Original Article

Risk factors for symptomatic malignant pleural effusion recurrence in patients with actionable mutations in advanced lung adenocarcinoma

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Background: Malignant pleural effusion (MPE) comes generally with high mortality and poor prognosis. Recurrence of symptomatic MPE is always accompanied by poor survival quality. In lung adenocarcinoma, researchers speculate whether patients with actionable mutation or without are applicable to different management models for MPE. Under the background of the high mutation probability and the encouraging therapeutic response in Asians, researches on the risk factors of MPE are in need.

Methods: This retrospective review included 343 metastatic lung adenocarcinoma patients with MPE. Recurrence was defined as recurrent symptomatic MPE requiring the second thoracentesis to relieve symptoms within 300 days after the first thoracentesis. Univariable and multivariable Cox regression analysis were utilized to investigate independent risk factors for MPE recurrence.

Results: Of the 343 patients involved, 139 experienced MPE recurrence within 300 days; 34.3% in 201 patients with actionable mutations and 51.2% in 129 patients without actionable mutations are in the recurrence. The median recurrence-free survival (RFS) of the group without mutations was 161 days. The median RFS of the other group with mutations was 300 days. Patients with actionable mutations showed a significantly lower hazard of MPE recurrence on univariate analysis. The multivariate analysis indicated that receiving targeted therapy after the first thoracentesis within 30 days, lower neutrophil-to-lymphocyte ratio (NLR) level, lower serum lactate dehydrogenase (s-LDH) level, and lower serum carcinoembryonic antigen (s-CEA) level were independent protective factors. In subgroup analysis, risk factors differed. Receiving targeted therapy after the first thoracentesis within 30 days remained an independent factor in the mutated patients.

Conclusions: The findings herein indicated the characteristics of specific patients at high risk for MPE recurrence in lung adenocarcinoma. Patients with actionable mutations benefit more in MPE recurrence and could benefit from targeted therapy and active intrapleural management.

Keywords: Lung adenocarcinoma; malignant pleural effusion (MPE); recurrence; mutations

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Introduction

Patients with malignant pleural effusion (MPE) are associated with high mortality and poor prognosis (1-3). It is generally recognized that the median overall survival (OS) of MPE in non-small cell lung cancer (NSCLC) is around 5.5 months despite a lack of updating on the data for a long time (4). Generally, MPE is identified as an adverse factor in cancer based on previous research (5). Several studies have explored the prognostic model for MPE, such as the LENT score and PROMISE score, widely known for exploring prognostic risk factors of MPE regardless of cancer type (6,7). Unlike the two models exploring unselected cancer types, our previous study focused on lung cancer patients with MPE and gained the RECLS score in lung cancer and the RECLSAM score in lung adenocarcinoma (8). In the RECLSAM score, activating gene mutations was considered the protective factor. Almost 40–60% of Asians and 10–30% of Caucasians display epidermal growth factor receptor (EGFR) activating mutation, achieving 8 months progression-free survival (PFS) improvement when taking Osimertinib in FLAURA (9). Meanwhile, the patients without mutations attained worse OS. The two groups fit into different management strategies in MPE. Chemotherapy or immunotherapy are usually applied to the mutation-negative group. Thoracentesis with active MPE control management are often displayed, such as indwelling pleural catheter (IPC) placement or pleurodesis. In mutation-positive lung adenocarcinoma, targeted therapy and thoracentesis are preferable in consideration of the high response rate of targeted therapy.

