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ORIGINAL ARTICLE

Predictors of survival in non-small cell lung cancer patients with pleural effusion undergoing thoracoscopy

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Abstract

Background: Malignant pleural effusion (MPE) predicts advanced disease and poor prognosis, and is usually diagnosed by medical thoracoscopy. It remains unclear whether the various representations visualized on thoracoscopy are reliable prognostic factors. The aim of this study was to evaluate prognostic factors for survival in patients who underwent thoracoscopy for MPE.

Methods: The medical records of consecutive patients with MPE who underwent medical thoracoscopy from 2007 to 2015 at a tertiary hospital were reviewed and theKaplan-Meier method and Cox regression analysis used to determine prognostic factors.

Results: A total of 125 patients with non-small cell lung cancer (NSCLC) were confirmed on tissue biopsy as having pleural metastasis. In NSCLC, factors adversely affecting overall survival (OS) in univariate analysis included extent of pleural carcinomatosis (EPC) score (P = 0.031), grade of adhesions (P = 0.037), costoparietal pleural lesions (P = 0.035) and bloody MPE (P = 0.023); Cox multivariate analysis revealed that EPC score (P = 0.007) and grade of adhesions (P = 0.019) were independent predictors of OS.

Conclusions: Under traditional chemotherapy, higher EPC score and higher grades of adhesions predicted poor prognosis in advanced NSCLC patients with pleural metastasis. Taking into account these factors may allow doctors to make more accurate predictions and provide individual therapy when treating patients with MPE.

Introduction

Malignant pleural effusion (MPE) is a frequent complication of advanced cancer which predicts reduced life expectancy, except for breast and ovarian carcinoma. Patients with MPE may suffer from significant dyspnea, poor exercise tolerance, or other complications related to recurrent pleural effusions. Thoracoscopy is usually performed to obtain pleural samples for histopathology to enable an accurate diagnosis, in addition to preventing recurrent effusions in patients with symptomatic MPE by pleurodesis.[1–3] Pleural tumor burden is assessed during thoracoscopy; however, the relationship between the various manifestations visualized on thoracoscopy and prognosis remains unknown.

Many factors have been reported to be prognostic indicators for MPE patients, including tumor characteristics, extent of disease, comorbidities and the composition of the effusion.[4–6] Some authors have reported that pleural fluid (PF) pH and glucose concentration are reliable prognostic factors.[7,8] However, the findings regarding the prognostic value of PF, pH and glucose concentration conflicted in subsequent studies.[6,9] Bloody MPE may increase the risk of malignancy,[10] but no data showed a relationship with prognosis. Moreover, it is unknown whether PF cytology and pleural brushing cytology have any potential prognostic value.

To date, there is no accurate approach to evaluate the prognosis of patients with MPE. However, other potential prognostic variables are worth studying. Previous studies have suggested that the extent of pleural carcinomatosis (EPC) and pleural adhesions as visualized on thoracoscopy

may be valuable in predicting prognosis.[6,8,11] Given the uncertainty of some factors, we designed a retrospective study to evaluate the prognostic indicators of survival in patients who underwent thoracoscopy with MPE.

Methods

Patients

A retrospective study was performed from 2007 to 2015 at Shandong Provincial Hospital. The medical records of all patients who underwent medical thoracoscopy were reviewed. Inclusion criteria was as follows: (i) The diagnosis of NSCLC with pleural effusion was confirmed by evidence of neoplasm on pleural biopsy. (ii) Survival status could be determined and included PFS and OS, recorded on the basis of follow-up clinic visits or telephone calls. (iii) Patients received traditional chemotherapy recommended by international guidelines as first-line therapy in advanced NSCLC. Cisplatin was combined with docetaxel, gemcitabine, or vinorelbine as first-line therapy for NSCLC. Exclusion criteria: (i) Patients with heart, kidney, liver and other disease were at high risk of chemotherapy and the diseases (including heart, kidney, liver and other disease) would lead to non-malignant pleural effusion. (ii) Patients were targeted therapies. (iii) The data was incomplete. The local ethics committee approved this study.

