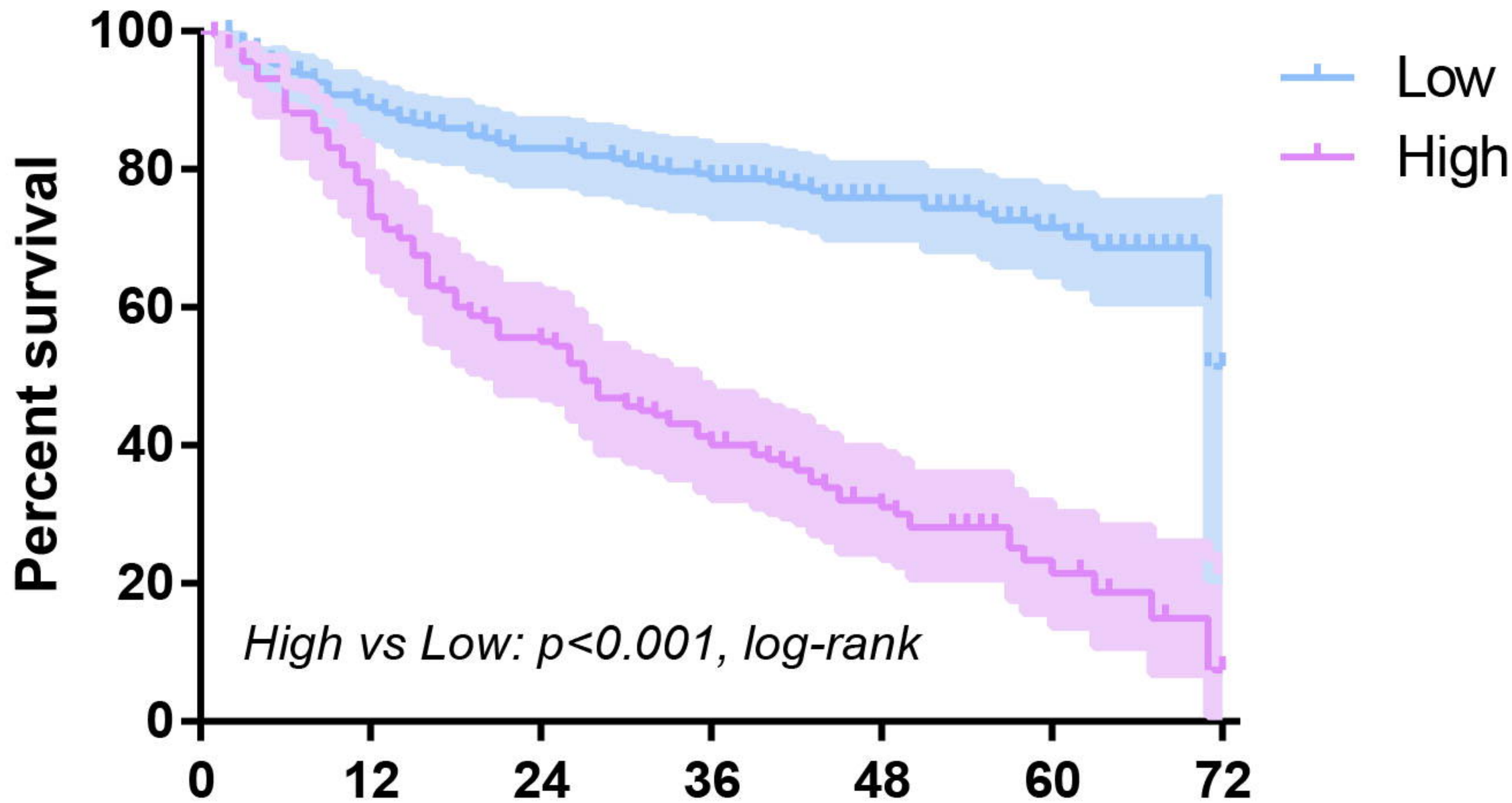
Category	Variables	HR (95% CI)	P[a]
Disease-free survival			
Procedure	VATS	Reference	
	Open	1.520(1.117-2.069)	**0.008**
N stage	N0	Reference	
	N1	2.319(1.584-3.396)	**<0.001**
	N2	2.584(1.845-3.620)	**<0.001**
Histological type	Adenocarcinoma	Reference	
	Squamous carcinoma	0.561(0.405-0.779)	**0.001**
Postoperation monocyte	< 0.845	Reference	
	≥0.845	3.684(2.729-4.975)	**<0.001**
Overall survival			
Age	Per year	1.034(1.014-1.054)	**0.001**
Procedure	VATS	Reference	
	Open	1.700(1.163-2.486)	**0.006**
Stage	I	Reference	
	II	2.228(1.383-3.592)	**0.001**
	IIIA	3.592(2.327-5.546)	**<0.001**
Postoperation monocyte	< 0.845	Reference	
	≥0.845	3.403(2.362-4.902)	**<0.001**

N stage, node; VATS, Video-assistant thoracoscopic surgery; HR, hazard ratio; CI, confidence interval.

[a] P value of multivariate analysis. P < 0.05 was considered statistically significant.

