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**Time to Sustained CEA Elevation From Start of First-Line Therapy
Predicts Initial Treatment Efficacy and Clinical Outcomes in Lung
Adenocarcinoma**

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Abstract

Objective: This study investigates the prognostic value of the time interval (ΔT) measured from first-line therapy start to the sustained elevation of serum carcinoembryonic antigen (CEA) for progression-free survival (PFS) and overall survival (OS) in lung adenocarcinoma patients, and analyzes its correlation with other clinical-pathologic characteristics.

Methods: This retrospective study enrolled 225 pathologically confirmed, first-line treatment-naïve lung adenocarcinoma patients with complete clinical and follow-up data. Defining ΔT as the time interval from first-line therapy start to the first documented sustained CEA elevation (two consecutive

measurements with $\geq 20\%$ increase). Patients were dichotomized based on ΔT median value=242 days and the optimal cut-off value for therapeutic efficacy determined by ROC curve analysis (134days). Baseline characteristics, objective response rate (ORR), and disease control rate (DCR) were compared between groups. Median PFS (mPFS) and OS were estimated using the Kaplan–Meier method and compared by log-rank test. Univariate and multivariate survival analyses were performed using Cox proportional-hazards models.

Results: Regardless of grouping by ΔT median value (242days) or ΔT cut-off value (134days), the “late CEA elevation” group exhibited significantly superior ORR, DCR, mPFS, and OS compared with the “early CEA elevation” group (all $P < 0.001$). Multivariate analysis identified sex, liver metastasis, and grouping by either median ΔT or cut-off ΔT as independent influencing factors for both mPFS and OS. Survival curves further confirmed marked prolongation of mPFS and OS in the “late elevation” versus “early elevation” cohorts.

Conclusion: The time interval from first-line therapy start to sustained CEA elevation remains a key predictor of therapeutic efficacy and prognosis in lung adenocarcinoma; a longer ΔT is correlated with better treatment response and more favorable survival outcomes.

Keywords: Adenocarcinoma; Carcinoembryonic Antigen (CEA); Median Progression-free Survival (mPFS); Overall Survival (OS); Prognostic Factors

Introduction

Lung adenocarcinoma represents the predominant pathological subtype within non-small cell lung cancer (NSCLC)⁽¹⁾, and its incidence remains persistently high worldwide⁽²⁾. Although genomics-guided precision medicine and immunotherapy have markedly improved survival in a subset of patients, developing simple and effective tools for response monitoring and prognostication remains a key focus of clinical research. Carcinoembryonic antigen (CEA), a classical serum tumor marker, is a cell-adhesion-related glycoprotein that is normally produced during fetal development but ceases to be secreted before birth⁽³⁾; accordingly, it is typically absent from the circulation of healthy adults. CEA is a glycosylphosphatidylinositol (GPI)-anchored glycoprotein⁽⁴⁾ whose sialylated glycans serve as functional ligands for L-selectin and E-selectin in colorectal cancer, potentially facilitating metastatic dissemination⁽⁵⁾. In lung adenocarcinoma, CEA has attracted sustained attention because of its relatively high positivity rate, particularly among patients with advanced disease.

At present, the clinical utility of CEA is mainly reflected in the following aspects. First, for adjunctive diagnosis, although its specificity and sensitivity are insufficient for lung cancer screening, markedly elevated CEA levels can provide important clues to the clinical diagnosis⁽⁶⁾. Second, for treatment evaluation, dynamic changes in CEA levels before and after therapy are commonly used as sensitive indicators of response to chemotherapy⁽⁷⁾,

targeted therapy⁽⁸⁾,or immunotherapy⁽⁹⁾.Third,in disease surveillance,a sustained rise in CEA often serves as an early signal of tumor recurrence or progression,helping to guide the timing of imaging examinations and inform adjustments to therapeutic strategies⁽¹⁰⁾.

However,current research on CEA has largely focused on absolute levels or short-term rates of change in relation to prognosis,whereas the association between the time interval from initiation of first-line therapy to a sustained elevation in serum carcinoembryonic antigen (CEA)—a dynamic,time-based parameter—and long-term survival outcomes has not been systematically investigated.This key metric may integrate information on tumor biological behavior,intrinsic sensitivity to first-line treatment,and the inherent dynamics of disease progression,thereby conferring potential predictive value for treatment efficacy and survival in lung adenocarcinoma patients.Therefore,this retrospective study aims to examine the relationships between the interval to CEA elevation from the beginning of first-line therapy and patients'clinical characteristics,therapeutic efficacy,and survival outcomes,with the goal of providing new evidence to inform prognostication and individualized treatment decision-making.

Materials and Methods

Clinical Datas

From January 2015 to December 2024,we recruited 225 non-small cell lung cancer (NSCLC) patients in the Affiliated Hospital of Guangdong Medical University,all with pathological confirmation of stage IIIB or IVB lung adenocarcinoma.These patients received first-line anti-tumor therapies tailored to their specific genetic mutations.The criteria including:(1)age $\geq$ 18years;(2)histopathologically confirmed lung adenocarcinoma;(3)baseline serum CEA positive at the first measurement ($>5.2\mu\text{g/L}$,determined by ELISA);(4) tumors at unresectable stage IIIB or IV,as defined by the 8th edition of the IASLC Thoracic Tumor Staging Manual;and (5) radiologically confirmed disease progression after first-line standard therapy, including molecularly targeted therapy,immunotherapy plus platinum-based chemotherapy,or immunotherapy combined with anti-angiogenic therapy. Exclusion criteria were:(1)concomitant or prior other primary malignancies;(2) absence of standardized systemic antitumor treatment;(3)negative baseline CEA at initial testing;and(4)incomplete clinical or follow-up data.The technical flow chart of this study is shown in Figure 1.This study was conducted in accordance with the Helsinki Declaration and its subsequent amendments, approved by the Institutional Ethics Committee of Guangdong Medical University Affiliated Hospital(No.PJKT2024-070),and exempted individual informed consent for this retrospective analysis.

