Original Article

EGFR mutations in patients with lung adenocarcinoma and malignant pleural effusion: a propensity score-matched analysis of a single-center database

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Background: Malignant pleural effusion (MPE) is associated with poor prognosis in patients with advanced lung adenocarcinoma (LUAD), and abnormal activation of epidermal growth factor receptor (EGFR) plays a crucial role in the development of LUAD. This study aimed to investigate the correlation between *EGFR* mutations and the occurrence of MPE in patients with LUAD and evaluate the effect of *EGFR* mutations on the prognosis of patients with LUAD with MPE.

Methods: A case-control study design was adopted that included patients pathologically diagnosed with LUAD. Clinical data were collected, and patients were divided into the MPE group and the non-MPE (N-MPE) group based on the presence of MPE. Propensity score matching (PSM) was used to control for confounding factors. The correlation between *EGFR* mutations and the occurrence of MPE in LUAD was initially examined. Additionally, various factors affecting the overall survival (OS) of patients with LUAD and MPE were evaluated.

Results: A total of 849 patients were included in the study. After 1:2 PSM, there were 180 patients in the MPE group and 360 in the N-MPE group. The *EGFR* mutation rate was significantly higher in the MPE group compared to the N-MPE group [62.7% *vs.* 50.2%; odds ratio (OR) =1.668; P=0.006]. This difference was primarily attributed to the T790M mutation (8.3% *vs.* 1.3%; OR =8.015; P<0.001), but no significant differences observed in other mutation sites between the groups. Further evaluation of factors affecting OS in patients with LUAD and MPE revealed that *EGFR* mutation was an independent protective factor for OS [hazard ratio (HR) 0.662, 95% CI: 0.456–0.962; P=0.03]. For patients with LUAD, MPE, and *EGFR* mutations, treatment with third-generation *EGFR*-tyrosine kinase inhibitors (TKIs) alone (HR 0.466, 95% CI: 0.233–0.930; P=0.03) or sequential first- and third-generation *EGFR*-TKIs (HR 0.385, 95% CI: 0.219–0.676; P=0.001) was associated with better median OS compared to first-generation *EGFR*-TKIs alone (first-generation *EGFR*-TKIs: 35 months, 95% CI: 28.4–41.6; third-generation *EGFR*-TKIs: 50 months, 95% CI: 37.3–62.7; sequential first- and third-generation *EGFR*-TKIs: 51 months, 95% CI: 45.6–56.4; P<0.001).

Conclusions: This study found there to be a positive correlation between *EGFR* mutations, particularly the T790M mutation, and MPE in patients with LUAD. *EGFR* mutation was associated with improved OS in patients with LUAD and MPE. For patients with LUAD, MPE, and *EGFR* mutations, sequential treatment with first- and third-generation *EGFR*-TKIs or third-generation *EGFR*-TKIs alone is recommended, as these regimens provide significant benefit to OS.

Keywords: Lung adenocarcinoma (LUAD); malignant pleural effusion (MPE); *EGFR* mutation; T790M mutation

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Introduction

Non-small cell lung cancer (NSCLC) is one of the leading causes of cancer-related death globally, and among the histological subtypes of NSCLC, lung adenocarcinoma (LUAD) is the most prevalent (1). In recent years, significant progress has been made in understanding the signaling pathways involved in the development and progression of LUAD. The abnormal activation of the epidermal growth factor receptor (*EGFR*) plays a crucial role in LUAD. *EGFR* is a member of the receptor tyrosine kinase *ErbB* family. Ligands binding to its extracellular domain induces conformational changes, leading to receptor dimerization, tyrosine phosphorylation, and activation of downstream signaling pathways, including RAS-MAPK, PI3K-AKT, and JAK-STAT, promoting cell growth and survival (2). *EGFR* tyrosine kinase inhibitors (TKIs) inhibit these pathways, thereby constraining tumor cell proliferation (3-5). The widespread clinical application of various *EGFR*-TKIs has significantly improved the prognosis of patients with LUAD and *EGFR* mutations (3,5).

Many studies have shown that *EGFR* mutations are closely related to various tumor metastases (6,7). In the field of lung cancer, previous research has focused more on the correlation between *EGFR* mutations and brain metastases (8,9), with the results indicating that patients with NSCLC and brain metastases have a higher frequency of *EGFR* mutations compared to those without brain metastases (52.0% *vs.* 22.0%; P<0.001) (10). The pleura is a common site for LUAD metastasis, which mainly manifests as pleural nodules and malignant pleural effusion (MPE). About 50% of patients with advanced NSCLC develop pleural effusion, which is more common in LUAD (11). Despite advances in multidisciplinary treatment improving overall care, the prognosis for patients with MPE remains poor, with a 5-year survival rate of only 6.4% (12,13). Two studies investigated the correlation between *EGFR* mutations and MPE in LUAD, but these studies were mostly based on nonpaired case-control designs with small sample sizes, resulting in potential bias for which further validation may be necessary (14,15).

Therefore, through a retrospective study, we aimed to determine the correlation between *EGFR* mutations and MPE in LUAD and evaluate the potential survival impact benefit of therapies based on *EGFR* mutations for patients with LUAD and MPE. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-757/rc).

Highlight box

Key findings

- Epidermal growth factor receptor (*EGFR*) mutations, particularly the T790M mutation, are associated with the occurrence of malignant pleural effusion (MPE) in lung adenocarcinoma (LUAD).

What is known and what is new?

- *EGFR* mutations promote tumor cell proliferation and migration. The application of *EGFR*-tyrosine kinase inhibitors (TKIs) can improve the prognosis of patients with LUAD and *EGFR* mutations.
- *EGFR* mutations, particularly the T790M mutation, were associated with MPE in LUAD. For patients with MPE and LUAD, *EGFR* mutation was associated with longer overall survival (OS). It is especially recommended to use a regimen of sequential first- and third-generation *EGFR*-TKIs or third-generation *EGFR*-TKIs alone for patients with LUAD, MPE, and *EGFR* mutations to get better survival benefit.