As we mentioned, we have explored the prognostic risk factors in lung adenocarcinoma with MPE, indicating a worse prognosis for patients without mutations. Except for the long-term survival, we found that both positive-mutated and negative-mutated patients were likely to develop recurrence of symptomatic MPE, implying short-term poor quality of life, including progressive dyspnea, cough, or other chest discomforts (10). Patients with recurrent symptomatic MPE often require repetitive thoracentesis for palliation of symptoms or IPC in certain conditions (11). Studies exploring patients with a high risk of MPE recurrence and identifying the difference in management between patients with actionable activating gene mutations and those without will make sense. There have been few articles that probes into the risk factors for the recurrence of MPE and the credibility of which also needs to be improved. Previous research on Caucasians indicated that patients with actionable mutations showed a similar risk of MPE recurrence. Patients could benefit from the same management strategy regardless of mutation status (12). Considering differences in the frequency of mutations and management strategies between Caucasians and Asians, we conducted the retrospective study and gathered data on clinical, hematic, and biochemical factors. We sought to select patients with a high risk of MPE recurrence in lung adenocarcinoma. Moreover, we intended to explore whether the two groups owning opposite mutation statuses performed differently at the time of MPE recurrence. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-151/rc).

Highlight box

Key findings

- Actionable mutations were found to lower the risk of malignant pleural effusion (MPE) recurrence. Targeted therapy and active intrapleural management were effective for inhibiting the MPE recurrence risk as well.

What is known and what is new?

- MPE comes generally with high mortality and poor prognosis. Recurrence of symptomatic MPE is always accompanied by poor survival quality.
- Patients with actionable mutations benefit more in MPE recurrence and could benefit from targeted therapy and active intrapleural management.

What is the implication, and what should change now?

- In Asian patients with actionable mutations, targeted therapy combined with active intrapleural management was preferred, whether choosing intrapleural injection or indwelling pleural catheter.

Methods

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the local ethics committee of Nanjing Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University (registration ID: NJJLH202103256). Informed consent from individuals was waived based on the retrospective nature of this study.

Participants

Patients experiencing the first thoracentesis for MPE in lung adenocarcinoma at Nanjing Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University from January 2008 to October 2021 were collected. Participants included patients pathologically diagnosed with lung adenocarcinoma and those receiving active therapy after the first thoracentesis of MPE. Those younger than 18 years old, failure to follow up immediately after the first thoracentesis, or lack of data when undergoing the first thoracentesis at other institutions were excluded. We collected exact baseline information such as age, gender, treatment-naïve patients or not, mutation status, presence of contralateral effusion, depth displayed by B ultrasound, the volume of drainage, and specific active treatment before and after the first thoracentesis within 30 days before active therapy at first thoracentesis. Hematic biomarkers included white blood cells (WBC), neutrophil-to-lymphocyte ratio (NLR), hemoglobin (Hb), platelet (PLT), C-reaction protein (CRP), serum glucose, serum albumin/globulin ratio (A/G), serum lactate dehydrogenase (s-LDH), and serum carcinoembryonic antigen (s-CEA). Pleural biomarkers such as pleural LDH (p-LDH), pleural protein (p-protein), pleural glucose (p-Glucose), and pleural CEA (p-CEA) in pleural effusion were also involved.

Definition

MPE was characterized as the presence of malignant cells in pleural effusion upon cytological examination or with pleural infiltration detected by biopsy specimens. Patients with recurrent MPE were regarded as those experiencing the second thoracentesis and their pleural effusion was confirmed malignant. Actionable mutations were defined as EGFR activating mutations (EGFR Del19, L858R, T790M) or anaplastic lymphoma kinase (ALK) rearrangement. Patients who received targeted therapy were those who received kinase inhibitors of oncogenic receptor tyrosine kinases, c-ros oncogene 1 receptor tyrosine kinase, and tropomyosin receptor kinases as well as downstream target kinases. The follow-up time was 300 days. This was a meaningful duration according to the patients included in this study, in which over 50% of patients developed a recurrent MPE within 300 days. Recurrence-free survival (RFS) was defined as the time from the first thoracentesis to MPE recurrence over the follow-up period.