Patients with advanced lung adenocarcinoma treated with anti-tumor at Guangdong Medical University Affiliated Hospital from January 2015 to December 2024 and met the inclusion criteria of this study (n=225)
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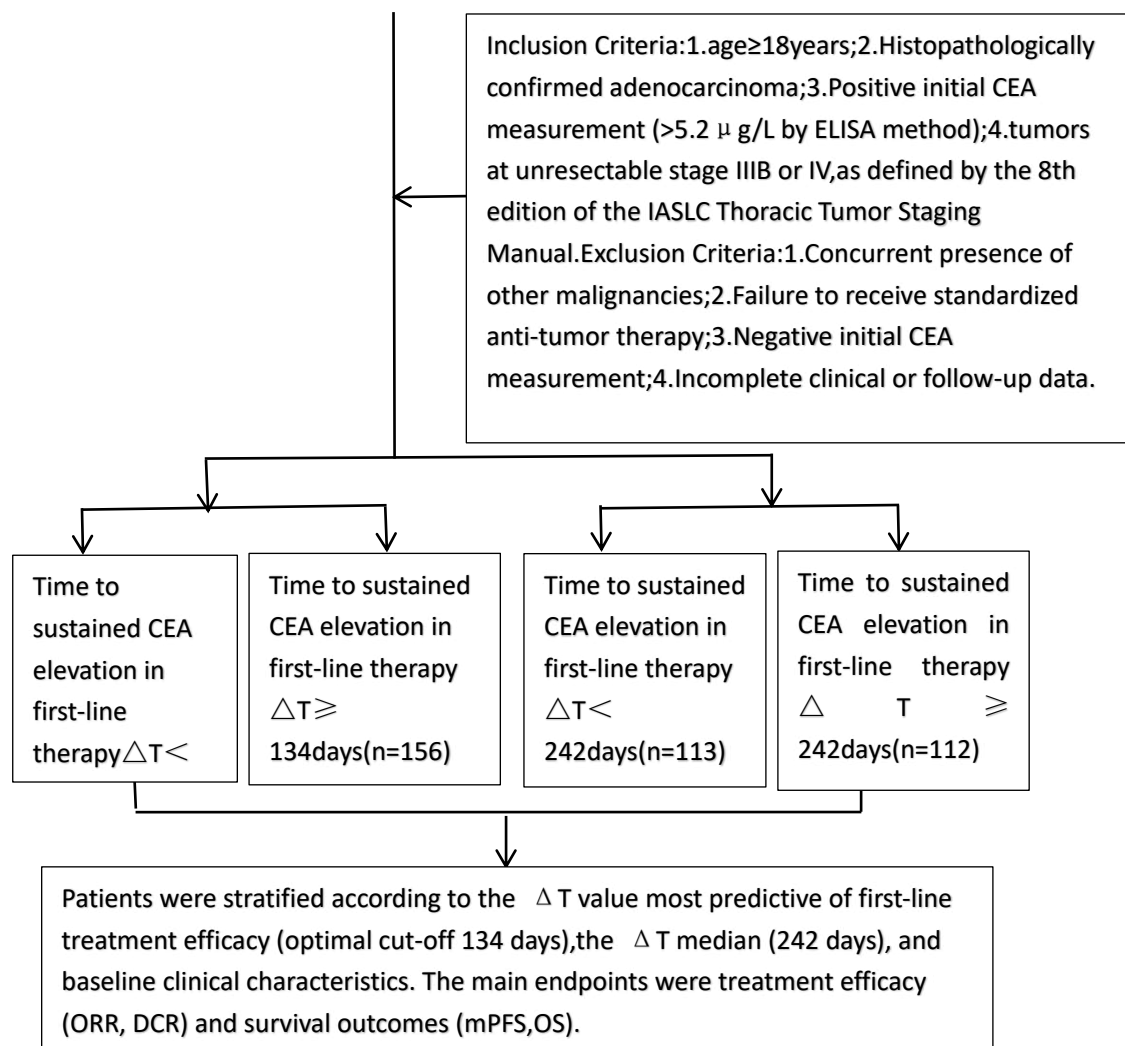


Figure 1 Flowchart of this study enrollment

Experimental methods

Blood sample collection and CEA measurement:

All patients had 5 mL of peripheral venous blood drawn in the early morning after an overnight fast. The samples were collected into serum separation coagulation tubes, leave it alone for 30 minutes, and then centrifuged at 3,000 r/min for 10 minutes; the supernatant serum was assayed immediately. Serum CEA concentrations were determined by an electrochemiluminescence immunoassay (ECLIA) on a Roche Cobas 8000 e801 module (Roche Diagnostics, Mannheim, Germany), with a validated analytical linearity of 0.5–1,000 ng/mL. Follow-up blood sampling was performed every 4 weeks (± 3 days) from the initiation of first-line therapy until radiologically confirmed disease progression or death.

Definition and grouping method of ΔT value:

We defined the interval from first-line therapy start to the time of sustained elevation in serum CEA as the ΔT value for each enrolled lung adenocarcinoma patient. Based on the median ΔT observed in the study population (ΔT median=242 days) and the efficacy-related optimal cut-off value determined by ROC curve analysis (ΔT cut-off=134 days), patients were dichotomized separately according to these two thresholds.

Efficacy assessment

Tumor response was first assessed one month after the start of first-line therapy. For patients with stable or an Effective response, contrast-enhanced CT and other imaging examinations were subsequently performed every two months. The efficacy evaluation was conducted using the Response Evaluation Criteria in Solid Tumors (RECIST), and categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The objective response rate (ORR) was calculated as $(CR+PR)/(CR+PR+SD+PD) \times 100\%$, whereas the disease control rate (DCR) was defined as $(CR+PR+SD)/(CR+PR+SD+PD) \times 100\%$.

Follow-up and survival analysis

Follow-up in this study was conducted through a combination of outpatient visits and telephone contacts. The last follow-up date was 1 June 2025. Overall survival (OS) was defined as the time from initiation of first-line therapy to death from any cause or to the last follow-up. PFS was defined as the time from the start of first-line therapy to the first documented tumor progression on imaging or death from any reasons, whichever occurred first.

statistical analysis

This study employed IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA) for all statistical analysis. Categorical variables such as baseline clinical features and treatment responses were compared using the χ^2 test. The survival analysis employed the Kaplan-Meier method and Cox proportional hazards model; graphical plots were produced with Prism software. The statistical significance threshold is set at $P < 0.05$. Pearson correlation coefficient was applied to explore the association between ΔT and PFS/OS. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal ΔT cut-off that best discriminated treatment efficacy in lung adenocarcinoma.