What is the implication, and what should change now?

- The conclusion that *EGFR* mutations, particularly the T790M mutation are associated with MPE can provide guidance and direction for research on the mechanisms of lung cancer metastasis.
- The identification of factors related to OS and a comparison of different *EGFR*-TKI treatment regimens are beneficial for clinical decision-making in patients with LUAD and MPE.

Methods

Patients

This retrospective study included patients with LUAD who visited the Thoracic Surgery Department and Oncology

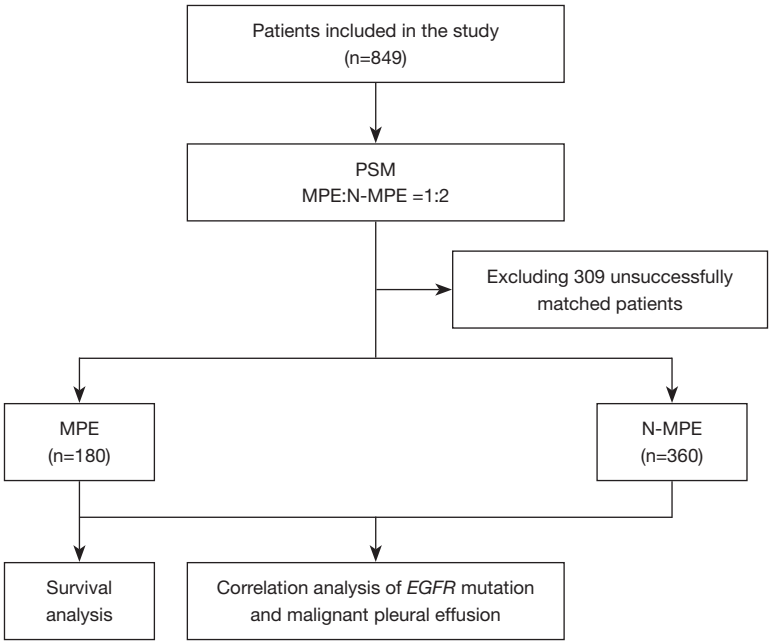

Figure 1 Flowchart of study. PSM, propensity score matching; MPE, malignant pleural effusion; N-MPE, non-malignant pleural effusion; *EGFR*, epidermal growth factor receptor.

Department of the First Hospital of China Medical University between January 2013 and December 2020. The inclusion criteria were as follows: (I) pathologically confirmed LUAD and (II) no history of other malignant tumors. A total of 4,461 patients met these criteria. Patients with incomplete clinical data, loss to follow-up, or death due to non-LUAD-related causes were excluded, resulting in a final sample size of 849 patients. Various clinical data were collected, including baseline information at admission, imaging findings, pathological results, genetic testing results, treatment regimens, and survival times. Tumor diameter and the number of lymph node metastases were restaged according to the ninth edition of the tumor-node-metastasis (TNM) staging system (16). Age was categorized into two groups: <60 and ≥60 years.

MPE was defined as the presence of pleural effusion on computed tomography (CT) imaging, confirmed by cytopathological examination showing tumor cells in the effusion (12). Patients were divided into MPE and non-MPE groups based on the presence of MPE at initial diagnosis. MPE group was categorized as stage IV according to the TNM staging system due to the presence of MPE, while the non-MPE group included patients ranging from stage I to stage IV. To control for confounding factors, propensity score matching (PSM) was performed between the two groups. After matching, the correlation between *EGFR* mutation and MPE in LUAD was analyzed. Furthermore, univariate and multivariate analyses were conducted to investigate factors associated with overall survival (OS) in patients with LUAD and MPE (*Figure 1*).

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of the First Hospital of China Medical University (No. 2023-54). The requirement for individual consent was waived due to the retrospective nature of the analysis.

EGFR mutation analysis

This study collected mutation information from patients diagnosed with LUAD who had undergone genetic testing. Testing methods included fluorescence polymerase chain reaction (PCR), amplification refractory mutation system PCR, and next-generation sequencing. All genetic test reports for patients were obtained from accredited genetic testing companies, such as Geneseeq Genetic Testing Company. The mutations in *EGFR* exons 18 to 21 were detected, including G719X, exon 19 deletion (19 Del), exon 20 insertion (20 Ins), S768I, T790M, L858R, and L681Q, among others.

Table 1 Patient characteristics in the MPE and N-MPE groups (n=540)

Characteristic	MPE (N=180), n (%)	N-MPE (N=360), n (%)	P value
Age			0.69
≥60 years	128 (71.1)	250 (69.4)	
<60 years	52 (28.8)	110 (30.5)	
Gender			0.95
Male	77 (42.7)	155 (43.0)	
Female	103 (57.2)	205 (56.9)	
Smoking			0.42
Yes	21 (11.6)	51 (14.1)	
No	159 (88.3)	309 (85.8)	
Stage at diagnosis			
T			0.28
T1	26 (14.4)	52 (14.4)	
T2	48 (26.6)	102 (28.3)	
T3	24 (13.3)	68 (18.8)	
T4	82 (45.5)	138 (38.3)	
N			0.56
N0	25 (13.8)	36 (10.0)	
N1	17 (9.4)	37 (10.2)	
N2	68 (37.7)	134 (37.2)	
N3	70 (38.8)	153 (42.5)	

MPE, malignant pleural effusion; N-MPE, non-malignant pleural effusion.