Data collection

The assessment of patients included age, gender, smoking status, diagnosis date, histopathological type, appearance of PF (bloody vs. non-bloody), PF cytology obtained by thoracentesis before thoracoscopy, cytological results of thoracoscopic pleural brushing, thoracoscopic findings (grade of adhesions, pleural lesion rating), date of progression, and date of death, or the most recent date at which the patient was confirmed alive.

Before thoracoscopy, the surgeon and anesthetist jointly assessed whether the patient could undergo thoracoscopy. All thoracoscopic examinations were fully video-recorded, and in the medical report, the surgeon reported the thoracoscopic findings in detail. A locally described score was developed to grade the EPC score[6,8,12] and we made reference to the EPC score. The individual scores ranged from 0 to 9 and consisted of a scale of 0 to 3 which assessed the diaphragmatic, costoparietal, and visceral pleura by thoracoscopy. For every pleural surface, 0 point was assigned for no visible lesions, 1 point for isolated lesions that covered a small part of the pleural surface, 2 points for diffuse lesions that covered most of the pleural surface and 3 points for massive lesions that covered the whole pleural surface. We referred to the figure from Sanchez-Armengol and Rodriquez-Panado[12]to explain the EPC score (Fig 1). Once a lesion was found, its position, size, texture, mobility, and relationship with the peripheral organs were carefully detected (Fig 2). The presence of adhesions was used to develop a local scoring system.[13] The scoring system ranged from 0 to 4. A score of 1 represented isolated adhesions that enable thoracoscopy without difficulty, a score of 2 adhesions that obstruct about one third of the vision, a score of 3 adhesions that obstruct about two-thirds of the vision and a score of 4 adhesions that do not permit access to the pleural space.

Statistical analysis

The Kaplan-Meier method was employed to examine the prognostic value of individual predictors (age, gender, smoking status, histopathological type, appearance of PF, PF cytology, pleural brushing cytology, grade of adhesions, and pleural lesion rating). The 95% confidence intervals were calculated and compared using the log-rank test. Cox regression analysis was performed for multivariate survival analysis. A P value less than 0.05 was considered statistically significant. Statistical software (SPSS version 17.0, Chicago, IL) was used for the analysis.

Results

A total of 178 patients with pleural effusion were confirmed NSCLC with evidence of neoplasm on pleural biopsy. Fifty-three patients were excluded for multiple reasons, including 11 who were lost to follow-up, 29 targeted therapies, 6 incomplete data and 7 at high risk of chemotherapy due to the combination of other diseases with high risk of chemotherapy. Finally, 125 patients were enrolled for further analysis (Fig 3).

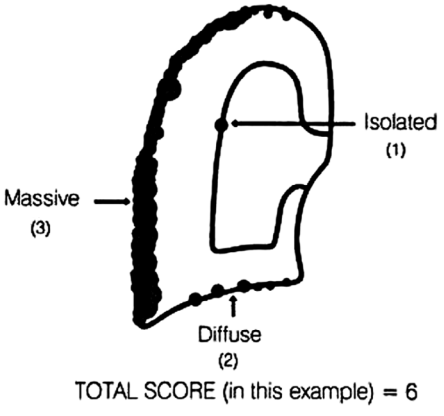

Figure 1 Thoracoscopic lesion rating. This figure is from Sanchez-Armengol and Rodriquez-Panado[12] and reproduced with permission.