Results

Clinical features of participating patients

The median age of the 225 enrolled patients was 67years.Using the two ΔT thresholds (242 days and 134 days),we compared baseline characteristics between subgroups,including sex,median age at diagnosis,smoking history, and Physical Status (PS),driver mutation status,clinical stage,presence of brain, liver or other distant metastases,and first-line treatment modality.When patients were grouped by ΔT median value (243days) ,sex and smoking history showed statistically significant differences;when grouped by either ΔT median value (243days) or ΔT cut-off value(134days),mutation status and treatment modality also differed significantly.Details of the intergroup comparisons of clinical features are presented in **Table 1**.

Table1 Comparision clinical features between groups with varying durations since first-line treatment and sustained CEA elevation (median 242 days versus efficacy-related optimal ΔCt value group of 134 days).

Variables	Total (n=225)	Time from first-line therapy to sustained CEA rise (<134d) (n=69)	Time from first-line therapy to sustained CEA rise ($\geq$ 134d) (n=156)	<i>P</i>	Time from first-line therapy to sustained CEA rise (<242d) (n=112)	Time from first-line therapy to sustained CEA rise ($\geq$ 242d) (n=113)	<i>P</i>
Gender, n (%)				0.105			0.012
Female	93 (41.33)	23 (33.33)	70 (44.87)		37 (33.04)	56 (49.56)	
Male	132 (58.67)	46 (66.67)	86 (55.13)		75 (66.96)	57 (50.44)	
Smoking history, n (%)				0.295			0.024
No	173 (76.89)	50 (72.46)	123 (78.85)		79 (70.54)	94 (83.19)	
Yes	52 (23.11)	19 (27.54)	33 (21.15)		33 (29.46)	19 (16.81)	
Performance status, n (%)				0.798			0.316
0-1	207 (92.00)	63 (91.30)	144 (92.31)		101 (90.18)	106 (93.81)	
>1	18 (8.00)	6 (8.70)	12 (7.69)		11 (9.82)	7 (6.19)	
Gene mutation status, n (%)				<0.001			0.002
Mutation-negative	58 (25.78)	28 (40.58)	30 (19.23)		42 (37.50)	21 (18.58)	
EGFR mutation and other actionable alterations	167 (74.22)	41 (59.42)	126 (80.77)		70 (62.50)	92 (81.42)	
Median age at diagnosis (years) ($\geq$ 65=1, <65=0), n (%)				0.950			0.448

Variables	Total (n=225)	Time from first-line therapy to sustained CEA rise (<134d) (n=69)	Time from first-line therapy to sustained CEA rise (≥134d) (n=156)	P	Time from first-line therapy to sustained CEA rise (<242d) (n=112)	Time from first-line therapy to sustained CEA rise (≥242d) (n=113)	P
<65	133 (59.11)	41 (59.42)	92 (58.97)		69 (61.61)	64 (56.64)	
≥65	92 (40.89)	28 (40.58)	64 (41.03)		43 (38.39)	49 (43.36)	
Clinical stage, n (%)				0.667			0.200
III	17 (7.56)	6 (8.70)	11 (7.05)		11 (9.82)	6 (5.31)	
IV	208 (92.44)	63 (91.30)	145 (92.95)		101 (90.18)	107 (94.69)	
Liver metastases, n (%)				0.360			0.881
No	188 (83.56)	60 (86.96)	128 (82.05)		94 (83.93)	94 (83.19)	
Yes	37 (16.44)	9 (13.04)	28 (17.95)		18 (16.07)	19 (16.81)	
Adenel metastases, n (%)				0.932			0.676
No	195 (86.67)	60 (86.96)	135 (86.54)		96 (85.71)	99 (87.61)	
Yes	30 (13.33)	9 (13.04)	21 (13.46)		16 (14.29)	14 (12.39)	
Brain metastases, n (%)				0.846			0.744
No	132 (58.93)	40 (57.97)	92 (59.35)		65 (58.04)	68 (60.18)	
Yes	92 (41.07)	29 (42.03)	63 (40.65)		47 (41.96)	45 (39.82)	
Bone metastases, n (%)				0.959			0.831
No	131 (58.22)	40 (57.97)	91 (58.33)		66 (58.93)	65 (57.52)	
Yes	94 (41.78)	29 (42.03)	65 (41.67)		46 (41.07)	48 (42.48)	
Treatment modality, n (%)				<0.001			<0.001
non-targeted therapy	80 (35.56)	36 (52.17)	44 (28.21)		54 (48.21)	26 (23.01)	
targeted therapy	145 (64.44)	33 (47.83)	112 (71.79)		58 (51.79)	87 (76.99)	

Therapeutic evaluation

Among 225 lung adenocarcinoma patients in the study, 103 achieved objective response (ORR) with an overall response rate of 45.8% (95% CI: 39.3 – 52.4%), while 197 patients demonstrated disease control (DCR) at 87.6% (95% CI: 82.7 – 91.3%). Analysis of baseline characteristics and treatment

efficacy revealed significant correlations: ORR was notably associated with physical status (PS 0 – 1 vs $\geq$ PS 2: 47.8% vs 22.2%, $P=0.036$), driver gene mutation status (positive vs negative: 54.9% vs 22.2%, $P<0.001$), and treatment modality (targeted vs non-targeted: 58.6% vs 22.5%, $P<0.001$). In contrast, gender, age, smoking history, clinical stage, and distant metastasis sites showed no significant impact on ORR (all $P>0.05$). DCR showed significant associations with gender (93.5% vs 83.3%, $P=0.022$), driver gene mutations (91.4% vs 77.8%, $P=0.006$), and targeted therapy (91.7% vs 80.0%, $P=0.011$); The remaining variables showed no statistically significant differences.

The ROC curve identified the optimal cut-off of 134 days: the ≥ 134 -day group showed significantly higher overall response rate (ORR) than the <134 -day group (58.9% vs 15.9%, $P<0.001$), with significantly better disease control rate (DCR) (98.7% vs 62.3%, $P<0.001$). When stratified by median progression-free survival (ΔT) of 242 days, the results remained consistent: the ≥ 242 -day group demonstrated significantly higher ORR (60.2% vs 31.3%, $P<0.001$) and significantly better DCR (99.1% vs 75.9%, $P<0.001$).