Study endpoints

The primary follow-up endpoint of this study was OS, which was defined as the time from the initial diagnosis of LUAD until death or the follow-up cutoff date of September 30, 2023. During the follow-up period, deaths due to LUAD-related causes were recorded as positive outcomes, while data from patients still alive at the end of the follow-up period were considered censored to calculate cumulative survival rates. Follow-up information was primarily obtained through hospital medical records and telephone communications with patients or their relatives.

Statistical methods

PSM analysis was performed using R version 4.2.1 (The R Foundation of Statistical Computing), Factors included in PSM were age, gender, smoking history, T-stage and N-stage, and the matched ratio of MPE group to non-MPE group was 1 to 2 with a caliper value of 0.02. Data processing and statistical analyses were conducted using SPSS 26.0 software (IBM Corp., Armonk, NY, USA). Categorical variables were analyzed using the Chi-squared test or Fisher exact test. Correlation analysis was conducted using binary logistic regression. Univariate analysis was performed using the Cox proportional hazards model, and factors with P values less than 0.05 were included in the multivariate analysis to identify those factors associated with OS. Kaplan-Meier curves were plotted using GraphPad Prism 10 software (GraphPad Software, Inc., La Jolla, CA, USA), and the log-rank test was used to compare survival curves across different subgroups for statistical differences. All statistical tests were two-sided, and P values less than 0.05 were considered statistically significant.

Results

Patient characteristics in the MPE and N-MPE groups

A total of 849 patients were included in the study, with 180 in the MPE group and 669 in the N-MPE group. To control for the influence of confounding factors, PSM analysis was performed between the MPE and N-MPE groups. After PSM, there were 180 patients in the MPE group and 360 in the N-MPE group. The distribution of the aforementioned covariates across the two groups was balanced (P>0.05) (*Table 1*).

Correlation analysis of EGFR mutation and MPE

The types of *EGFR* mutations included in this study were exon 18 G719X mutations, 19 Del, 20 Ins, exon 20 S768I mutations, T790M mutations, and exon 21 L858R and L681Q mutations. Among the 540 patients who remained after PSM, 294 had *EGFR* mutations. The *EGFR* mutation rate was significantly higher in patients with LUAD and MPE compared to those without MPE, indicating a positive correlation between *EGFR* mutation and MPE occurrence [62.7% *vs.* 50.2%; odds ratio (OR) =1.668; P=0.006].

Table 2 Correlation analysis of *EGFR* mutation with MPE in 540 patients

Variable	MPE (N=180), n (%)	N-MPE (N=360), n (%)	OR (95% CI)	P value
EGFR status				
EGFR WT	67 (37.2)	179 (49.7)	Reference	
EGFR MT	113 (62.7)	181 (50.2)	1.668 (1.157–2.405)	0.006
EGFR mutation sites				
EGFR WT	67 (37.2)	179 (49.7)	Reference	
G719X	4 (2.2)	8 (2.2)	1.336 (0.389–4.582)	0.65
19 Del	49 (27.2)	84 (23.3)	1.558 (0.993–2.445)	0.054
20 Ins	5 (2.7)	9 (2.5)	1.484 (0.480–4.589)	0.49
S768I	0 (0.0)	2 (0.5)	–	–
T790M	15 (8.3)	5 (1.3)	8.015 (2.804–22.911)	<0.001
L858R	38 (21.1)	63 (17.5)	1.611 (0.986–2.632)	0.057
L681Q	2 (1.1)	10 (2.7)	0.534 (0.114–2.502)	0.43

MPE, malignant pleural effusion; N-MPE, non-malignant pleural effusion; OR, odds ratio; CI, confidence interval; *EGFR*, epidermal growth factor receptor; WT, wild type; MT, mutant type.

Notably, there was a significant difference in T790M mutation rates between the two groups (8.3% *vs.* 1.3%; OR =8.015; P<0.001), while no significant differences were observed for other mutation sites (*Table 2*).

Patient characteristics in the MPE group

Among the 180 patients with LUAD and MPE, 113 (62.8%) patients were EGFR mutant type and 67 (37.2%) patients were EGFR wild type. Therefore, the 180 patients were divided into two groups (*EGFR* MT group and *EGFR* WT group), and their characteristics are presented in *Table 3*. There were 77 male patients (42.7%), and 132 patients (73.3%) had an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1. 117 patients (65%) were receiving *EGFR*-TKI treatment, while 63 patients (35%) were receiving non-*EGFR*-TKI treatment. A total of 77 patients (42.7%) received systemic antiangiogenic targeted

Table 3 Characteristics of patients in the MPE group (n=180)

Characteristic	*EGFR* MT (n=113), n (%)	*EGFR* WT (n=67), n (%)	P value
Age			0.42
≥60 years	78 (69.0)	50 (74.6)	
<60 years	35 (30.9)	17 (25.3)	
Gender			0.009
Male	40 (35.3)	37 (55.2)	
Female	73 (64.6)	30 (44.7)	
Smoking			0.93
No	100 (88.4)	59 (88.0)	
Yes	13 (11.5)	8 (11.9)	
ECOG			0.46
0–1	85 (75.2)	47 (70.1)	
≥2	28 (24.7)	20 (29.8)	
Stage at diagnosis			
T			0.65
T1	16 (14.1)	10 (14.9)	
T2	32 (28.3)	16 (23.8)	
T3	17 (15.0)	7 (10.4)	
T4	48 (42.4)	34 (50.7)	
N			0.14
N0	14 (12.3)	11 (16.4)	
N1	10 (8.8)	7 (10.4)	
N2	50 (44.2)	18 (26.8)	
N3	39 (34.5)	31 (46.2)	
EGFR-TKIs treatment			<000.1
No	2 (1.7)	61 (91.0)	
Yes	111 (98.2)	6 (8.9)	
Antiangiogenic therapy			0.61
No	63 (55.7)	40 (59.7)	
Yes	50 (44.2)	27 (40.2)	
Other targeted therapy			0.053
No	111 (98.2)	61 (91.0)	
Yes	2 (1.7)	6 (8.9)	
Systemic chemotherapy			0.19
No	28 (24.7)	11 (16.4)	
Yes	85 (75.2)	56 (83.5)	