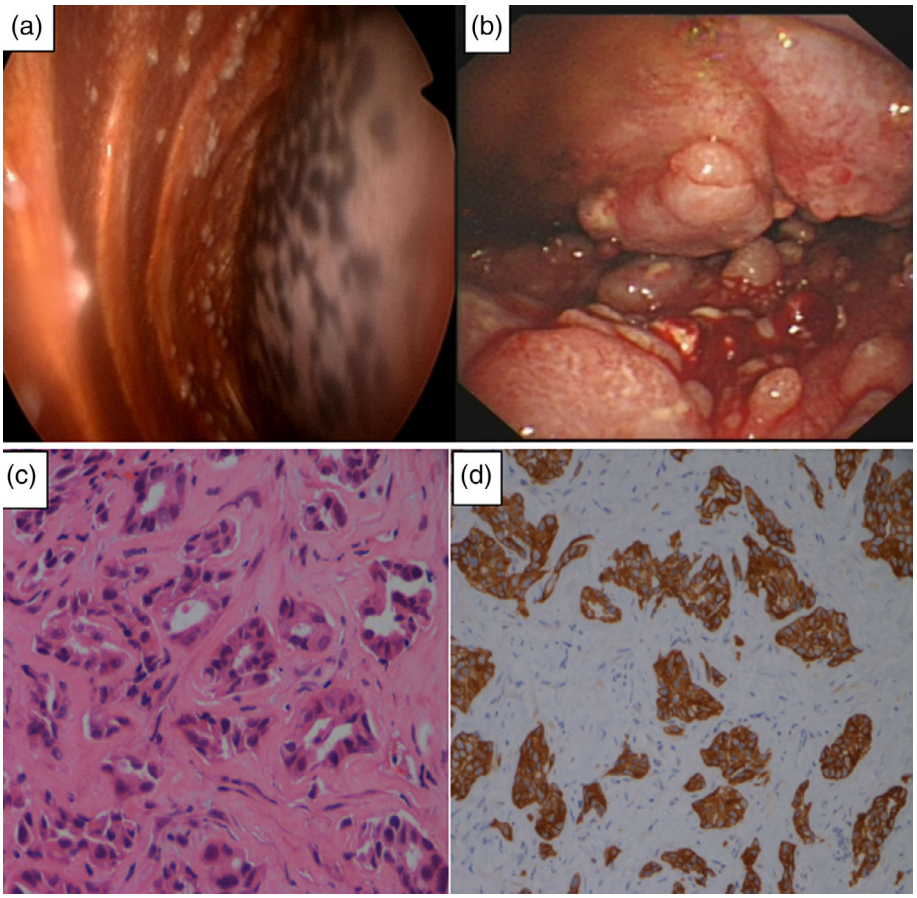

Figure 2 The gross features under thoracoscopy (**a** and **b**); pathological diagnosis lung adenocarcinoma and melanocarcinoma, respectively (**c** and **d**, respectively).

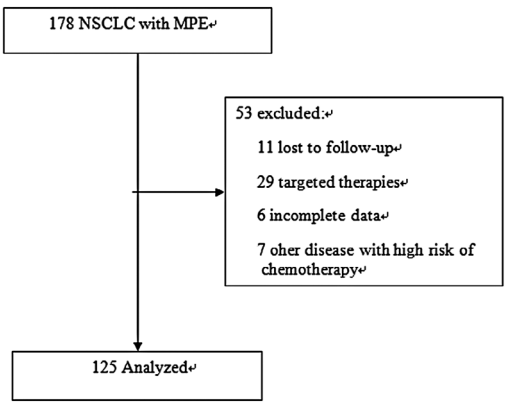

Figure 3 Flowchart of patient numbers.

This retrospective study consisted of 125 NSCLC with MPE (mean age, 58 years; 59 men and 66 women), of which 116 had adenocarcinoma and nine squamous cell carcinoma (Table 1).

The patients who underwent thoracoscopy were used to analyze the factors affecting prognosis. Median PFS and OS of the 125 patients were six and 12.5 months, respectively (Fig 4a,b, respectively). Among the 125 patients, pleural metastasis of the diaphragmatic pleura, costoparietal pleura, and visceral pleura occurred in 63, 112 and 62 patients, respectively. The presence of adhesions was observed in 52 of 125 patients. PF cytology was positive in 72 patients and negative in 42. The diagnosis of pleural brushing cytology was positive in 97 patients and negative in 10. PF cytology results and pleural brushing cytology results were not available for 11 and 18 patients, respectively. Those factors are described in detail in Table 1.

Among patients with NSCLC, factors adversely affecting OS in univariate analysis included EPC score (P = 0.031), grade of adhesions (P = 0.037), costoparietal pleural lesions (P = 0.035) and bloody MPE (P = 0.023; Fig 5). Age, gender, PF cytology, pleural brushing cytology, smoking, diaphragmatic pleural lesions and visceral pleura lesions were not prognostic factors of OS in this study (Table 1).