Statistical analysis

We analyzed data with SPSS version 26 (IBM Corp., Chicago, IL, USA). Risk factors affecting recurrence were extracted using univariable and multivariable Cox regression analysis. Variables with $P<0.10$ on univariate analysis were incorporated into the multivariable analyses. Variables with $P<0.05$ were finally considered independent factors for MPE recurrence. The cut-off values of continuous variables were ensured upon the receiver operating characteristic (ROC) curve.

Results

Patient characteristics

Between January 2008 and October 2021, 343 patients with MPE in Nanjing Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University were included. Of those with detected mutation statuses, 201 (60.9%) were EGFR or ALK mutated. A total of 154 patients with actionable mutations received targeted therapy after diagnosis of MPE. Furthermore, 67.1% were treatment naïve (*Table 1*).

The incidence of recurrence and RFS

Of the 343 included patients, 139 experienced MPE recurrence within 300 days, while 62 participants were lost to follow-up. When the 330 patients with mutation status were divided into a group with mutation and another group without mutation, the latter, including 129 patients, reached its median RFS of 161 days. The group with mutations did not meet its median RFS.

Risk factors for the recurrence of MPE

On univariate analysis, variables such as experienced no systematic treatment before [hazard ratio (HR), 0.628; 95% confidence interval (CI): 0.445–0.886; P=0.008], older than 59 years old (HR, 1.576; 95% CI: 1.121–2.214; P=0.009), the higher level of NLR (HR, 1.566; 95% CI: 1.087–2.256; P=0.016), the higher level of CRP (HR, 1.904; 95% CI: 1.183–3.066; P=0.008), the higher level of s-LDH (HR, 1.791; 95% CI: 1.281–2.506; P=0.001), the higher level of s-CEA (HR, 1.565; 95% CI: 1.120–2.185; P=0.009), and the higher level of p-LDH (HR, 1.498; 95% CI: 1.051–2.134; P=0.025) were associated with the recurrence of MPE. Patients with actionable mutations showed a lower hazard

Table 1 Baseline and treatment characteristics of patients with MPE and patients with MPE recurrence

Baseline information	Patients with MPE (N=343), n (%)	Patients with recurrence (N=139), n (%)
Baseline information		
Treatment history	N=343	N=139
Previously untreated	230 (67.1)	87 (62.6)
Previously treated	113 (32.9)	52 (37.4)
Mutation status	N=330	N=135
EGFR/ALK+	201 (60.9)	69 (51.1)
EGFR/ALK–	129 (39.1)	66 (48.9)
Gender	N=343	N=139
Female	164 (47.8)	66 (47.5)
Male	179 (52.2)	73 (52.5)
Median age (years)	59	62
Pleural effusion		
The volume of drainage	N=174	N=67
≥1,000 mL	122 (70.1)	42 (62.7)
<1,000 mL	52 (29.9)	25 (37.3)
Depth displayed by B ultrasound	N=76	N=33
≥50 mm	71 (93.4)	31 (93.9)
<50 mm	5 (6.6)	2 (6.1)
Cytologic results	N=318	N=125
Positive	279 (87.7)	113 (90.4)
Negative	39 (12.3)	12 (9.6)
Presence of contralateral effusion	N=332	N=133
Yes	49 (14.8)	22 (16.5)
No	283 (85.2)	111 (83.5)
Specific active treatment before the first thoracentesis within 30 days	N=340	N=136
Chemotherapy	27 (7.9)	16 (11.8)
Targeted therapy	62 (18.2)	31 (22.8)
Radiotherapy	12 (3.5)	6 (4.4)
Anti-angiogenesis therapy	12 (3.5)	9 (6.6)
Immunotherapy	8 (2.4)	1 (0.7)
No specific treatment	247 (72.6)	88 (64.7)
Specific active treatment after the first thoracentesis within 30 days*	N=341	N=137
Chemotherapy	159 (46.6)	72 (52.6)
Targeted therapy	175 (51.3)	54 (39.4)
MPE control measures		
Intrapleural injection	240 (70.4)	100 (73.0)
Indwelling pleural catheter	101 (29.6)	37 (27.0)
Anti-angiogenesis therapy	39 (11.4)	22 (16.1)
Immunotherapy	16 (4.7)	7 (5.1)