Table 3 (*continued*)

Table 3 (*continued*)

Characteristic	*EGFR* MT (n=113), n (%)	*EGFR* WT (n=67), n (%)	P value
Immunotherapy			0.23
No	82 (72.5)	54 (80.5)	
Yes	31 (27.4)	13 (19.4)	
Intrapleural perfusion			0.09
No	76 (67.2)	53 (79.1)	
Yes	37 (32.7)	14 (20.8)	
Local treatment			0.30
No	91 (80.5)	58 (86.5)	
Yes	22 (19.4)	9 (13.4)	

MPE, malignant pleural effusion; *EGFR*, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; WT, wild type; MT, mutant type; ECOG, Eastern Cooperative Oncology Group.

therapy, mainly consisting of bevacizumab. Moreover, 8 patients (4.4%) had mutations other than *EGFR* and received corresponding targeted drug therapy. These included four patients with *ALK* mutations treated with crizotinib, two patients treated with the selective *MET* kinase inhibitor savolitinib, one patient treated with the selective *RET* inhibitor pralsetinib, and one patient with a *BRAF* V600 mutation treated with a combination of dabrafenib and trametinib. Due to the small number of cases, these were collectively classified as "other targeted drug treatments". A total of 141 patients (78.3%) received systemic chemotherapy, mainly platinum-based doublet chemotherapy, 44 patients (24.4%) received immunotherapy with anti-PD-1/PD-L1 drugs, and 51 patients (28.3%) received intrapleural perfusion therapy, which involved indwelling chest catheters and infusion of cisplatin or cisplatin combined with bevacizumab or recombinant human endostatin. Local treatment was administered to 31 patients (17.2%), with 6 patients receiving interventional therapy and 29 patients receiving radiotherapy for primary or metastatic lesions.

Prognostic factors analysis in patients with MPE

We followed up with 180 patients with LUAD and MPE with a median follow-up duration of 61 months and plotted survival curves (*Figure 2*). As of the follow-up cutoff date, 55 patients (30.5%) were still alive, representing a median

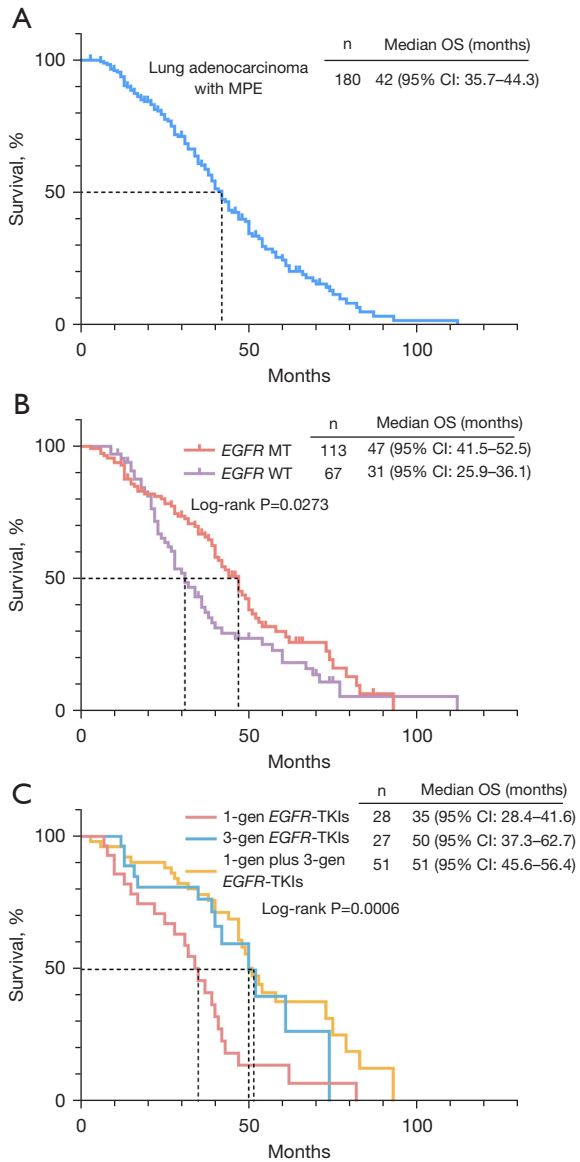

Figure 2 Kaplan-Meier curves for overall survival in different populations. (A) Survival curves for patients with LUAD and MPE. (B) Survival curves for patients with LUAD and MPE stratified by the *EGFR* mutant type and *EGFR* wild type. (C) Survival curves for patients with LUAD, MPE, and *EGFR* mutations stratified by different *EGFR*-TKI treatment regimens. MPE, malignant pleural effusion; OS, overall survival; CI, confidence interval; *EGFR*, epidermal growth factor receptor; WT, wild type; MT, mutant type; TKI, tyrosine kinase inhibitor; gen, generation; LUAD, lung adenocarcinoma.