Age, gender, PF cytology, pleural brushing cytology, smoking, EPC score, the grade of adhesions and bloody MPE were not prognostic factors of PFS in this study (Table 1).

Multivariate survival analysis incorporating EPC score, grade of adhesions and bloody MPE was conducted to

Table 1 Variables predicting overall survival and progression-free survival in NSCLC

Variables	Value	n(%)	Median OS (months)	95% CI OS	Median PFS (months)	95% CI PFS	*P*†	*P*‡
NSCLC		125	12.5	9.21–15.79	6.0	5.37–6.64	0.262	0.832
	Adenocarcinoma	116	13.0	9.92–16.08	6.0	5.39–6.61		
	Squamous	9	8.6	3.34–13.86	6.7	0.56–12.84		
Sex							0.147	0.830
	Male	59	11.0	8.64–13.37	6.0	5.13–6.87		
	Female	66	14.5	10.96–18.04	6.0	5.22–6.78		
Age, mean (SD)							0.928	0.854
	< 58	57	11.1	6.13–16.07	5.6	4.78–6.42		
	≥58	68	12.5	8.96–16.04	6.0	5.30–6.70		
Smoking							0.104	0.853
	No	71	15.3	12.41–18.19	5.5	4.63–6.58		
	Yes	54	10.4	8.12–12.68	6.0	5.12–6.89		
PF cytology							0.222	0.502
	Negative	42	11.7	9.05–14.35	6.0	5.11–6.90		
	Positive	72	14.2	10.87–17.53	6.0	5.09–6.92		
Pleural brushing cytology							0.601	0.318
	Negative	10	16.0	15.23–16.78	5.6	2.97–8.23		
	Positive	97	13.0	10.19–15.82	6.0	5.27–6.73		
PF appearance							0.023	0.123
	Nonbloody	64	15.3	11.77–18.83	6.0	4.96–7.05		
	Bloody	61	10.4	7.01–13.79	5.3	4.54–6.07		
Diaphragmatic pleural lesions							0.088	0.941
	0	62	15.3	10.28–20.32	5.0	3.90–6.10		
	1	12	12.0	7.42–16.58	6.0	5.67–6.34		
	2	43	10.6	7.71–13.49	5.5	4.26–6.74		
	3	8	11.1	4.31–17.89	5.5	1.65–9.35		
Costoparietal pleural lesions							0.035	0.455
	0	13	17.0	5.84–28.16	5.3	3.19–7.41		
	1	19	25.0	5.87–44.13	6.0	4.95–7.06		
	2	79	10.4	7.30–13.50	6.0	5.33–6.67		
	3	14	11.1	5.23–16.97	4.0	0.88–7.12		
Visceral pleural lesions							0.415	0.264
	0	63	13.5	9.83–17.17	6.0	5.23–6.77		
	1	9	25.0	10.85–39.15	6.0	2.12–9.88		
	2	47	10.6	7.91–13.29	5.6	4.76–6.44		
	3	6	8.6	0.10–19.52	2.0	0.10–7.40		
EPC score (0–9)							0.031	0.296
	0–3	58	14.5	10.40–18.61	6.0	5.43–6.58		
	4–6	62	10.6	8.00–13.20	5.0	4.28–5.72		
	7–9	5	11.1	5.73–16.47	5.5	1.85–9.15		
Grade of adhesions							0.037	0.567
	0	68	15.3	11.26–19.34	6.0	5.50–6.50		
	1	16	12.0	1.02–22.98	3.5	1.80–5.20		
	2	18	9.3	3.69–14.91	6.0	4.65–7.35		
	3	14	8.5	3.61–13.39	5.0	2.31–7.69		
	4	9	8.6	1.30–15.90	4.6	2.26–6.94		

†The value of overall survival. ‡The value of progression-free survival. CI, confidence interval; EPC, extent of pleural carcinomatosis; NSCLC, non-small cell lung cancer; OS, overall survival; PF, pleural fluid; PFS, progression-free survival.

explore independent prognostic factors. Results showed that the EPC score (HR 1.121, 95% CI 1.031–1.219; $P = 0.007$) and the grade of adhesions (HR 1.188, 95% CI 1.029–1.371; P = 0.019; Table 2) were statistically significant predictor variables.