Overall, the good physical condition (PS 0 – 1) patients, positive genetic mutations, and those receiving targeted therapy demonstrated superior overall response rates (ORR) and disease control rates (DCR). Gender showed significant difference in DCR but no significant difference in ORR. Other clinical features (age, disease stage, and metastatic sites) were not significantly associated with ORR or DCR. Notably, patients with longer CEA elevation duration from first-line treatment initiation (regardless of group assignment using ΔT median value or ΔT cut-off value) exhibited significantly higher ORR and DCR, suggesting that the temporal dimension of CEA dynamics is closely linked to short-term therapeutic efficacy. The response evaluation results for each clinical feature group are presented in Table 2.

Table 2 Comparison table of efficacy between groups, categorized by clinical characteristics and duration of first-line treatment with sustained CEA elevation (median 242 days versus the efficacy-related cutoff of 134 days).

Variables	N	ORR	Statistic	P	DCR	Statistic	P
Overall rate	225	103			197		
Gender, n(%)			$\chi^2=2.17$	0.140		$\chi^2=5.23$	0.022
Female	93(41.33)	48(46.60)			87(44.16)		
Male	132(58.67)	55(53.40)			110(55.84)		
Smoking history, n(%)			$\chi^2=2.33$	0.127		$\chi^2=0.54$	0.464
No	173(76.89)	84(81.55)			153(77.66)		
Yes	52(23.11)	19(18.45)			44(22.34)		

Variables	N	ORR	Statistic	P	DCR	Statistic	P
Performance status,n(%)			$\chi^2=4.37$	0.036		$\chi^2=0.00$	1.000
0-1	207(92.00)	99(96.12)			181(91.88)		
>1	18(8.00)	4(3.88)			16(8.12)		
Gene mutation status,n(%)			$\chi^2=19.56$	<.001		$\chi^2=7.68$	0.006
Mutation-negative	63(28.00)	14(13.59)			49(24.87)		
EGFR mutation and other actionable alterations	162(72.00)	89(86.41)			148(75.13)		
Median age at diagnosis (years), n(%)			$\chi^2=1.25$	0.263		$\chi^2=0.05$	0.821
<65	133(59.11)	65(63.11)			117(59.39)		
≥65	92(40.89)	38(36.89)			80(40.61)		
Clinical stage,n(%)			$\chi^2=0.16$	0.692		$\chi^2=1.52$	0.217
III	17(7.56)	7(6.80)			17(8.63)		
IV	208(92.44)	96(93.20)			180(91.37)		
Liver metastases, n(%)			$\chi^2=2.02$	0.155		$\chi^2=0.24$	0.626
No	188(83.56)	90(87.38)			166(84.26)		
Yes	37(16.44)	13(12.62)			31(15.74)		
Adenel metastases, n(%)			$\chi^2=0.08$	0.773		$\chi^2=1.10$	0.294
No	195(86.67)	90(87.38)			173(87.82)		
Yes	30(13.33)	13(12.62)			24(12.18)		
Brain metastases,n(%)			$\chi^2=0.33$	0.565		$\chi^2=1.10$	0.295
No	133(59.11)	63(61.17)			119(60.41)		
Yes	92(40.89)	40(38.83)			78(39.59)		
Bone metastases,n(%)			$\chi^2=0.68$	0.411		$\chi^2=0.02$	0.902
No	131(58.22)	63(61.17)			115(58.38)		

Variables	N	ORR	Statistic	P	DCR	Statistic	P
Yes	94(41.78)	40(38.83)			82(41.62)		
Treatment modality, n(%)			$\chi^2=27.10$	<.001		$\chi^2=6.50$	0.011
non-targeted therapy	80(35.56)	18(17.48)			64(32.49)		
targeted therapy	145(64.44)	85(82.52)			133(67.51)		
Time from first-line therapy to sustained CEA rise			$\chi^2=35.69$	<.001		$\chi^2=58.17$	<.001
<134d	69(30.67)	11(10.68)			43(21.83)		
≥134d	156(69.33)	92(89.32)			154(78.17)		
Time from first-line therapy to sustained CEA rise			$\chi^2=18.96$	<.001		$\chi^2=27.84$	<.001
<242d	112(49.78)	35(33.98)			85(43.15)		
≥242d	113(50.22)	68(66.02)			112(56.85)		

Data are presented as n [%].CEA:carcinoembryonic antigen;EGFR:epidermal growth factor receptor.

Survival Prognosis Analysis

The gender subgroup analysis revealed that female patients demonstrated significantly better median progression-free survival (PFS) than males (12.0 months vs 9.0 months, $P=0.025$), whereas median OS exhibited only a nonsignificant trend toward improvement (29.0 months vs.22.0 months, $P = 0.11$). This suggests that women may exhibit independent protective effects only in terms of short-term disease control, with long-term survival benefits requiring validation through large-sample multivariate analysis. With respect to liver metastasis, patients without liver involvement achieved significantly longer median PFS (12.0 months vs.11.0 months, $P=0.010$) and median OS (27.0 months vs. 22.0 months, $P=0.007$) than those with liver metastasis, with a consistent direction of effect, indicating that liver metastasis is a strong adverse prognostic indicator in lung adenocarcinoma and may serve as an important parameter for risk stratification. Kaplan – Meier curves for PFS and OS stratified by sex and liver metastasis status are shown in Figure 2.