OS of 42 months (95% CI: 35.7–44.3) and a 5-year survival rate of 25.5% (*Figure 2A*). Using the Cox regression model, we conducted univariate and multivariate analyses to

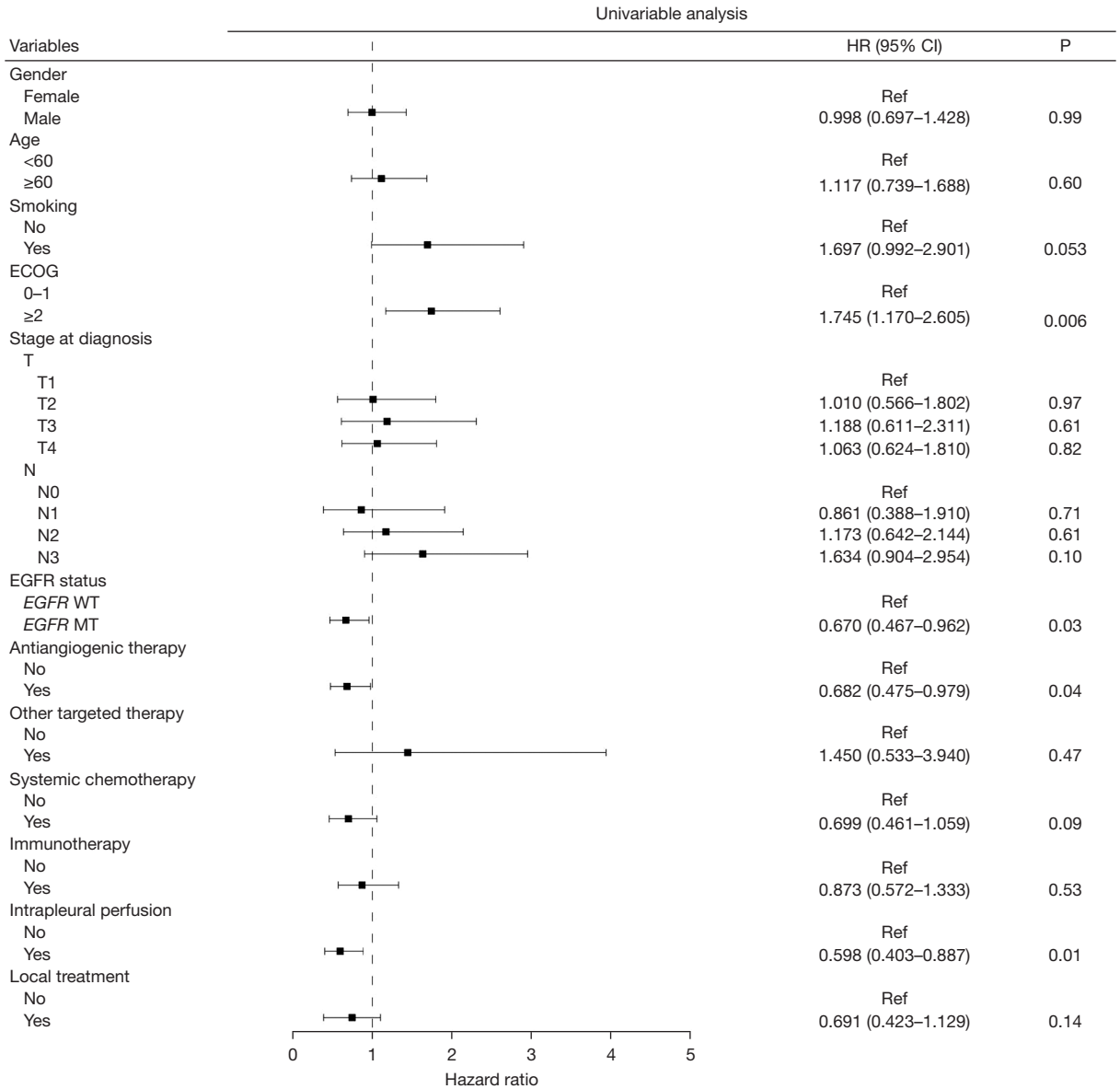

Figure 3 Univariate analyses for OS in patients with LUAD and MPE. HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; WT, wild type; MT, mutant type; OS, overall survival; LUAD, lung adenocarcinoma; MPE, malignant pleural effusion.

identify the factors associated with OS in the 180 patients with LUAD and MPE. In the univariate analysis, an ECOG score ≥2 was associated with shorter OS. Conversely, *EGFR* mutation, antiangiogenic therapy, and intrapleural perfusion therapy were associated with a longer OS (*Figure 3*). Multivariate analysis showed that *EGFR* mutation was an independent prognostic factor for prolonged OS [hazard ratio (HR) 0.662, 95% CI: 0.456–0.962; P=0.03]. Additionally, the factors independently associated with longer OS were antiangiogenic therapy (HR 0.684, 95% CI: 0.474–0.987; P=0.043) and intrapleural perfusion therapy (HR 0.622, 95% CI: 0.441–0.992; P=0.046), Conversely, ECOG scores ≥2 were independently associated with shorter OS (HR 1.911, 95% CI: 1.226–2.886; P=0.002) (*Figure 4*).