Discussion

Malignant pleural effusion (MPE) represents advanced stage and poor prognosis in cancer patients. Median survival depend on the stage and type of the primary tumor.

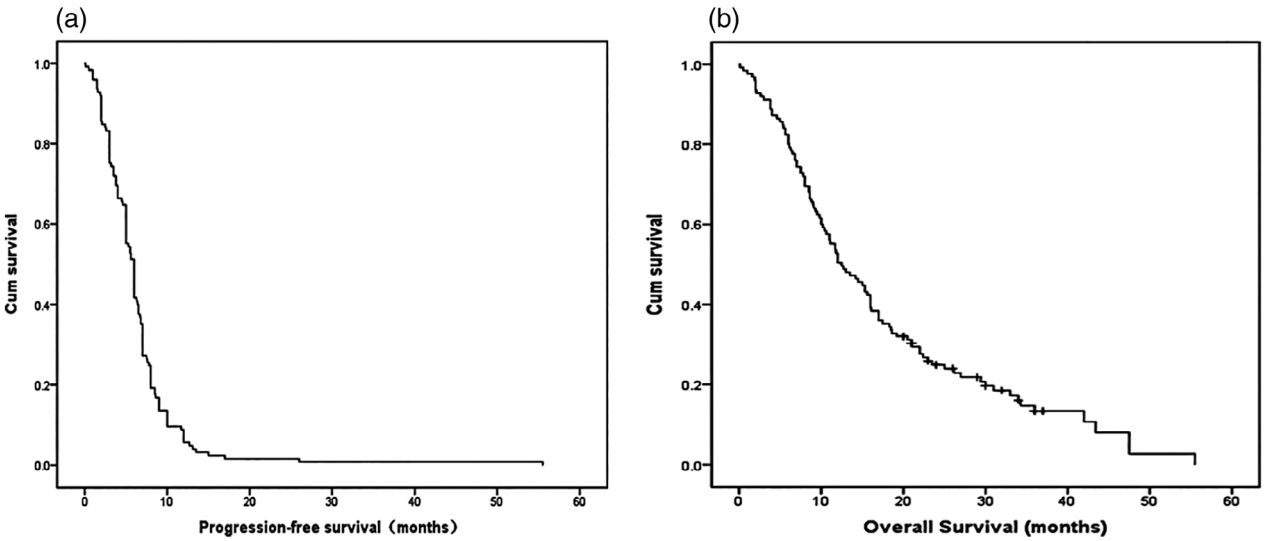

Figure 4 Kaplan-Meier curve demonstrating the progression-free survival (PFS) and overall survival (OS) of the non-small cell lung cancer patients. (**a**) The median survival for PFS was 6.0 months. (**b**) The median survival for OS was 12.5 months. (——) 1 and (—|—) 1-censored.

Patients with lung cancer had the shortest survival times.[14] In our study, results showed that higher EPC score and higher grades of adhesions predicted poor prognosis in advanced NSCLC patients with pleural metastasis.

We found that the EPC score was a prognostic risk factor for OS in patients with NSCLC. Burrows *et al.* reported that the EPC score was not associated with a decreased survival rate.[6] Sakr *et al.* showed that the extent and localization of pleural tumor burden were not prognostic risk factors for OS.[11] Their research was focused on the relationship between different types of metastatic pleural carcinomas and pleural tumor burden as occurring pleural lesions are likely to be related to advanced stages of the neoplastic process. We found that higher EPC score predicted poor prognosis in advanced NSCLC patients with pleural metastasis.