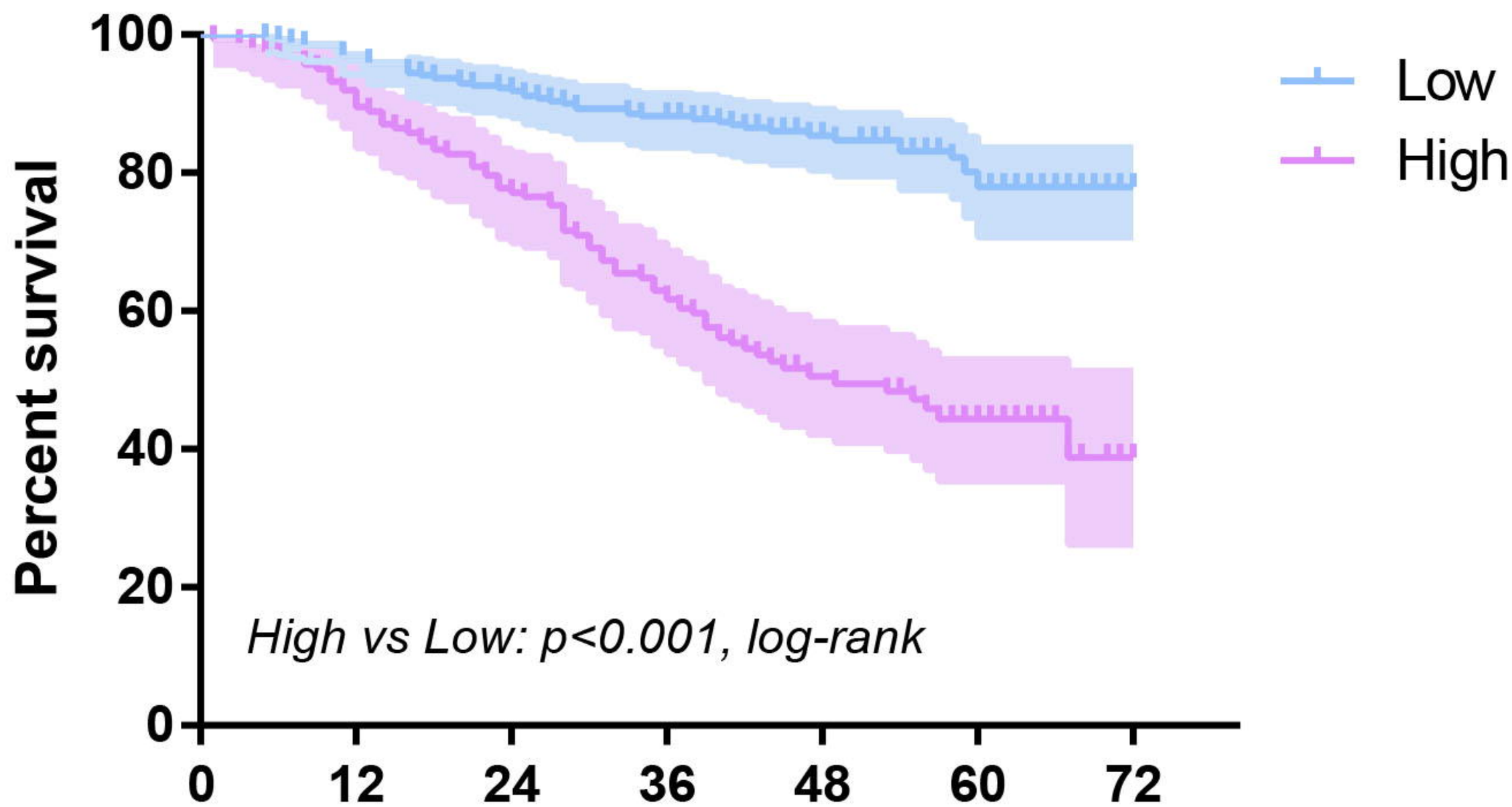

ROC curve
Sensitivity(%)
100
75
50
25
0
0
25
50
75
100
1-Specificity(%)
Postoperation
Preoperation
Reference
Postoperation AUC: 0.6922
Preoperation AUC: 0.5594

(a)



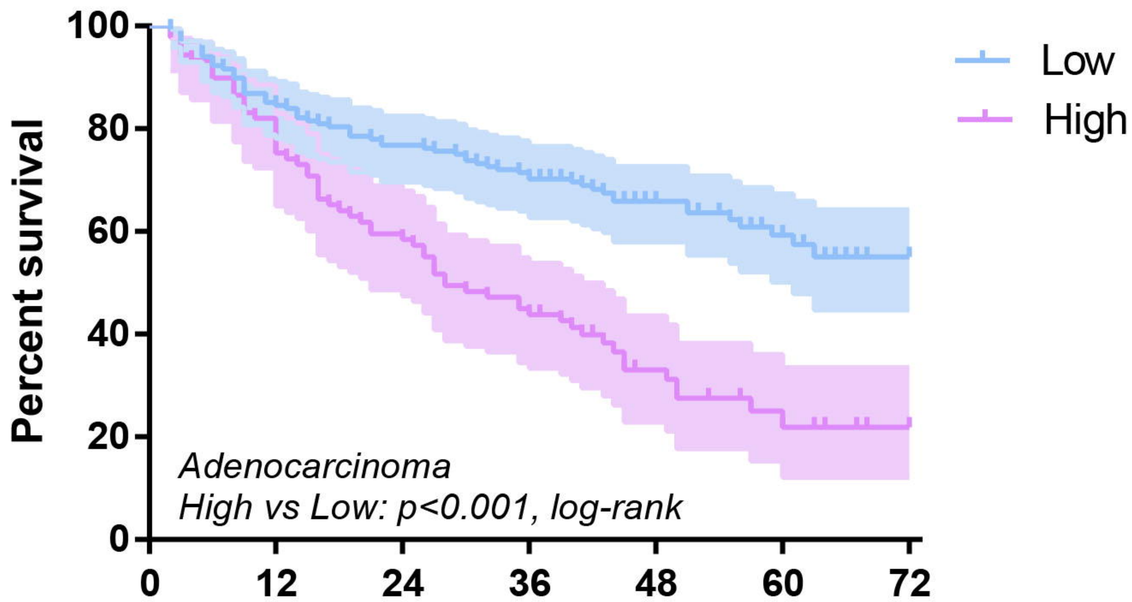
Number at risk							
Low	271	243	227	215	109	62	3
High	162	125	89	66	33	12	1

(b)