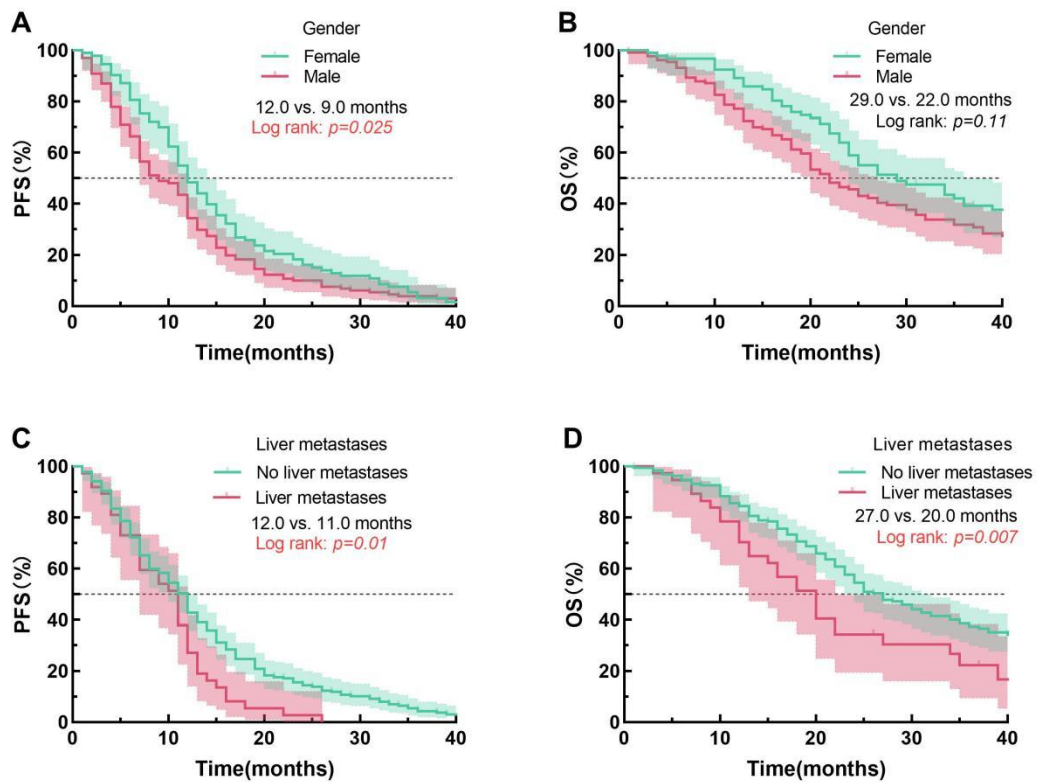


Figure 2 Survival analysis curves of PFS and OS by gender and liver metastasis.mPFS:median progression-free survival;OS:overall survival.

To clarify the temporal correlation between carcinoembryonic antigen (CEA) dynamics and prognosis, this study conducted stratified survival analyses using the receiver operating characteristic (ROC) cutoff value of 134 days and the median ΔT of 242 days. Results indicated that the group with $\Delta T \geq 134$ days exhibited significantly better median progression-free survival (PFS) (14.0 vs. 4.0 months, $P < 0.001$) and extended median overall survival (OS) (32.0 vs. 14.0 months, $P < 0.001$) compared to the group with $\Delta T < 134$ days. For the group with $\Delta T \geq 242$ days, median PFS reached 16.0 months versus 6.0 months in the group with $\Delta T < 242$ days ($P < 0.001$), with median OS of 35.0 and 18.0 months respectively ($P < 0.001$). Patients with a ≥ 134 -day interval from the first-line treatment start to sustained CEA elevation showed significantly reduced risks of progression and mortality, suggesting that a longer pre-trigger buffer period for CEA elevation is associated with a better prognosis. Consistent results were obtained through stratification using both median ΔT and cutoff ΔT values, further confirming the clinical value of the delayed onset of sustained CEA elevation as a robust prognostic stratification indicator. The PFS and OS survival curve analyses based on the time interval from the initiation of first-line treatment to sustained CEA elevation (grouped by median ΔT or cutoff ΔT) are depicted in Figure 3.

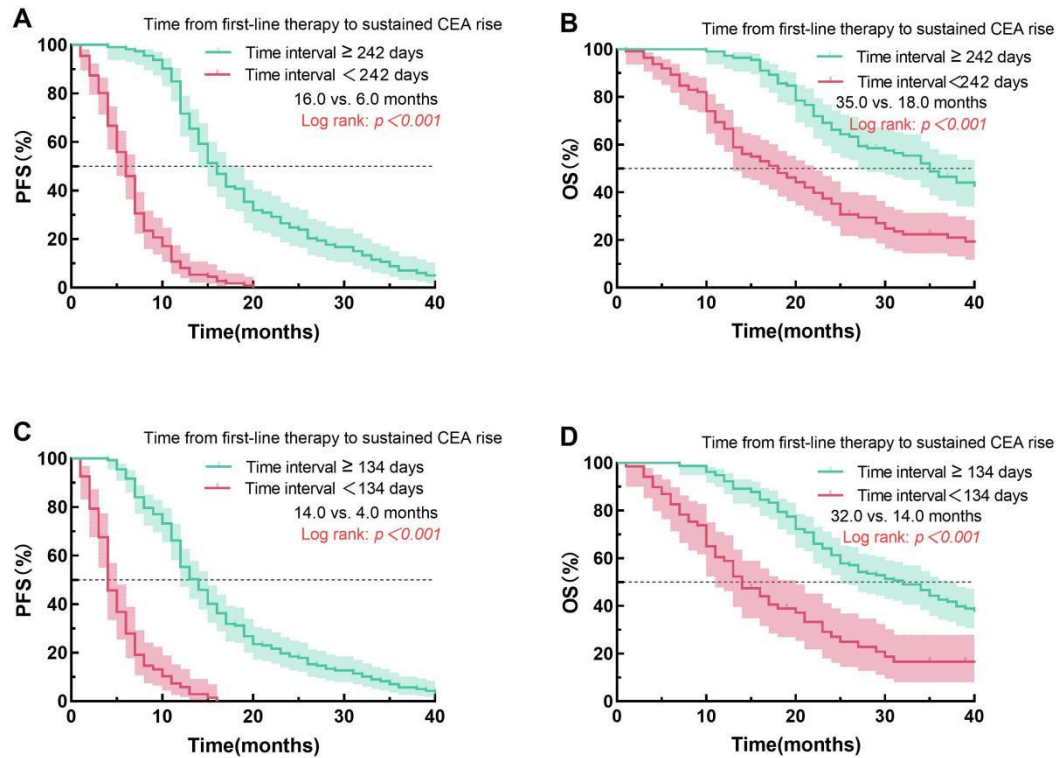


Figure 3 Plot survival analysis curves for PFS and OS based on the time from line-of-care initiation to sustained CEA elevation (grouped according to median 242 days and the efficacy-related cutoff value of 134 days).mPFS:median progression-free survival;OS:overall survival;CEA:carcinoembryonic antigen.