To visually present the association of *EGFR* mutation

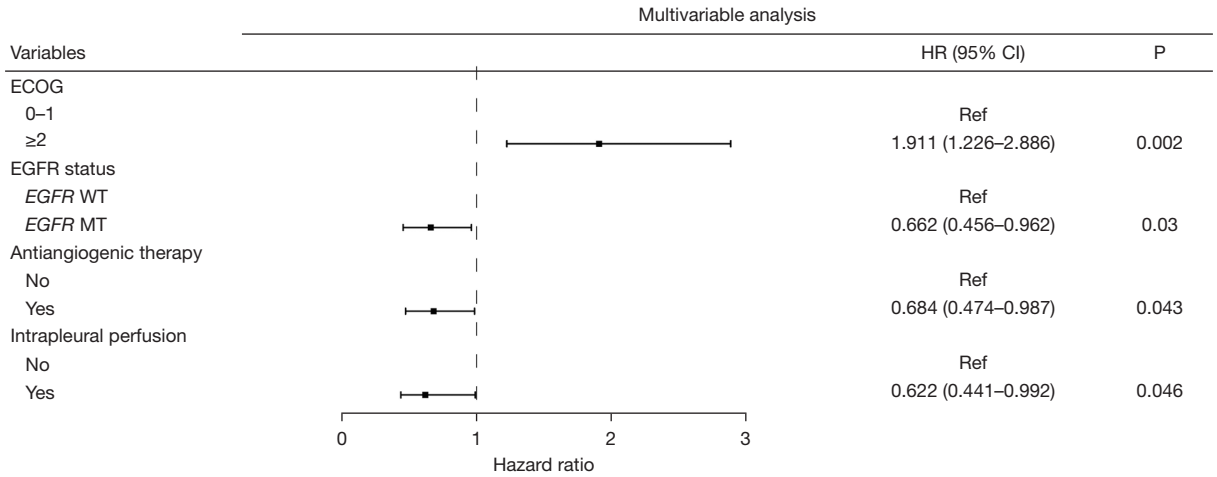

Figure 4 Multivariate analyses for OS in patients with LUAD and MPE. HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; WT, wild type; MT, mutant type; OS, overall survival; LUAD, lung adenocarcinoma; MPE, malignant pleural effusion.

with OS in patients with LUAD and MPE, we plotted survival curves. The median OS for *EGFR*-mutant patients was 47 months (95% CI: 41.5–52.5), which was significantly better than the 31 months in those with the *EGFR* wild type (95% CI: 25.9–36.1; P=0.03) (*Figure 2B*).

Prognostic factor analysis of patients with EGFR mutations and MPE

To overcome the inevitable resistance to *EGFR*-TKIs, new *EGFR*-TKIs drugs continue to be developed, providing various options and strategies for clinical applications. To clarify the impact of different *EGFR*-TKIs treatment regimens on OS in patients with LUAD, MPE, and *EGFR* mutations, we further analyzed these patients. Among the 111 patients with *EGFR* mutations and MPE who received *EGFR*-TKI treatment, 28 received first-generation *EGFR*-TKIs alone, 51 received sequential first- and third-generation *EGFR*-TKIs, and 27 received third-generation *EGFR*-TKIs alone (5 patients who received second-generation *EGFR*-TKIs were excluded from the analysis due to the small sample size). The Cox regression model was used for univariate and multivariate analyses. The results showed that the independent prognostic factors for prolonged OS were administration of third-generation *EGFR*-TKIs alone (HR 0.466, 95% CI: 0.233–0.930; P=0.03) and sequential first- and third-generation *EGFR*-TKIs (HR 0.385, 95% CI: 0.219–0.676; P=0.001) but not administration of first-generation *EGFR*-TKIs alone. Additionally, intrapleural perfusion therapy (HR 0.557, 95% CI: 0.327–0.951; P=0.03) was also independently associated with a longer OS (*Figures 5*,*6*).

Survival curves were plotted to compare the survival benefits of the three main *EGFR*-TKI treatment regimens for patients with LUAD and MPE. The results showed that compared to first-generation *EGFR*-TKIs alone, both third-generation *EGFR*-TKIs alone and sequential first- and third-generation *EGFR*-TKIs had better median OS (first-generation *EGFR*-TKIs: 35 months, 95% CI: 28.4–41.6; third-generation *EGFR*-TKIs: 50 months, 95% CI: 37.3–62.7; sequential first- and third-generation *EGFR*-TKIs: 51 months, 95% CI: 45.6–56.4; P<0.001) (*Figure 2C*).

Discussion

This study demonstrated that *EGFR* mutations, especially the T790M mutation, are associated with the occurrence of MPE in LUAD. For patients with LUAD and MPE, *EGFR* mutations independently associated with prolonged OS.

Previous studies have shown that *EGFR* activation, triggered by ligand binding, activates *EGFR* intrinsic tyrosine kinase activity and a series of downstream signals, thereby mediating invasion and metastasis in various tumors (7,17,18). In NSCLC, *EGFR* mutation is most commonly associated with brain metastasis (19-21). Recently, the correlation between *EGFR* mutation and MPE has also been reported: Zou *et al.* collected data from 136 East Asian patients with LUAD and found a significant