*, one patient might receive more than one types of therapy. MPE, malignant pleural effusion; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

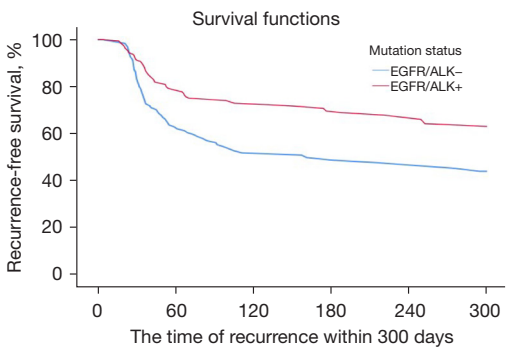

Figure 1 Comparison of the actuarial risk of MPE recurrence among patients with different mutation status in univariate analysis. MPE, malignant pleural effusion; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

of recurrence (HR, 0.544; 95% CI: 0.388–0.764; P<0.001) (*Figure 1*). In addition, in specific treatment before the first thoracentesis within 30 days, receiving chemotherapy (HR, 2.120; 95% CI: 1.255–3.579; P=0.005), targeted therapy (HR, 1.834; 95% CI: 1.228–2.739; P=0.003), and anti-angiogenic therapy (HR, 2.899; 95% CI: 1.469–5.720; P=0.002) were relevant factors for MPE recurrence. In specific treatment after the first thoracentesis within 30 days, receiving targeted therapy (HR, 0.472; 95% CI: 0.335–0.666; P<0.001) and anti-angiogenic therapy (HR, 1.664; 95% CI: 1.054–2.628; P=0.029) were regarded as relevant factors for MPE recurrence and shown in *Table 2*.

Table 2 Univariate and multivariate analyses of the factors associated with risks for recurrence of MPE

Characteristics	Univariate analysis incidence of recurrence (P<0.1)			Multivariate analysis incidence of recurrence (P<0.05)		
	HR	95% CI	P	HR	95% CI	P
Baseline information						
Treatment-naïve	0.628	0.445–0.886	0.008			
Mutation	0.544	0.388–0.764	<0.001			
Female	0.939	0.673–1.310	0.710			
Age	1.576	1.121–2.214	0.009			
Pleural effusion						
The volume of drainage (≥1,000 mL)	0.719	0.438–1.18	0.191			
Depth displayed by B ultrasound (≥50 mm)	1.501	0.359–6.278	0.578			
Positive cytologic results	1.228	0.677–2.227	0.498			
Contralateral effusion	1.378	0.871–2.179	0.170			
Specific active treatment before the first thoracentesis						
Chemotherapy	2.120	1.255–3.579	0.005			
Targeted therapy	1.834	1.228–2.739	0.003			
Radiotherapy	1.923	0.848–4.365	0.118			
Anti-angiogenesis therapy	2.899	1.469–5.720	0.002			
Immunotherapy	0.276	0.039–1.975	0.200			
Specific active treatment after the first thoracentesis						
Chemotherapy	1.307	0.934–1.829	0.118			
Targeted therapy	0.472	0.335–0.666	<0.001	0.454	0.315–0.654	<0.001
Indwelling pleural catheter	1.133	0.777–1.652	0.516			
Anti-angiogenesis therapy	1.664	1.054–2.628	0.029			
Immunotherapy	1.331	0.622–2.849	0.462			
Hematic biomarkers						
WBC (≥6.03/L)	1.281	0.901–1.821	0.167			
NLR (≥2.645)	1.566	1.087–2.256	0.016	1.612	1.070–2.427	0.022
Hb (≥114.5 g/L)	1.016	0.663–1.556	0.941			
PLT (≥238.5/L)	1.087	0.779–1.517	0.622			
CRP (≥1.35 mg/L)	1.904	1.183–3.066	0.008			
Glucose (≥6.75 mmol/L)	1.448	0.925–2.266	0.106			
A/G (≥1.28)	1.115	0.795–1.565	0.528			
s-LDH (≥223.5 U/L)	1.791	1.281–2.506	0.001	1.624	1.126–2.342	0.009
s-CEA (≥21.1 μg/L)	1.565	1.120–2.185	0.009	1.883	1.314–2.698	0.001
Pleural biomarkers						
p-LDH (≥358 U/L)	1.498	1.051–2.134	0.025			
p-protein (≥53.95 g/L)	1.200	0.738–1.950	0.462			
p-Glucose (≥6.25 mmol/L)	1.165	0.824–1.647	0.388			
p-CEA (≥143.05 μg/L)	1.261	0.880–1.806	0.206			