The grade of pleural adhesions was a prognostic risk factor for OS in patients with NSCLC, in accordance with the results of Bielsa *et al.* and Sakr *et al.*[11,15] Pleural inflammation leads to fibrin deposition, possibly leading to a series of additional reactions that result in tissue reconstruction and ultimately fibrosis. Proteases and products of coagulation and fibrinolysis can activate the complement and kinin systems, promoting inflammatory responses and increasing vascular permeability. Some inflammatory stimuli, including infection, trauma and malignancy, led to pleural adhesions in the pleural cavity.[16] Cellular immune responses appear to comprise the primary pathogenesis of most inflammatory pleural effusions, and inflammatory immunological processes may play a role in the homing mechanisms involved in pleural metastasis.[17] The grade of pleural adhesions may vary depending on the cause of the inflammatory pleural effusion.[17,18] The grade of pleural adhesions may be helpful in evaluation of the prognosis of patients who undergo thoracoscopy.

In the present study, bloody MPE was a prognostic risk factor for survival, in accordance with the findings of Sakr *et al.*[11]. The primary tumor directly invaded blood vessels, obstructed venules, induced angiogenesis, increased capillary permeability and eventually led to bloody pleural effusions. Overexpression of endothelial-cell-specific molecule-1 (ESM-1) in carcinoma endothelial cells played an important role in inducing angiogenesis.[19] High levels of ESM-1 expression correlate with certain angiogenic factors, such as vascular endothelial growth factor A (VEGF-A) and fibroblast growth factor-2 (FGF-2).[19] A prospective study found that the number of red blood cells and VEGF values in MPE had a significant positive correlation. ESM-1 gene expression levels increased under stimulation of VEGF and FGF-2,[20] thereby inducing angiogenesis. Moreover, the level of EMS-1 in NSCLC-related MPE was significantly higher than that of benign pleural effusion, paralleling distant metastasis of NSCLC. In a study by Hsu *et al.*, high VEGF levels in pleural effusion of NSCLC were a prognostic risk factor for survival.[21]

Our study had several limitations. The sample size was relatively small and a large sample size would have increased the robustness of our conclusions. In addition, the EPC score system and the grade of pleural adhesions are needed for confirmation in the future. Moreover, we only studied patients who were suitable for thoracoscopy and those patients enrolled in the study were fit to undergo this procedure; therefore, selection bias was a problem in our study. Finally, targeted therapy may affect survival; our study did not involve a comparative analysis of the population treated with targeted versus non-targeted therapies.