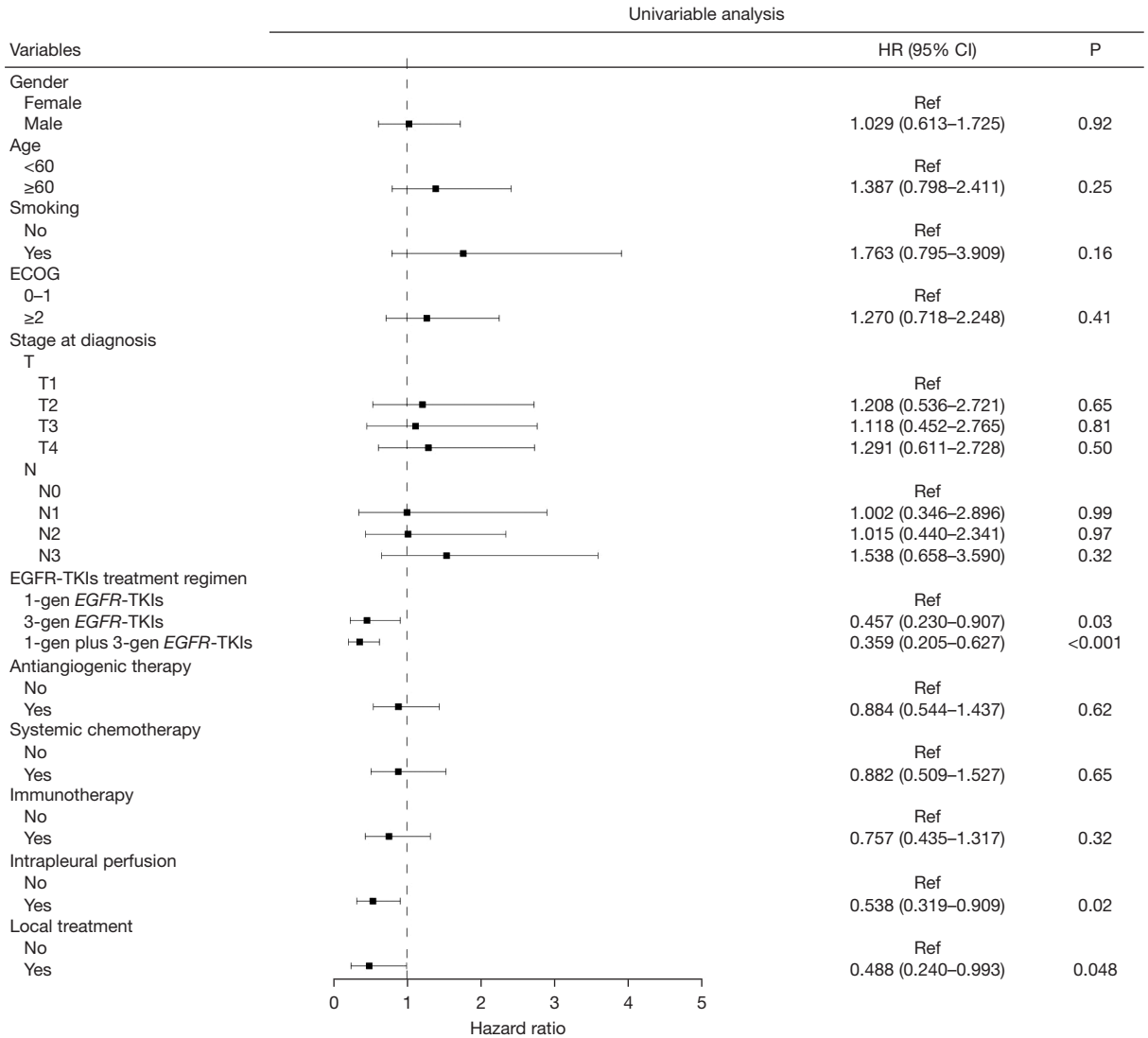

Figure 5 Univariate analyses for OS in patients with LUAD, MPE, and EGFR mutations. HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; gen, generation; OS, overall survival; LUAD, lung adenocarcinoma; MPE, malignant pleural effusion.

correlation between MPE occurrence and *EGFR* mutation (P=0.03) (14). Smits *et al.* analyzed 394 patients with LUAD from 13 hospitals in Western Europe and found that *EGFR* mutation frequency was significantly higher in patients with MPE (P=0.02) (22). The specific *EGFR* mutation sites and the precise targeting of metastatic lesions remain a focus of interest for researchers worldwide. Notably, the T790M mutation is particularly relevant due to its association with *EGFR*-TKI resistance in lung cancer (23-25). A real-world clinical study indicated a positive correlation between T790M mutation and NSCLC brain metastasis (P=0.03) (26). Chen *et al.* conducted a retrospective study on 365 patients with *EGFR*-mutant NSCLC and found that the T790M mutation carriers were more prone to metastasis, including brain, bone, liver, and intrapulmonary metastases (P<0.001) (24).

Previous studies on the correlation between *EGFR* mutation and MPE in NSCLC included relatively small sample sizes, affecting the accuracy of results (14,15). Moreover, limited by gene detection technologies and sample sizes, these studies often only analyzed the presence or absence of *EGFR* mutations or focused solely on classic

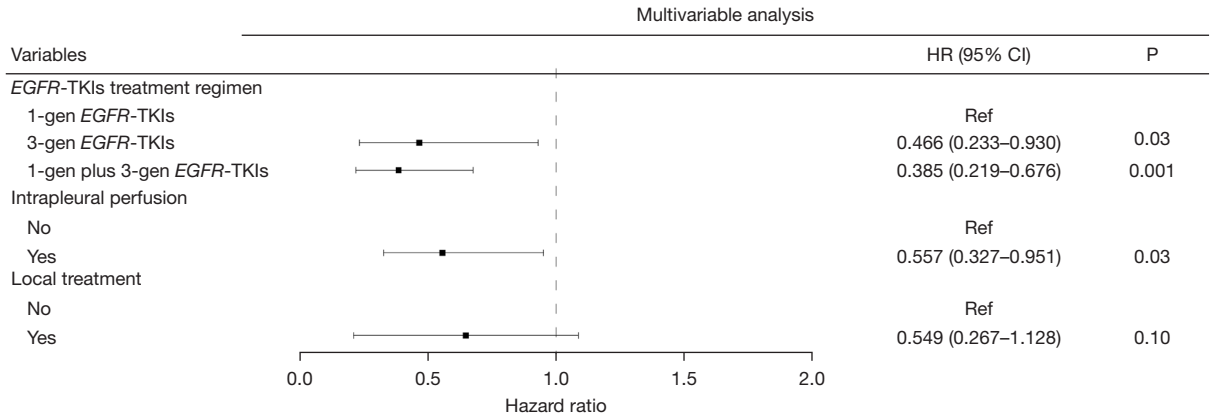

Figure 6 Multivariate analyses for OS in patients with LUAD, MPE, and EGFR mutations. *EGFR*, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; gen, generation; HR, hazard ratio; CI, confidence interval; OS, overall survival; LUAD, lung adenocarcinoma; MPE, malignant pleural effusion.

mutations such L858R and 19 Dels, neglecting T790M mutation rates in MPE. In our study, the *EGFR* mutation rate in patients with LUAD and MPE was 62.7% compared to 50.2% in those without MPE (OR =1.668; P=0.006), suggesting a potential association between *EGFR* mutation and MPE occurrence. Additionally, this study, being the first to examine the correlation between specific *EGFR* mutation sites and MPE, demonstrated a significant positive correlation between T790M mutation and MPE occurrence (8.3% *vs.* 1.3%; OR =8.015; P<0.001).