MPE, malignant pleural effusion; HR, hazard ratio; CI, confidence interval; WBC, white blood cells; NLR, neutrophil-to-lymphocyte ratio; Hb, hemoglobin; PLT, platelet; CRP, C-reaction protein; glucose, serum glucose; A/G, serum albumin/globulin ratio; s-LDH, serum lactate dehydrogenase; s-CEA, serum carcinoembryonic antigen; p-LDH, pleural lactate dehydrogenase; p-Glucose, pleural glucose; p-CEA, pleural carcinoembryonic antigen.

Table 3 Multivariate analyses of the factors associated with risks for recurrence of MPE in EGFR/ALK mutated patients

Variable	HR	95% CI	P
Targeted therapy after the first thoracentesis within 30 days	0.438	0.250–0.768	0.004
CRP (≥1.35 mg/L)	2.523	1.183–5.381	0.017
s-LDH (≥197.5 U/L)	2.305	1.295–4.103	0.005
p-Glucose (≥6.25 mmol/L)	2.148	1.242–3.715	0.006
p-CEA (≥869.4 μg/L)	2.150	1.225–3.774	0.008

MPE, malignant pleural effusion; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; HR, hazard ratio; CI, confidence interval; CRP, C-reaction protein; s-LDH, serum lactate dehydrogenase; p-Glucose, pleural glucose; p-CEA, pleural carcinoembryonic antigen.

Table 4 Multivariate analyses of the factors associated with risks for recurrence of MPE in patients with wild-type EGFR/ALK

Variable	HR	95% CI	P
Age (≥71.5 years)	2.918	1.191–7.147	0.019
Glucose (≥6.75 mmol/L)	4.186	1.623–10.791	0.003
s-CEA (≥203.0 μg/L)	2.719	1.147–6.446	0.023

MPE, malignant pleural effusion; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; HR, hazard ratio; CI, confidence interval; glucose, serum glucose; s-CEA, serum carcinoembryonic antigen.

We then put all these variables into multivariate analysis. Receiving treatment except targeted therapy after the first thoracentesis within 30 days (HR, 0.454; 95% CI: 0.315–0.654; P<0.001), higher NLR level (HR, 1.612; 95% CI: 1.070–2.427; P=0.022), higher s-LDH level (HR, 1.624; 95% CI: 1.126–2.342; P=0.009) and higher s-CEA level (HR, 1.883; 95% CI: 1.314–2.698; P=0.001) were finally perceived as risk factors (*Table 2*).