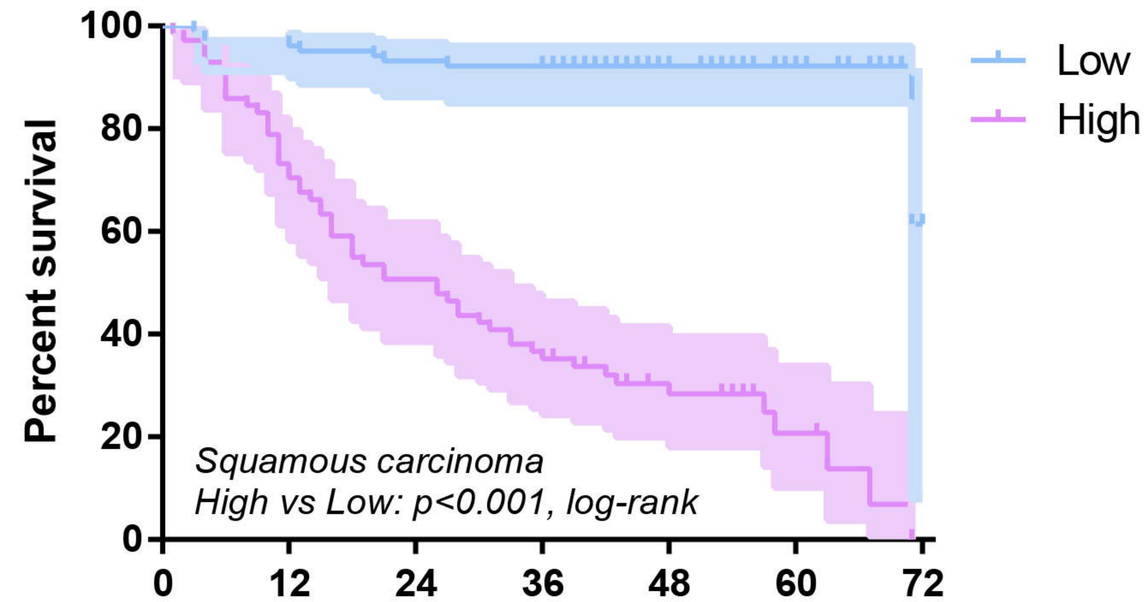
Number at risk							
Low	271	267	250	236	126	74	3
High	162	149	126	102	47	22	1

(a)



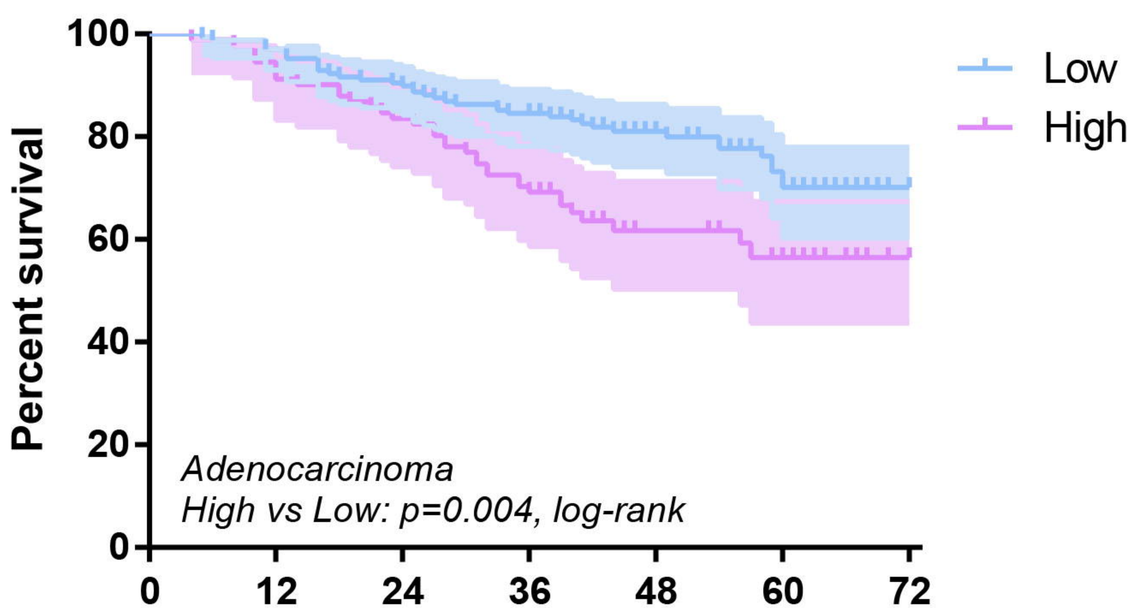
Number at risk							
Low	168	143	131	120	60	35	1
High	91	73	53	40	19	8	1

(c)



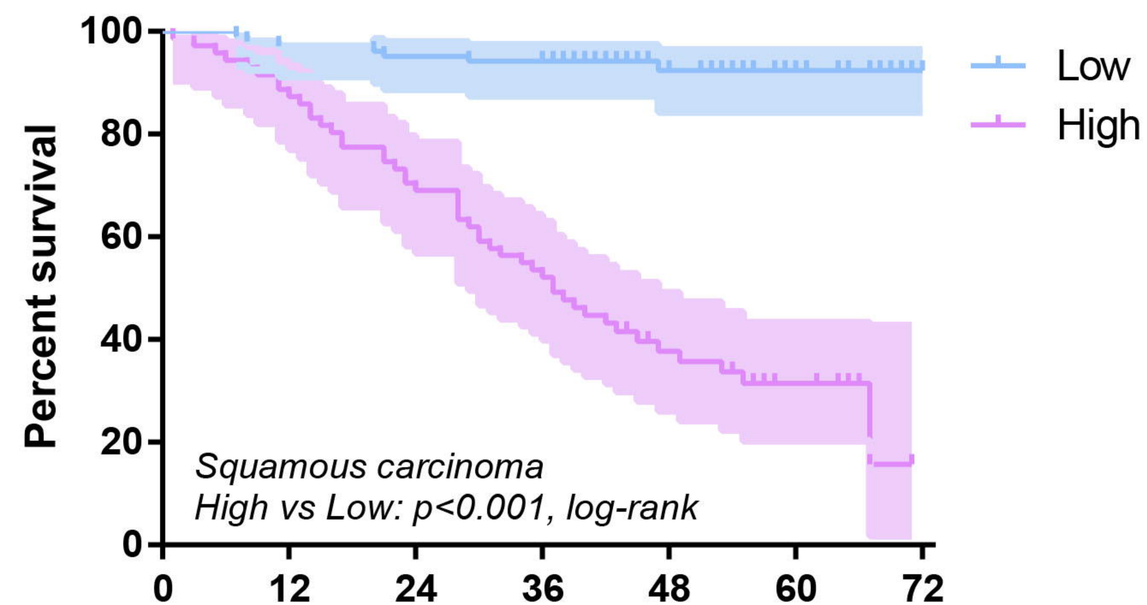
Number at risk							
Low	103	99	97	95	49	27	2
High	71	50	38	26	15	6	1