Targeted therapy had significantly prolonged survival than those treated with non-targeted regimens (PFS:12.0 vs.7.5 months, $P < 0.001$;OS:30.0 vs.20.0 months, $P=0.01$).Patients harboring EGFR mutations or other actionable alterations also achieved a longer PFS than those without detectable driver mutations (12.0 vs. 7.0 months, $P < 0.001$),whereas the difference in OS was not statistically significant (20.0vs.27.0 months, $P=0.21$). Absence of bone metastasis was associated with superior outcomes,with both PFS and OS exceeding those of patients with bone involvement (PFS:12.0vs10.5 months, $P=0.02$;OS:30.0vs22.0 months, $P=0.019$).With respect to smoking history,no evident difference in PFS was observed between ever-smokers and never-smokers ($P=0.89$),but OS differed significantly ($P=0.037$):the median OS of patients with a smoking history (27.0 months) was unexpectedly longer than that of patients without a smoking history (20.0 months),suggesting that treatment patterns,mutation spectrum,or other confounders may have influenced this result and warrant further multivariable adjustment.Age,performance status,disease stage,and the presence of adrenal or brain metastases were not significantly associated with either PFS or OS (all $P > 0.05$).Survival analyses for other clinical characteristics are summarized in Table 3.

Table 3 Results of survival analysis of other clinical features.

Variables	mPFS	Log Rank <i>p</i>	OS	Log Rank <i>p</i>
Gender,n(%)		0.025		0.11
Female	12.0		29.0	
Male	9.0		22.0	
Smoking history,n(%)		0.89		0.037
No	12.0		20.0	
Yes	9.0		27.0	
Performance status,n(%)		0.83		0.85
0-1	11.0		27.0	
> 1	8.5		25.0	
Gene mutation status,n(%)		<0.001		0.21
Mutation-negative	7.0		27.0	
EGFR mutation and other actionable alterations	12.0		20.0	
Median age at diagnosis (years),n(%)				
<65	10.5	0.68	25.0	0.54
≥65	12.0		25.0	
Clinical stage,n(%)		0.69		0.68
III	9.0		25.0	
IV	11.0		25.0	
Liver metastases,n(%)		0.01		0.007
No	12.0		27.0	
Yes	11.0		22.0	
Adenel metastases,n(%)		0.61		0.15
No	11.0		25.0	
Yes	11.5		21.0	
Brain metastases,n(%)		0.22		0.07
No	11.0		22.0	
Yes	12.0		30.0	
Bone metastases,n(%)		0.02		0.019

Variables	mPFS	Log Rank <i>p</i>	OS	Log Rank <i>p</i>
No	12.0		30.0	
Yes	10.5		22.0	
Treatment modality,n(%)		<0.001		0.01
non-targeted therapy	7.5		20.0	
targeted therapy	12.0		30.0	
Time from first-line therapy to sustained CEA rise		<0.001		<0.001
<134d	4.0		14.0	
≥134d	14.0		32.0	
Time from first-line therapy to sustained CEA rise		<0.001		<0.001
<242d	6.0		18.0	
≥242d	16.0		35.0	

Table3 Detailed survival analyses of PFS and OS for all clinical characteristics,including the time to sustained CEA elevation (median $\Delta T=242$ days,with an optimal cut-off of 134 days for efficacy-related ΔT) in first-line treatment groups.Data are presented as n[%].CEA:carcinoembryonic antigen;EGFR:epidermal growth factor receptor;mPFS: median progression-free survival;OS:overall survival.

Multivariate analysis

Clinical characteristics together with the interval from initiation of first-line therapy to sustained elevation of CEA (ΔT ;using either the median value of 242 days or the ROC-derived cut-off of 134 days) were first entered into univariable analyses.Variables with $P<0.20$ in univariable testing were subsequently included in the multivariable analysis.This model identified sex, liver metastasis status,and ΔT -based grouping (by either the median value or the 134-day cut-off) as independent factors significantly associated with PFS, whereas the remaining covariates (smoking status,mutation status,bone metastasis,and treatment modality) did not reach statistical significance.

These findings indicate that female sex,as the only variable solely affecting PFS,was associated with a lower risk of disease progression,which is consistent with the direction of the Kaplan - Meier curves.Liver metastasis emerged as a common adverse factor for both PFS and OS (adjustedHR ≈ 0.78 ,95% CI $\approx 0.64 - 0.95$, $P=0.011$);in other words,patients with liver

involvement had an approximately $1/0.78 \approx 1.28$ -fold higher risk of progression than those without liver metastasis. Moreover, the interval from first-line therapy start to sustained CEA elevation can be regarded as a dynamic prognostic marker: a persistently rising CEA occurring earlier than 134 or 242 days signals a higher risk of progression and may warrant closer imaging and/or biomarker surveillance, as well as earlier consideration of treatment modification.