After dividing the 330 patients into two groups upon mutation status, we found that in the group with actionable mutations, receiving treatment except targeted therapy after the first thoracentesis within 30 days (HR, 0.438; 95% CI: 0.250–0.768; P=0.004), higher CRP level (HR, 2.523; 95% CI: 1.183–5.381; P=0.017), higher s-LDH level (HR, 2.305; 95% CI: 1.295–4.103; P=0.005), higher p-Glucose level (HR, 2.148; 95% CI: 1.242–3.715; P=0.006) and higher p-CEA level (HR, 2.150; 95% CI: 1.225–3.774; P=0.008) were thought as independent risk factors (*Table 3*). In the other group, risk factors included elder (HR, 2.918; 95% CI: 1.191–7.147; P=0.019), higher s-Glucose level (HR, 4.186; 95% CI: 1.623–10.791; P=0.003) and higher s-CEA level (HR, 2.719; 95% CI: 1.147–6.446; P=0.023) (*Table 4*).

Discussion

A total of 343 patients with advanced metastasis lung adenocarcinoma were included in the study. Among them, 58.6% had actionable mutations. On univariate analysis, mutation status was an effective predictor for RFS. However, in multivariate analysis, only targeted therapy after the first thoracentesis, lower level of NLR, lower s-LDH level, and lower level of s-CEA could be valid factors protecting patients from MPE recurrence.

Previously, researchers have focused on the risk factors for the OS of MPE. The first risk stratification system for patients with MPE, the LENT score, highlighted the disparate survival prospects (6). The clinical PROMISE score was the largest study to use a systematic approach for identifying biomarkers and it was a prognostic score for MPE (7). However, exploring unselected cancer types might reduce the accuracy of specific types of malignancy. To focus on lung cancer, our research team designed a retrospective study and discovered the RECLS score and the RECLSAM score, the first prognostic score for lung cancer and lung adenocarcinoma (8). Our findings were more suitable for Asians, whose mutation frequencies were notably higher than Caucasians. In our score system, the low-risk group had a median survival of 716 days, relatively longer than the 319 days in the low-risk group in the LENT score. In summary, differences did exist in patients of different races. Our previous research investigated the prognosis of MPE while we explored the recurrence of MPE in Asians in this study.

Several studies on risk factors of MPE recurrence were conducted. One prospective study demonstrated that patients receiving the first or second line of systemic treatment were more likely to experience MPE recurrence (13). However, the study included all cancer types and did not

evaluate the effects of specific systemic therapies, such as targeted therapy in EGFR-mutated patients. Schwalk *et al.* focused on actionable mutated patients in NSCLC (12). By utilizing the Fine-Gray sub-distribution hazard model, researchers showed that larger pleural effusion size on chest radiography, higher p-LDH level, and positive cytologic results were related to the time of MPE recurrence. It also demonstrated that patients could benefit from the same management strategy regardless of mutation status. It is at variance with previous research in Asia (14). Chiang *et al.* (14) investigated 233 patients with lung cancer in Asia. The median time to MPE re-intervention in groups with targeted and systemic therapy was 182 days and 88 days, respectively. Regrettably, no direct comparison was conducted between those with and without driver mutations. Evidence indicates that more studies about risk factors for MPE in Asians were necessary.

Our study intended to explore the underlying risk factors for MPE recurrence in Asian and figure out the possible relationship between the recurrence of MPE and the status of actionable mutations. Though the univariate analysis demonstrated that the factor might be protective against the recurrence of MPE, actionable mutations were not included in our final results. However, our subgroup analysis indicated that targeted therapy after the first thoracentesis within 30 days, lower CRP level, lower s-LDH level, lower p-Glucose level, and lower p-CEA level were thought as independent protective factors in the mutated group. Factors related closely to MPE recurrence were absolutely different in the mutated group. Moreover, our study showed that targeted therapy after the first thoracentesis, always received by mutated patients, was an independent protective factor in recurrent MPE. Differences existed between different mutation statuses. Articles published previously were consistent with our results. First of all, it was widely known that first-line targeted therapy improves PFS and OS compared with carboplatin/paclitaxel, according to IPASS (15). In the last couple of years, targeted therapy was preferable in MPE for patients with EGFR mutation. In the study comparing intrathoracic effects of different therapy in MPE, the MPE-FS in chemotherapy with pleurodesis and targeted therapy with pleurodesis was 10.1 and 19.2 months, respectively. The gap was more prominent (2.5 *vs.* 21.7 months) when patients received chemotherapy or targeted therapy alone without pleurodesis (16). Targeted therapy proved remarkably effective in extending the time to re-accumulation. To sum up, targeted therapy tended to have a preferable exhibition in protecting patients from MPE recurrence, consistent with our results. However, among the 108 patients who received the first-generation EGFR tyrosine kinase inhibitors (TKIs) and 31 patients who received the third-generation EGFR-TKIs, no significance in recurrence was found between the two groups (P=0.802). The median RFS of the two groups was both 300 days. More patients should be included and longer follow-up time should be determined to explore the difference in intrapleural effects between the different kinds of EGFR-TKIs in the future.