(b)



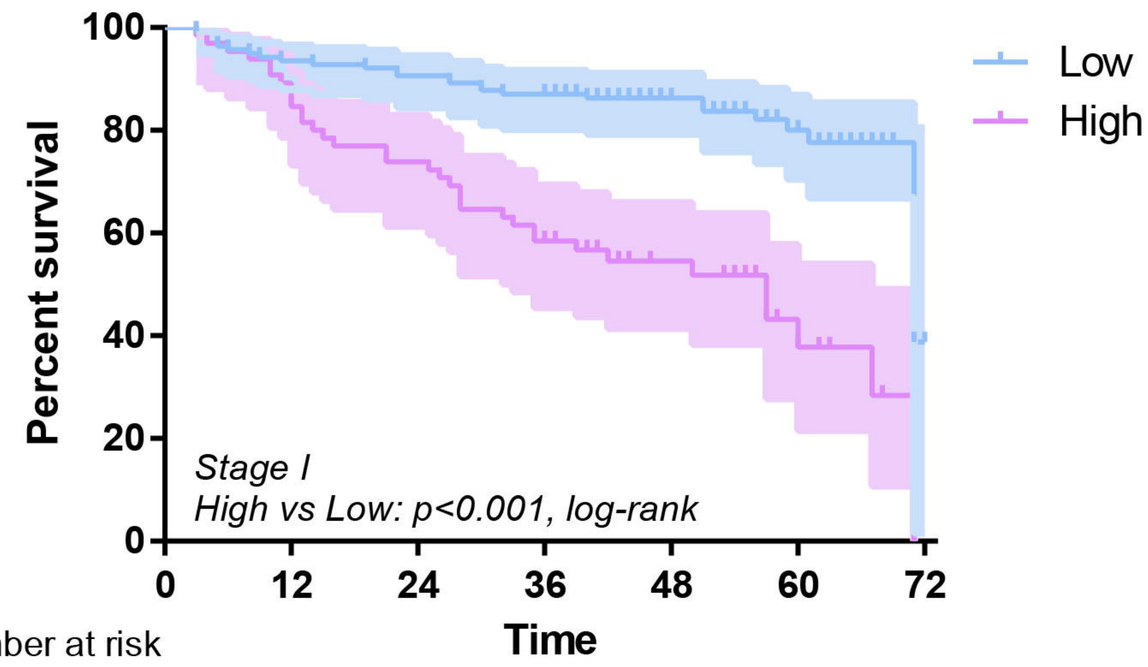
Number at risk							
Low	168	166	152	142	77	47	1
High	91	86	77	64	28	16	1

(d)



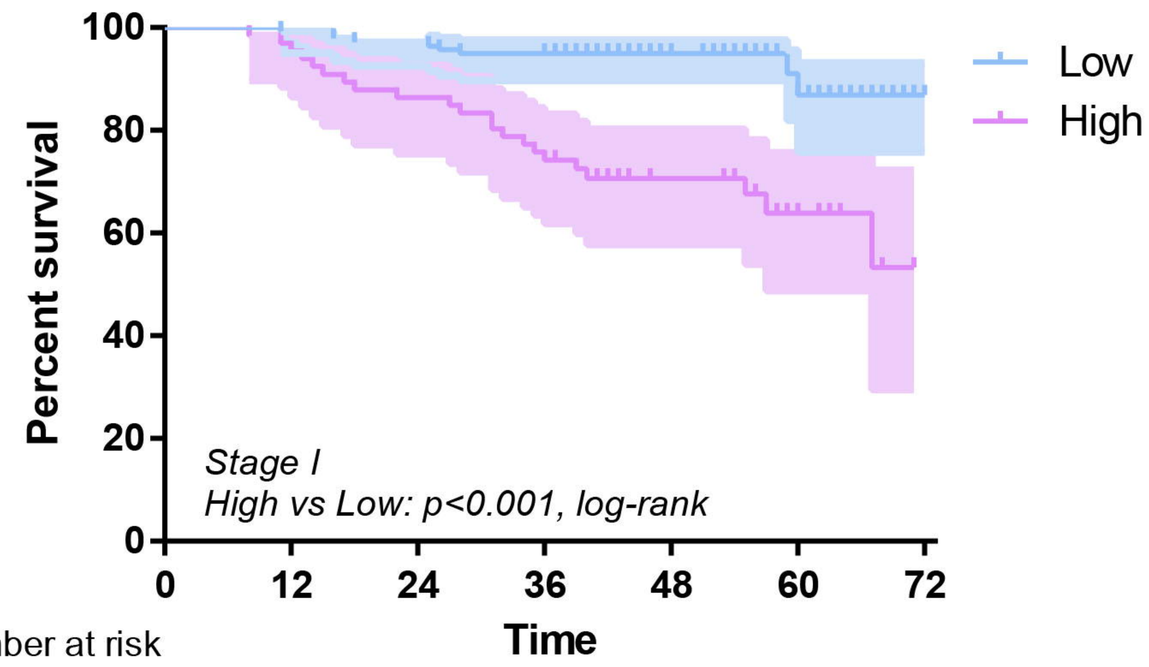
Number at risk							
Low	103	101	99	97	49	27	2
High	71	63	50	38	20	8	1

(a)