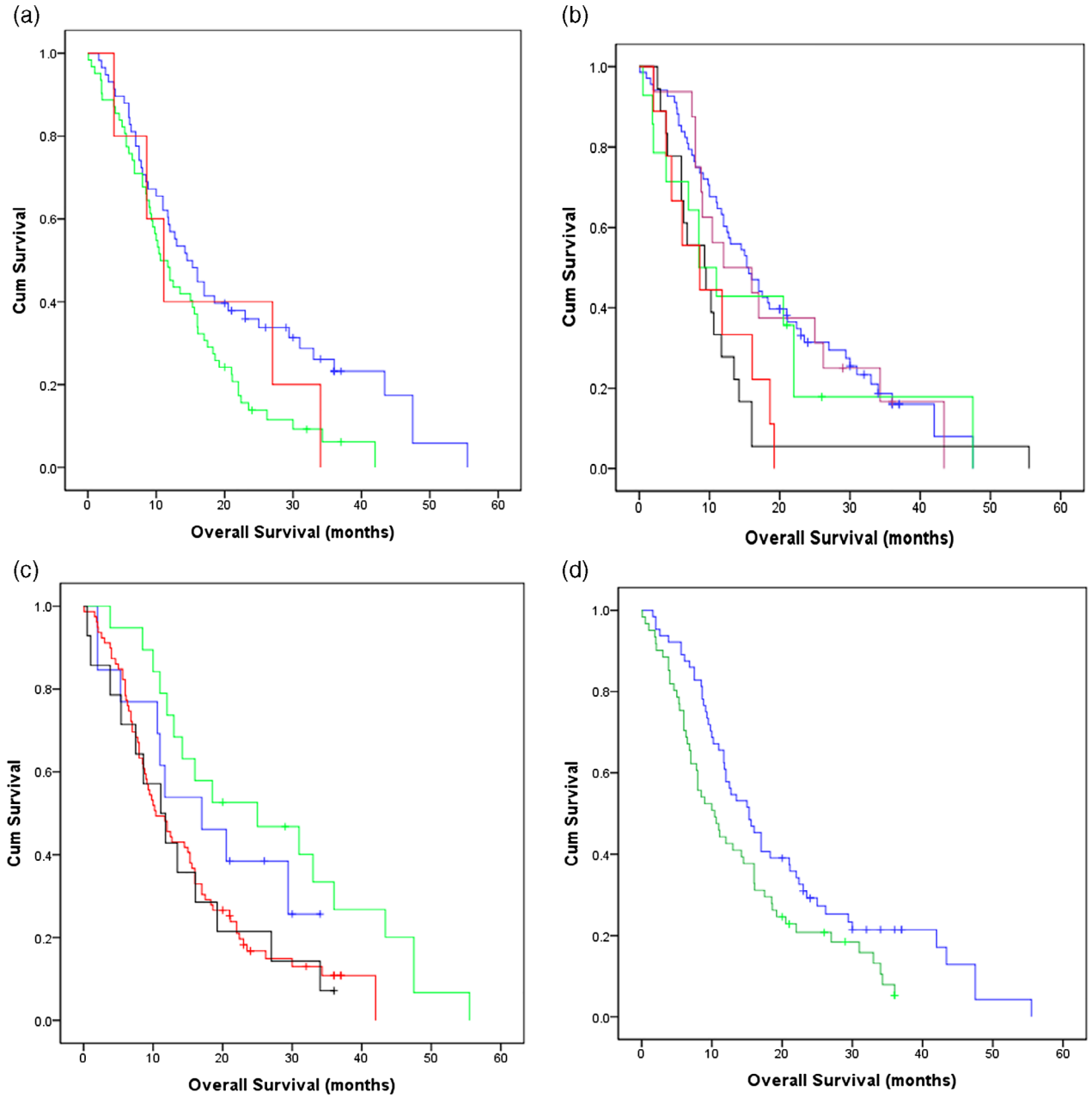

Figure 5 Kaplan-Meier curves demonstrating the relationship of the variables with the overall survival in non-small cell lung cancer patients. There was a significant difference in survival of patients with: (**a**) EPC score ($P = 0.031$). (——) 0–3, (——) 4–6, (——) 7–9, (——) 0–3-censored, (——) 4–6-censored, and (——) 7–9-censored. (**b**) grade of adhesions ($P = 0.037$). (——) 0, (——) 1, (——) 2, (——) 3, (——) 4, (——) 0-censored, (——) 1-censored, (——) 2-censored, (——) 3-censored, and (——) 1-censored. (**c**) costoparietal pleural lesions ($P = 0.035$). (——) 0, (——) 1, (——) 2, (——) 3, (——) 0-censored, (——) 1-censored, (——) 2-censored, and (——) 3-censored. (**d**) bloody pleural fluid ($P = 0.023$). (——) nonbloody, (——) bloody, (——) nonbloody-censored, and (——) bloody-censored.

Gene testing was performed in a few patients, but the positive rate of gene testing was low, and is therefore not statistically significant. We hope to elucidate the impacts of targeted therapy on prognosis in the future.

In conclusion, using conventional chemotherapy, the EPC score and the grade of adhesions were predictors of OS in NSCLC patients with pleural effusion who underwent thoracoscopy. These findings may allow doctors to

Table 2 Multivatiate analysis of factors associated with overall survival in NSCLC who underwent thoracoscopy

Predictor	HR	95%CI	*P*
EPC score	1.121	1.031–1.219	0.007
Grade of adhesions	1.188	1.029–1.371	0.019
PF appearance	1.399	0.939–2.085	0.099

CI, confidence interval; EPC, extent of pleural carcinomatosis; HR, hazard ratio; NSCLC, non-small cell lung cancer; PF, pleural fluid.

make more accurate predictions and provide individual therapy when treating patients with MPE.

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The authors are responsible for the content and writing of the paper.

Disclosure

The authors report no conflicts of interest.

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