The T790M mutation is a well-established mechanism of secondary resistance to EGFR-TKI therapy. Numerous studies have shown that approximately 50% of NSCLC patients who initially respond to *EGFR*-TKI eventually develop secondary resistance due to the emergence of the T790M mutation (27,28). Chen *et al.* have suggested that a significant proportion of untreated NSCLC cases may harbor the T790M mutation from the outset. In this scenario, while first- or second-generation TKIs target and eliminate the initial sensitive mutation sites, T790M-resistant clones can proliferate and become predominant (29). Consequently, the disease progression associated with primary T790M mutation may occur earlier than that driven by acquired T790M mutation, leading to a more rapid disease progression in cases with primary mutations. In our study, we also compared the differences in OS between T790M mutation and common mutations. However, due to the limited sample size, we did not observe significant differences between the two groups.

Reports suggest that the prevalence of primary T790M mutations is quite low, ranging from 1-3%, which is consistent with our study's finding (overall T790M mutation rate was 3.7%, and 1.3% in the non-MPE group) (30,31). However, we observed a higher rate of 8.3% for T790M mutations in the MPE group, suggesting a potential association between the presence of T790M mutation and MPE. Currently, clinical research has predominantly focused on managing resistance due to secondary T790M mutations after treatment, with limited studies investigating the role of T790M in regulating tumor biology. Our findings suggest that primary T790M mutations may facilitate invasion and metastasis in LUAD. This highlights the need for further research into the underlying signaling pathways and potential therapeutic targets related to T790M mutations. We further sought to identify prognostic factors in patients with LUAD and MPE, particularly the association between *EGFR* mutation and the OS. ECOG score is a recognized prognostic factor for patients with MPE (32), with higher scores indicating poorer prognosis. We found that an ECOG score ≥2, as compared to lower ECOG scores, was associated with an increase in mortality rate of 91.1% (HR 1.911, 95% CI: 1.226–2.886; P=0.002). Angiogenesis is crucial to tumor growth, proliferation, and metastasis, and numerous preclinical and clinical studies have examined antiangiogenic therapies for inhibiting tumor growth (33,34). In our study, antiangiogenic targeted therapy was associated with better OS. In NSCLC, bevacizumab, U.S. Food and Drug Administration (FDA)-approved antiangiogenic inhibitor, combined with platinum-based chemotherapy is recommended as first-

line treatment for patients with advanced LUAD (35). Additionally, intrapleural perfusion therapy is a primary method for treating MPE. Injecting drugs into the pleural cavity can kill metastatic tumor cells, stimulate pleural inflammation, and reduce pleural effusion. A previous study has shown that intravenous cisplatin (100 mg/m^2) results in a maximum blood concentration of 6 μg/mL (36), while intrapleural infusion of cisplatin (80 mg/m^2) yields a maximum blood concentration of only 0.66±0.31 μg/mL, increasing intrapleural drug concentration and reducing adverse systemic effects (37).

Previous studies have shown that *EGFR*-mutant patients treated with *EGFR*-TKIs have better survival than do those with the *EGFR* wild type (38-40). Similarly, we found that the median OS of *EGFR*-mutant patients was longer than that of those with the *EGFR* wild type (*EGFR* mutant: 47 months, 95% CI: 41.5–52.5; *EGFR* wild-type: 31 months, 95% CI: 25.9–36.1; P=0.03). Another finding of our study was that among patients with LUAD, *EGFR* mutations, and MPE, sequential first- and third-generation *EGFR*-TKIs or third-generation *EGFR*-TKIs alone were associated with longer OS compared to first-generation *EGFR*-TKIs alone. First-generation *EGFR*-TKIs lead to good initial treatment response in patients with classic *EGFR* mutations; however, most patients develop resistance after 9–14 months, with the T790M mutation being the most common mechanism of resistance(40,41). After resistance, a switch to third-generation *EGFR*-TKIs, which inhibit the T790M mutation, can significantly improve prognosis as compared to continuation on first-generation *EGFR*-TKIs or a switch to chemotherapy (40). Therefore, patients receiving sequential first- and third-generation *EGFR*-TKIs or third-generation *EGFR*-TKIs alone have a longer median OS, likely due to prolonged inhibition of the *EGFR* pathway, whereas patients receiving first-generation *EGFR*-TKIs alone do not benefit from new *EGFR* inhibitors after the emergence of resistance, resulting in a shorter median OS. This suggests that continuous inhibition of the *EGFR* pathway is beneficial for OS in patients with LUAD, MPE, and *EGFR* mutations.

This study involved certain limitations which should be acknowledged. First, although we attempted to reduce bias through PSM analysis and multivariable regression models, there were confounding factors not included in the models, and selection bias could not be completely excluded. Second, grouping certain variables might have simplified certain types of information, such as age, tumor diameter, and the number of lymph node metastases. Finally, as we employed a single-center, retrospective design, this study may be limited by a small sample size and a lack of regional differences and thus may not be more broadly generalizable.

Conclusions

Patients with LUAD with MPE exhibiteda higher incidence of *EGFR* mutations, including T790M mutations, compared to those without MPE. Specifically, *EGFR* mutations, especially the T790M mutations, were positively associated with the development of MPE in LUAD. Among patients with LUAD and MPE, *EGFR* mutations were linked to improved survival. For those with LUAD, MPE, and *EGFR* mutations, the use of sequential first-generation and third-generation *EGFR*-TKIs, or third-generation *EGFR*-TKIs alone, may lead to an improved OS benefit.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-757/rc

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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. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of the First Hospital of China Medical University (No. 2023-54). The requirement for individual consent was waived due to the retrospective nature of the analysis.

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