Except targeted therapy, the level of NLR, LDH, and CEA were independent factors in our results. NLR was connected closely with prognostic in lung cancer with MPE, whether in serum or pleural effusion (6,17). Different from our results, Abrão *et al.* regarded NLR as a possible variable for MPE recurrence while receiving negative results in the final analysis (13). However, few studies investigated the relationship between NLR and MPE recurrence. On the other hand, statistical difference between groups with different s-LDH levels was significant in our study. LDH was related to tissue injury and could rise in many clinical conditions (18). pleural ADA and s-LDH always appeared in diagnosing MPE, known as CR (18-20). Except s-LDH, p-LDH was proven to have a relationship with poor prognosis and recurrence of MPE (12,21,22). However, p-LDH was not included in our multivariable analysis. More studies should be carried out. Additionally, a higher level of s-CEA was related to recurrence closely in our results. Previous studies indicated that the level of CEA influenced the prognostic of MPE (23). The ratio of p-CEA and s-CEA could be an excellent biomarker for predicting the effects of intrathoracic therapy (24). The existing research did not involve tumor biomarkers as variables of MPE recurrence.

A previous study demonstrated that active MPE control measures should be conducted in the early stage (14). Our study further demonstrated that no difference in the time of MPE recurrence between intrapleural injection and IPC existed. The question about the effectiveness of intrapleural injection and IPC has been controversial for a few years (25-27). Different from other countries, due to the lack of production of medical purified talc in China, clinicians used intrapleural injections such as TNF-α, platinum-containing chemotherapy drugs, and anti-angiogenesis drugs. Different chemotherapy medications in intrapleural injection might lead to a difference in results. Researchers have intended to investigate new chemotherapy medications in the past few years. For example, our team previously conducted an

intrapleural injection of anti-programmed cell death protein 1 monoclonal antibody in the MPE mouse model and found it effective in controlling MPE and cancer growth by activating local cytotoxic T cells (28). We also carried out a small clinical study containing nine NSCLC patients who received intrapleural injections of sintilimab and gained a satisfying short-term control rate. Based on the encouraging results, more clinical trials and comparative studies could be conducted in the future.

Our study was a retrospective study with a few patients lost to follow-up. These might contribute to a selection bias. Also, the patients were selected from one institution, decreasing the generalizability of the results. Multicenter researches and prospective researches are necessary.

Conclusions

In conclusion, patients utilizing targeted therapy after the first thoracentesis, with a lower level of NLR, lower level of s-LDH, and s-CEA were less likely to experience early recurrence of symptomatic MPE. In Asian patients with actionable mutations, targeted therapy combined with active intrapleural management was preferred, whether choosing intrapleural injection or IPC.

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Footnote

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Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-151/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-151/coif). YS serves as an Editors-in-Chief of *Translational Lung Cancer Research*. TL serves as an unpaid Associate Editors-in-Chief of *Translational Lung Cancer Research* from December 2022 to November 2023. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the local ethics committee of Nanjing Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University (registration ID. NJJLH202103256). Informed consent from individuals was waived based on the retrospective nature of this study.

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