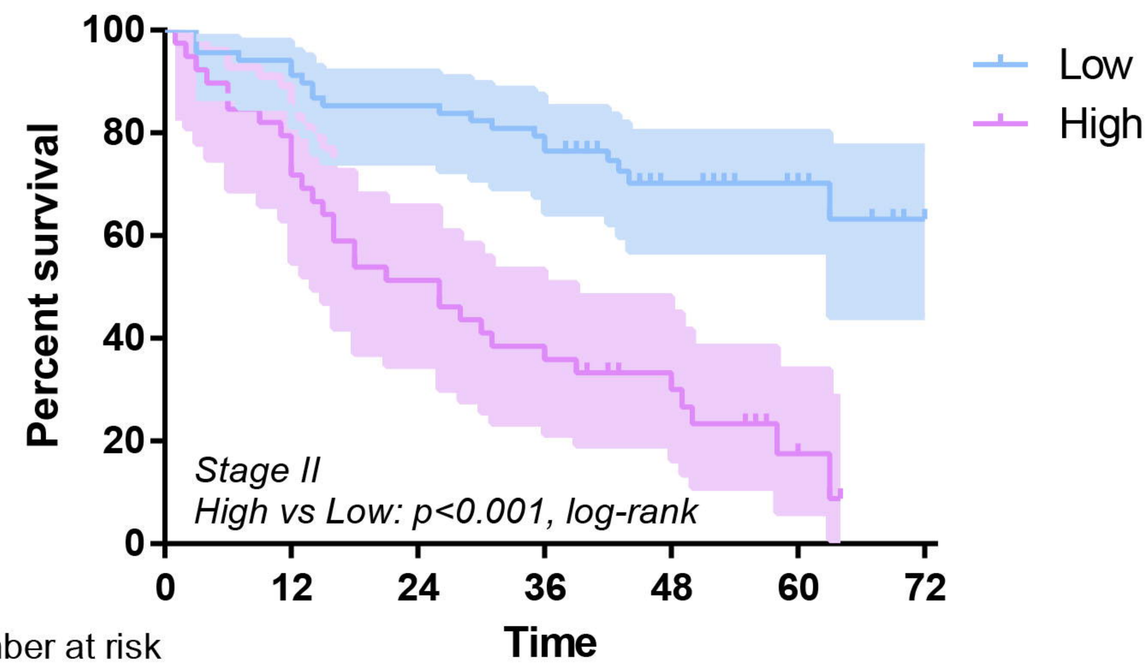
Number at risk	0	12	24	36	48	60	72
Low	139	131	128	121	69	37	1
High	66	58	50	38	22	8	1

(b)



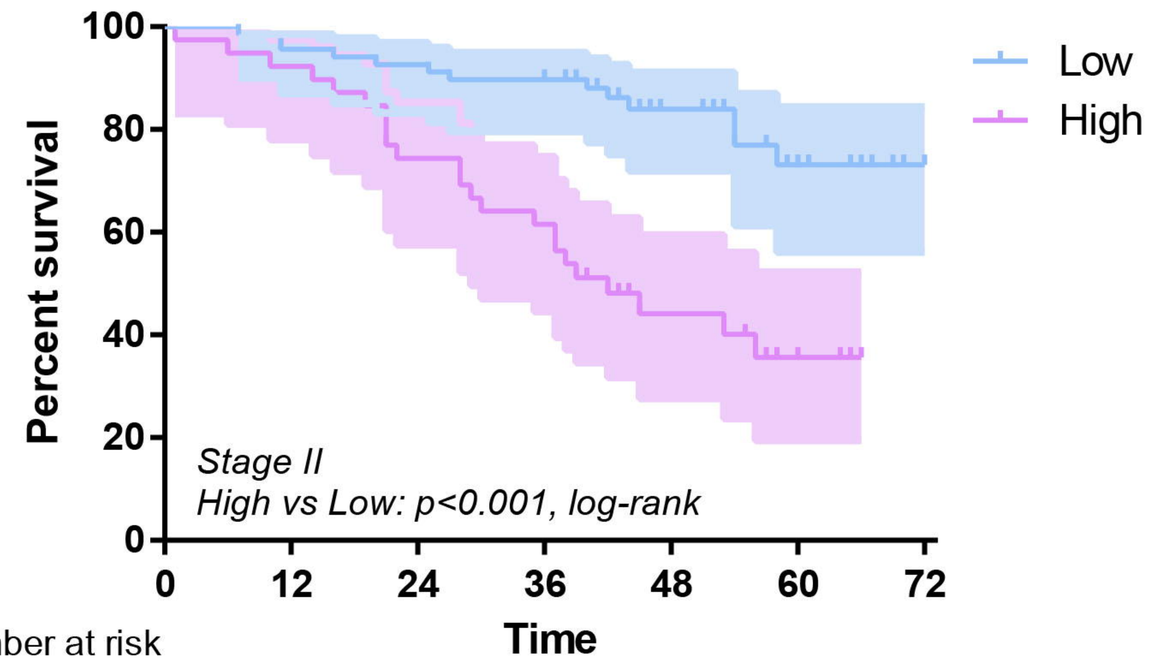
Number at risk	0	12	24	36	48	60	72
Low	139	139	136	132	77	44	1
High	66	64	58	50	29	13	1

(c)



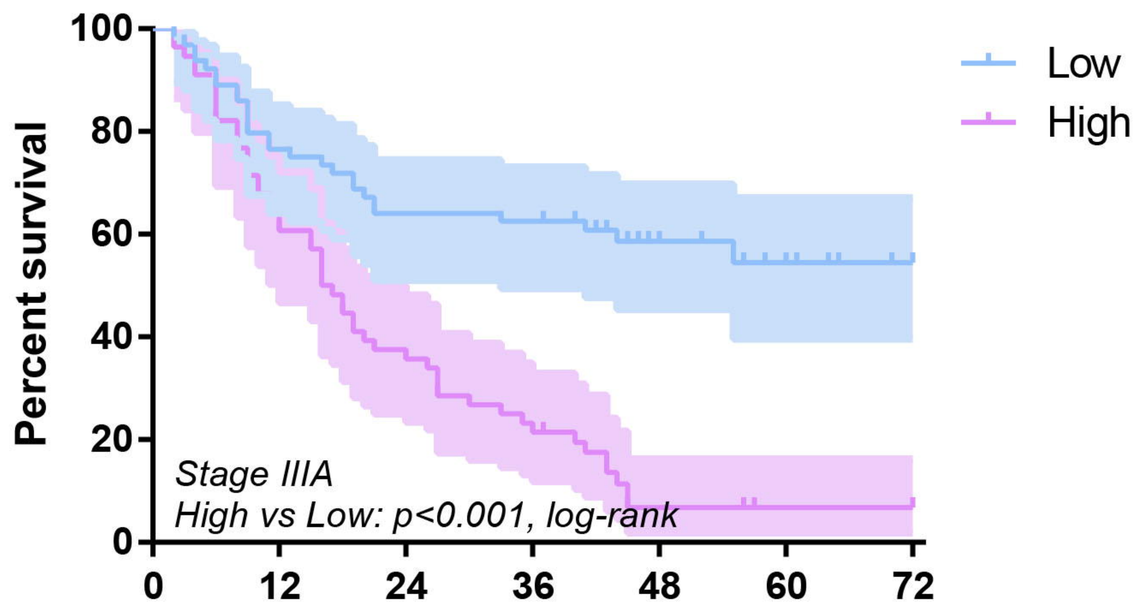
Number at risk	0	12	24	36	48	60	72
Low	68	64	59	54	24	15	1
High	39	31	21	15	10	3	