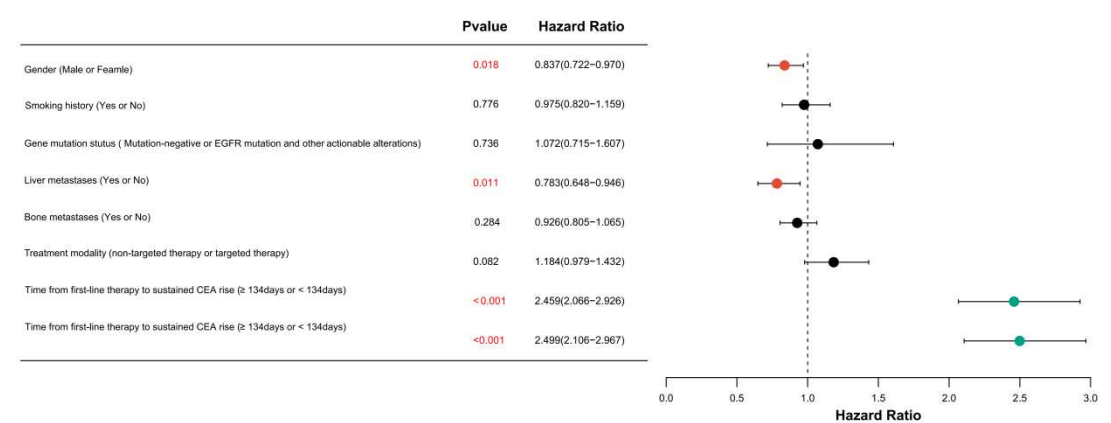


Figure 4 The multivariate Cox regression analysis of PFS evaluated associations between multiple stratification factors (including median ΔT groups (<242 days vs. ≥ 242 days), ΔT cutoff groups (<134 days vs. ≥ 134 days), sex, smoking history (present or absent), genetic mutation status, brain metastases (present or absent), liver metastases (present or absent), physical status score (≥ 1 vs. $0-1$), treatment modality, and median age at diagnosis (≥ 65 vs. <65 years) with progression-free survival (PFS). A hazard ratio (HR) >1 indicated favorable PFS, while <1 indicated unfavorable PFS. ΔT : time interval from first-line therapy start to sustained elevation of serum CEA.

Clinical characteristics and the time from first-line therapy start to persistent elevation of carcinoembryonic antigen (CEA) (grouped based on the median value of 242 days and the optimal efficacy-related cut-off value of 134 days) were included as variables in the univariate analysis. Variables with $P < 0.2$ in the univariate analysis were subsequently entered into the multivariate analysis. The multivariate analysis indicated that the independent factors associated with patients' overall survival (OS) were: the presence or absence of liver metastasis, and the time to persistent CEA elevation (using two cut-off values of 134 days and 242 days). Other variables (gender, smoking history, gene mutation status, bone and brain metastasis, and treatment modality) did not reach statistical significance. The results demonstrated that the risk of death in patients with liver metastasis was approximately 39% higher than that in patients without liver metastasis. The time from first-line treatment to persistent CEA elevation can serve as a dynamic prognostic stratification tool during follow-up. If persistent CEA elevation occurs before 134 days or 242 days, it indicates a high risk of death. It is recommended to shorten the monitoring interval for tumor markers or imaging examinations (imaging/tumor markers) during treatment and proactively evaluate strategies for adjusting treatment regimens. Additionally, the adverse impact of liver metastasis on OS

exists independently,so patients should be included in a more aggressive comprehensive management and monitoring pathway at the initiation of treatment.

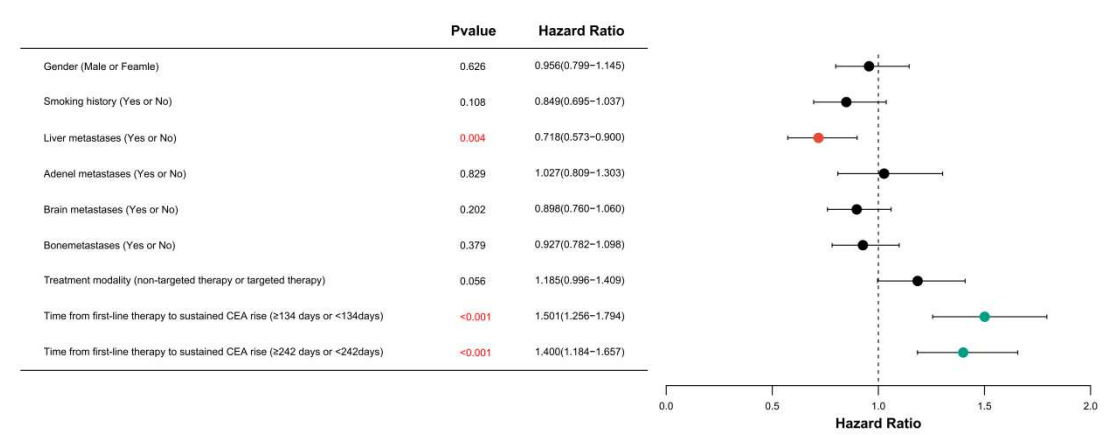


Figure 5 The multivariate Cox regression analysis of OS evaluated associations between multiple stratification factors (including median ΔT groups (<242 days or ≥ 242 days), ΔT cutoff groups (<134 days or ≥ 134 days),sex,smoking history (present or absent),genetic mutation status,brain metastasis (present or absent),liver metastasis (present or absent),physical status score (>1 or $0-1$),treatment modality,median age at the time of diagnosis (≥ 65 years or <65 years),and progression-free survival (PFS).A hazard ratio (HR) >1 indicated favorable PFS,while <1 indicated unfavorable PFS. ΔT :time interval from initiation of first-line therapy to sustained elevation of serum carcinoembryonic antigen (CEA).

Discussion

This study systematically evaluated the association between the time from first-line treatment to the sustained elevation of carcinoembryonic antigen (CEA) and the outcomes of patients with lung adenocarcinoma in a real-world population.The results showed that:whether stratified by the efficacy-related optimal cut-off value of ΔT (134 days) or the median value of ΔT (242 days), the later the occurrence of sustained CEA elevation,the longer progression-free survival (PFS) and overall survival (OS) of patients.This result remained independent in the multivariate model and,together with liver metastasis and gender (females had better outcomes),constituted stable prognostic indicators.This "sustained change time-threshold" framework provides a new evidence base for the dynamic application of CEA.

Previous studies on CEA have mostly focused on the correlation between its baseline level,the magnitude of increase/decrease during treatment or its dynamics,and patient survival.Multiple cohort studies and systematic reviews have indicated that higher serum CEA levels or insufficient CEA reduction during treatment are associated with shorter progression-free survival (PFS) and overall survival (OS).This finding is consistent across treatment modalities, including chemotherapy,targeted and immunotherapy⁽¹¹⁻¹³⁾.Even in the maintenance treatment phase,dynamic changes in CEA can serve as an early

warning signal for disease progression,preceding radiological evidence⁽¹⁴⁾.The innovation of this study lies in shifting the focus from merely observing CEA absolute values or the magnitude of its changes.Instead,it models the "duration from first-line therapy start to the onset of sustained CEA elevation"as a temporal indicator,and validates the robustness of this indicator using two independent thresholds (134 days and 242 days).This approach incorporates the temporal dimension of molecular and biological progression into the application of CEA.This aligns with the growing emphasis on the value of "dynamic biomarkers" in the follow-up of non-small cell lung cancer (NSCLC) in recent years,Including tumor marker sequence monitoring in the context of immunotherapy⁽¹⁵⁾.