(d)



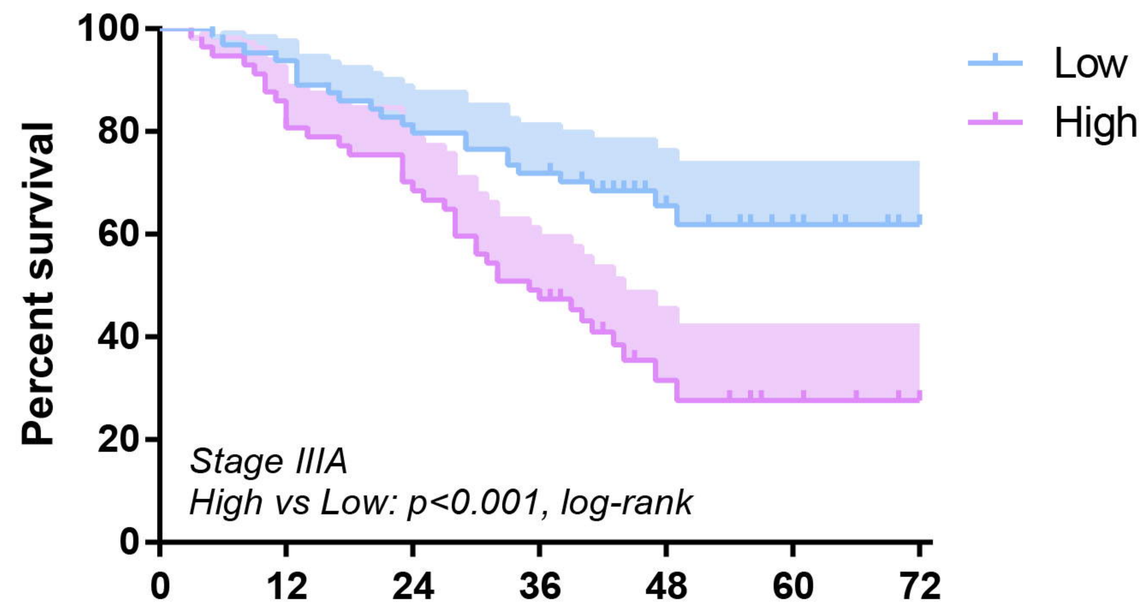
Number at risk	0	12	24	36	48	60	72
Low	68	67	64	61	31	18	1
High	39	37	30	25	12	5	

(e)



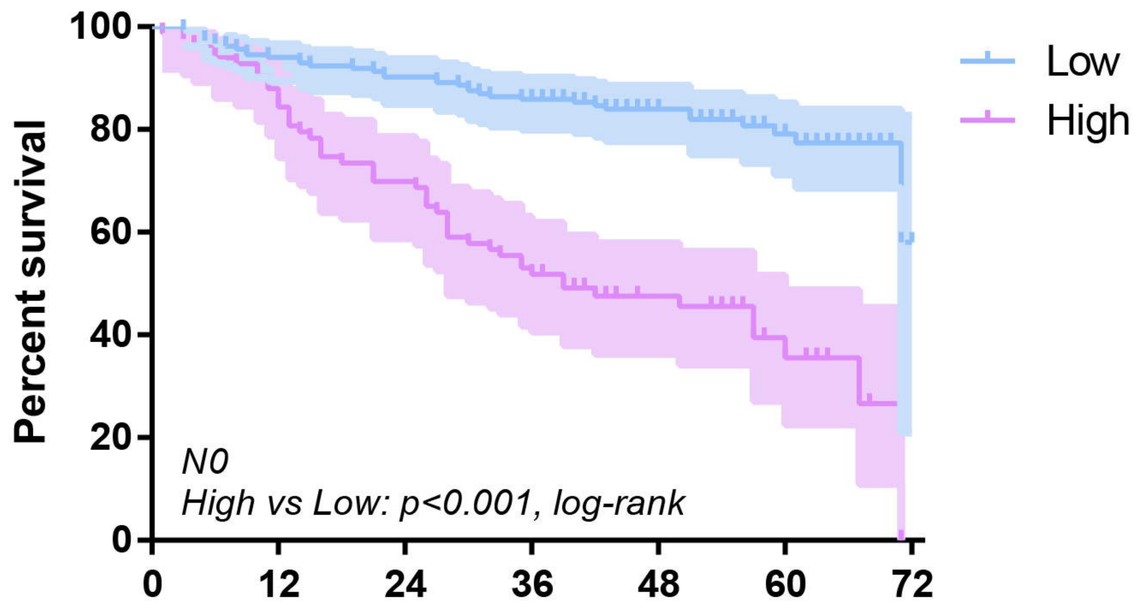
Number at risk	0	12	24	36	48	60	72
Low	64	51	43	41	18	10	1
High	57	36	21	13	5	2	1

(f)



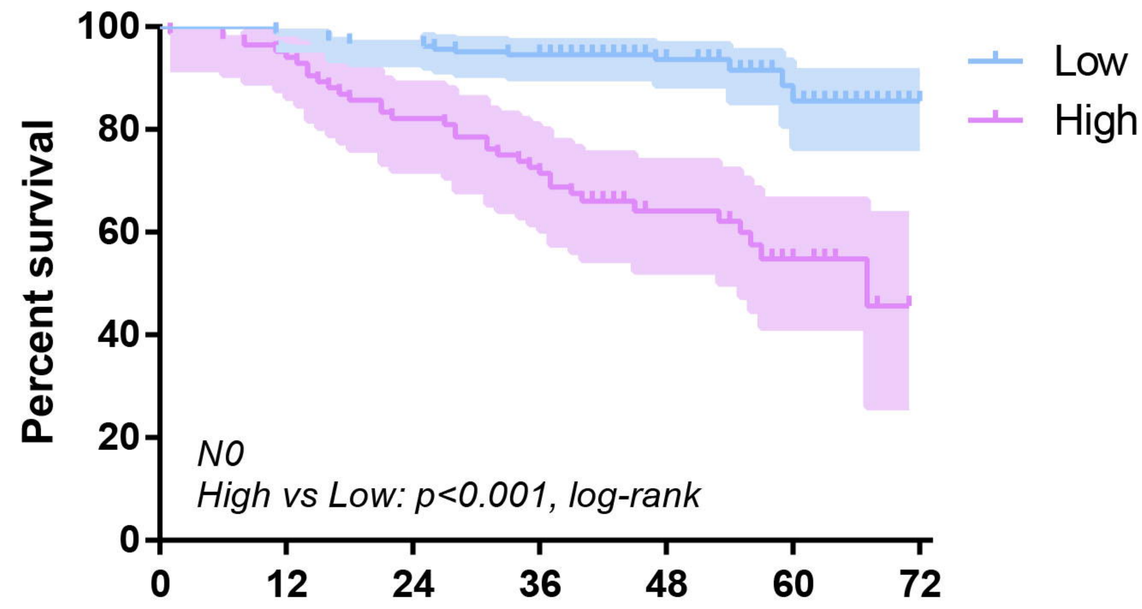
Number at risk	0	12	24	36	48	60	72
Low	64	61	52	47	20	12	1
High	57	49	40	28	9	5	1

(a)



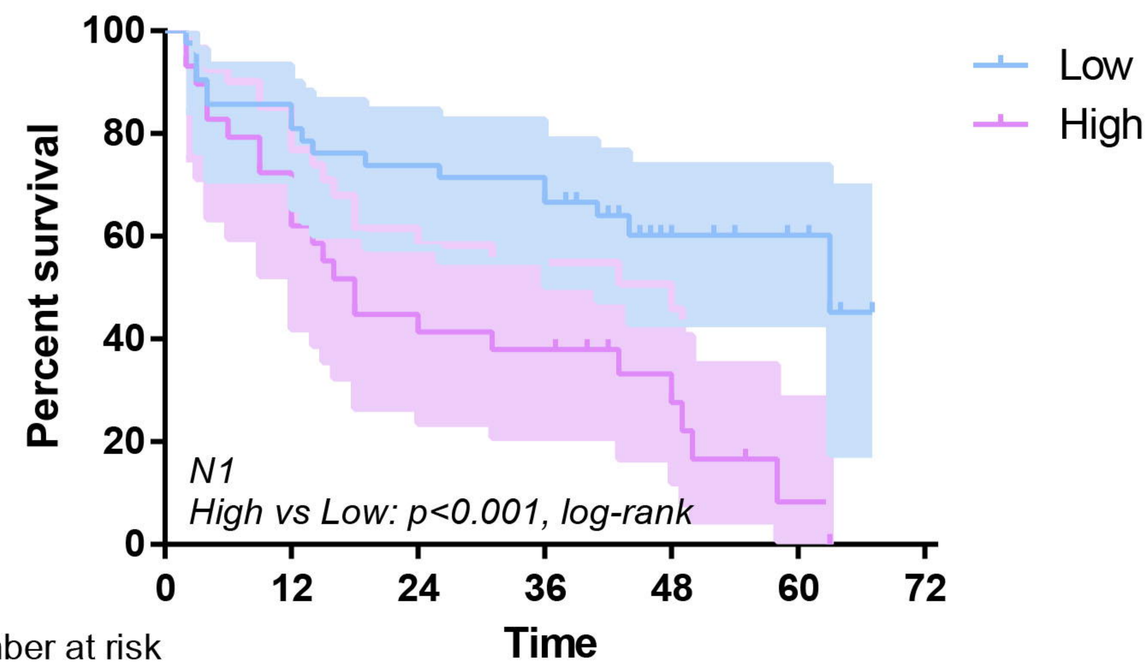
Number at risk							
Low	184	174	168	158	86	49	3
High	84	73	61	44	26	10	1

(b)



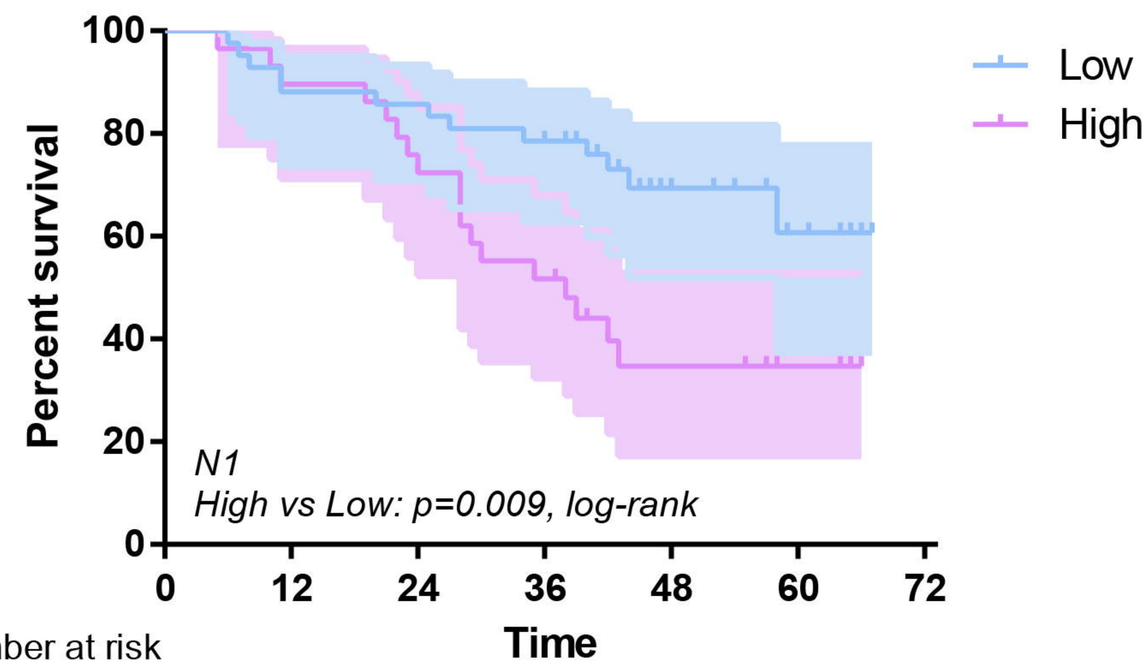
Number at risk							
Low	184	184	179	174	98	58	3
High	84	80	70	61	34	15	1