CEA is a glycosylphosphatidylinositol (GPI)-anchored glycoprotein associated with cell adhesion.It participates in selectin-mediated adhesion of tumor cells and the metastatic cascade,and its elevation usually indicates increased tumor burden,enhanced proliferation and invasive activity,as well as clonal evolution under therapeutic pressure^(16,17).Thus,a later occurrence of sustained CEA elevation may reflect three aspects:Deeper or more durable tumor control achieved by initial treatment⁽¹⁸⁾;Significant delay in the emergence and expansion of therapy-resistant clones⁽¹⁹⁾;Delayed occurrence of key molecular events in the actionable EGFR mutation pathway,such as bypass activation or secondary mutations,which in turn retards the sustained increase in serum markers.This is also logically supported by clinical guidelines and translational studies⁽⁹⁾.

This study identified liver metastasis as an independent adverse factor for both progression-free survival (PFS) and overall survival (OS),which is consistent with previous evidence.A number of reports have shown that NSCLC patients presenting with liver metastasis exhibit significantly shortened survival⁽²⁰⁾.Additionally,the liver's immune-tolerant microenvironment (where T cells are unable to respond to immunosuppressive signals) may limit the efficacy of systemic therapy,leading to the formation of a high-risk subgroup⁽²¹⁻²³⁾.Regarding gender,our study observed longer PFS in female patients.Large-sample studies and reviews have also indicated that female patients have a lower overall risk of death,a higher prevalence of EGFR mutations,and more significant benefits in certain treatment settings—findings that align with our directional interpretation of gender differences⁽²⁴⁻²⁶⁾.

This study assigns clinical practical value to the 134-day and 242-day time cutoffs—marking the onset of sustained CEA elevation after first-line treatment—as follow-up milestones.If sustained CEA elevation occurs before these cutoffs,the interval for imaging re-evaluation or tumor marker re-testing should be shortened in efficacy assessment.Additionally,the evaluation of treatment strategy adjustments (e.g.drug resistance gene testing,sequential or combination therapy,and clinical trials) should be advanced to shift the decision-making window earlier,prior to radiologically confirmed progression.This strategy aligns with the direction of individualized monitoring and stratified

management emphasized in clinical guidelines⁽⁹⁾. For patients with liver metastasis, an enhanced monitoring pathway can be integrated at the initiation of treatment. For cases with both liver metastasis and early sustained CEA elevation after treatment, such patients should be regarded as a dual high-risk group, and discussions on treatment escalation or multidisciplinary combined treatment strategies (e.g. systemic therapy combined with local therapy) should be advanced^(27,28). In subsequent prospective trials, the time from first-line therapy start to the onset of sustained CEA elevation can be incorporated as a component of composite surrogate endpoints or as a stratification factor. This incorporation enables earlier detection of efficacy differences, optimization of sample size and follow-up resource allocation, while reporting this indicator in parallel with traditional median PFS and OS.

Univariate and multivariate analyses revealed that gene mutation status and targeted therapy were associated with better progression-free survival (PFS); but it is not always independent in the multivariate model. This inconsistency may be attributed to treatment selection, mutation profile structure, and confounding factors. The NCCN Guidelines Version 2025 also emphasize that individualized first-line treatment based on gene mutation status significantly impacts survival outcomes, suggesting that stratification or interaction analyses by pathways such as EGFR, ALK, ROS1, MET, and RET are necessary during external validation to reduce confounding bias⁽²⁹⁾.

The innovations and strengths of this study are as follows: It used both the efficacy-related optimal cut-off value of ΔT (134 days) and the median value of ΔT (242 days) for stratification. The consistency in the direction and significance of the conclusions demonstrates the robustness and extrapolation potential of this "time-threshold" model. In the multivariate model, after adjusting for gender, systemic metastasis status, treatment modality, and gene mutation status, the time to sustained CEA elevation remained an independent influencing factor, which enhances the credibility of causal interpretation. The study builds on the existing framework that CEA dynamics can early indicate disease progression, and further introduces the "time to sustained elevation" as a quantifiable and actionable clinical milestone⁽³⁰⁾.

As a retrospective analysis conducted at a single center, this study is subject to several limitations: Selection bias and information bias may exist. The determination of sustained CEA elevation is affected by sampling frequency and platform differences, requiring further validation through prospective studies with standardized protocols. Owing to limited sample size, sufficient stratification analyses for the immunotherapy subgroup and different generations of TKIs were not conducted. Although two thresholds were used to verify robustness, the optimal threshold still needs revalidation in other cohorts (e.g. multicenter cohorts). Additionally, exploration of risk-based dynamic thresholds combined with ctDNA or multiple tumor markers for assessment is warranted. The applicability of the findings is limited to patients with negative or low baseline CEA secretion. Combining CEA with other tumor markers

(e.g. CYFRA21-1, NSE, CA-125) or ctDNA is required to improve coverage and accuracy^(31,32).

Conclusions

The interval from first-line therapy initiation to the first sustained CEA rise is an independent predictor of both progression-free survival (PFS) and overall survival (OS) in patients with lung adenocarcinoma. Multivariable modelling showed that a longer ΔT (≥ 134 d or ≥ 242 d) consistently translated into a lower hazard of progression and death; liver metastases were a significant negative determinant, whereas female sex conferred a survival advantage. We recommend integrating the temporal dynamics of CEA into routine risk-stratification and clinical decision-making algorithms. Prospective, multicentre trials that incorporate molecular resistance profiles and quantitative imaging biomarkers are warranted to refine the applicability and therapeutic implications of this metric.

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Declarations

Data availability statement: The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

Ethics statement: The studies involving humans were approved by the institutional ethics board of the Affiliated Hospital of Guangdong Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because the institutional ethics board of the Affiliated Hospital of Guangdong Medical University approved this research (Approval No. PJKT2024-070), and

individual permission for this retrospective analysis was waived.

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