(c)



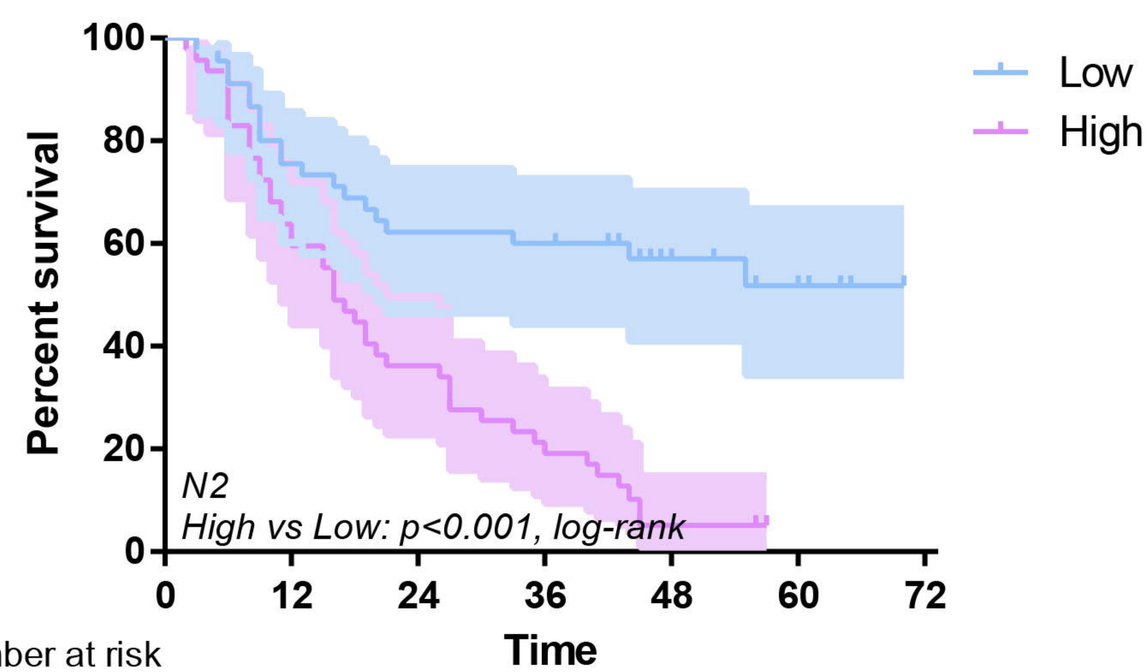
Number at risk						
Low	42	36	32	30	10	6
High	29	21	13	12	6	2

(d)



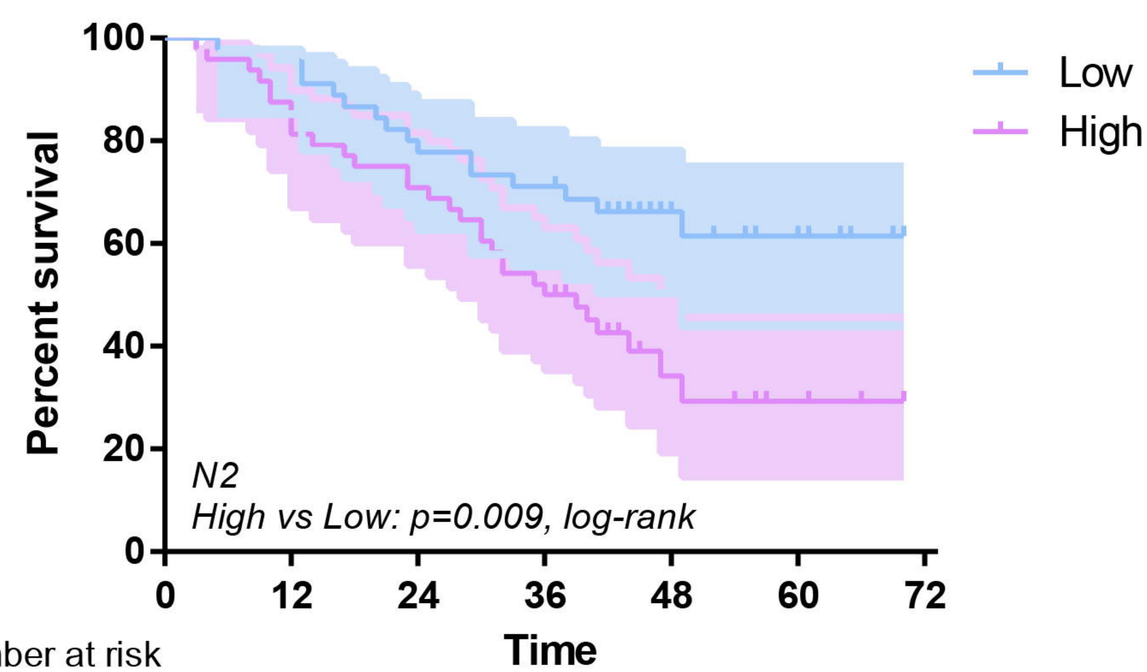
Number at risk						
Low	42	39	37	33	13	7
High	29	27	22	16	8	4

(e)



Number at risk						
Low	45	36	29	28	13	8
High	48	30	18	10	4	

(f)



Number at risk						
Low	45	45	36	33	15	10
High	48	42	36	25	8	4