



Clinical value of peripheral blood circulating tumor DNA in predicting the efficacy of immunotherapy for non-small cell lung cancer

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Background: The high expression of programmed cell death 1-ligand 1 (PD-L1) is a valid biological indicator of the therapeutic benefit of pembrolizumab in non-small cell lung cancer (NSCLC) patients. However, the response rate of NSCLC patients with positive PD-L1 expression to anti-PD-1/PD-L1 therapy is still low.

Methods: From January 2019 to January 2021, a retrospective study was conducted at the Fujian Medical University Xiamen Humanity Hospital. In total, 143 patients with advanced NSCLC were treated with immune checkpoint inhibitors, and the efficacy of the treatment [complete remission (CR), partial remission (PR), stable disease (SD), or progression disease (PD)] was evaluated. Patients with a CR and PR were defined as an objective response (OR) group (n=67), and the other patients were defined as a control group (n=76). The differences in the circulating tumor DNA (ctDNA) and clinical features between the 2 groups were compared, and the receiver operating characteristic (ROC) curve was used to analyze the value of ctDNA in predicting the failure to achieve an OR after immunotherapy in patients with NSCLC, and a multivariate regression analysis was conducted to analyze the factors affecting the OR after immunotherapy in NSCLC patients. R4.0.3 statistical software (Ross Ihaka Robert Gentleman, New Zealand) was used to establish and verify the prediction model of OR after immunotherapy in NSCLC patients.

Results: CtDNA was valuable in predicting the non-OR of patients with NSCLC after immunotherapy, and the area under the curve was 0.750 [95% CI: 0.673–0.828, P<0.001]. CtDNA <3.72 ng/μL can be used to predict which NSCLC patients will achieve objective remission after immunotherapy (P<0.001). Based on the regression model, a prediction model was established. The data set was randomly divided into the training set and validation set. The sample size of the training set was 72 and that of the validation set was 71. The area under the ROC curve of the training set was 0.850 (95% CI: 0.760–0.940), and that of the validation set was 0.732 (95% CI: 0.616–0.847).

Conclusions: CtDNA was valuable in predicting the efficacy of immunotherapy in NSCLC patients.

Keywords: Circulating tumor DNA (ctDNA); non-small cell lung cancer (NSCLC); immunotherapy; relapse

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Introduction

Lung cancer is one of the most common malignant tumors worldwide, second only to breast cancer (1). Nearly 85% of lung cancer patients have non-small cell lung cancer (NSCLC), among which adenocarcinoma and squamous cell carcinoma are the most common subtypes (2-4). The most common epidemiologically pathogenic factor of lung cancer is smoking (5,6). In the past 20 years, the emergence of multiple targeted therapies and the effective application of immunotherapy in some patients with advanced NSCLC have brought hope to the field of lung cancer treatment (7-9).

Immune checkpoint inhibitors (ICIs) produce a lasting anti-tumor immune response by inhibiting the programmed death cell protein-1 (PD-1) and cytotoxic T lymphocyte-associated antigen 4 on the surface of the T cells. The Food and Drug Administration (FDA) has approved 4 ICIs for the treatment of NSCLC (i.e., nivolumab, pembrolizumab, atezolizumab, and durvalumab). In addition, a variety of immune combination regimens have been approved by the FDA for the treatment of patients with NSCLC. However, NSCLC patients treated with anti-PD-1/programmed cell death 1-ligand 1 (PD-L1) have a response rate of only 30% (10-12).

Because immunotherapy does not benefit most lung cancer patients and immunotherapy drugs are also very expensive, the identification of reliable markers that can accurately predict the efficacy of immunotherapy has important clinical value and significance (10-12). The

detection of PD-L1 expression in tumor tissue samples by immunohistochemistry has proven to be a relatively reliable biological indicator. However, in NSCLC patients with positive PD-L1 expression, the response rate to anti-PD-1/PD-L1 therapy is still only 15.6% to 48% (10-12). Additionally, some patients with negative PD-L1 expression can also benefit from anti-PD-1/PD-L1 immunotherapy. Thus, a single biological indicator, such as PD-L1, can no longer be used to predict treatment efficacy, as it cannot meet the urgent needs of precision immunotherapy in tumor patients.

Circulating tumor DNA (ctDNA) is a small piece of DNA derived from necrotic tumor cells in the peripheral blood, which is tumor-specific. The detection of ctDNA by second-generation gene sequencing provides doctors with biological information about tumors that can be used for early diagnosis and individualized treatment (13-16). Previous studies also showed that ctDNA may be helpful in predicting the immunotherapy efficacy in NSCLC patients (17-20). However, previous studies have not constructed predictive models based on the results. We present this article in accordance with the TRIPOD reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-379/rc>).

Methods

General information

A retrospective study was conducted at the Fujian Medical University Xiamen Humanity Hospital from January 2019 to January 2021. A total of 143 patients with advanced NSCLC were treated with ICIs, and the efficacy of treatment [complete remission (CR), partial remission (PR), stable disease (SD), or progression disease (PD)] was evaluated according to the efficacy evaluation criteria of solid tumors every two cycles. Patients with CR and PR were defined as an objective response (OR) group (n=67), and the other patients were defined as a control group (n=76) at the end of 4 cycles.

To be eligible for inclusion in this study, the patients had to meet the following inclusion criteria: (I) have a pathological diagnosis of stage III B or IV NSCLC, PD-L1 high expression; (II) be aged ≥ 18 years; and (III) have completed at least 4 cycles of anti-PD-1/PD-L1 treatment. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had a co-infection; (II) had NSCLC combined with other malignant tumors; (III) had

Highlight box

Key findings

- Circulating tumor DNA (ctDNA) levels are valuable in predicting the efficacy of immunotherapy in non-small cell lung cancer (NSCLC) patients.

What is known and what is new?

- A single biological indicator, such as programmed cell death 1-ligand 1 (PD-L1), can no longer be used to screen the patients that would benefit from immunotherapy, as it cannot meet the urgent needs of precision immunotherapy in tumor patients.
- CtDNA < 3.72 ng/ μ L can be used to predict which NSCLC patients will achieve objective remission after immunotherapy.

What is the implication, and what should change now?

- CtDNA levels are valuable in predicting the efficacy of immunotherapy in NSCLC patients, and the use of ctDNA to guide immunotherapy may help to improve the outcomes of NSCLC patients.

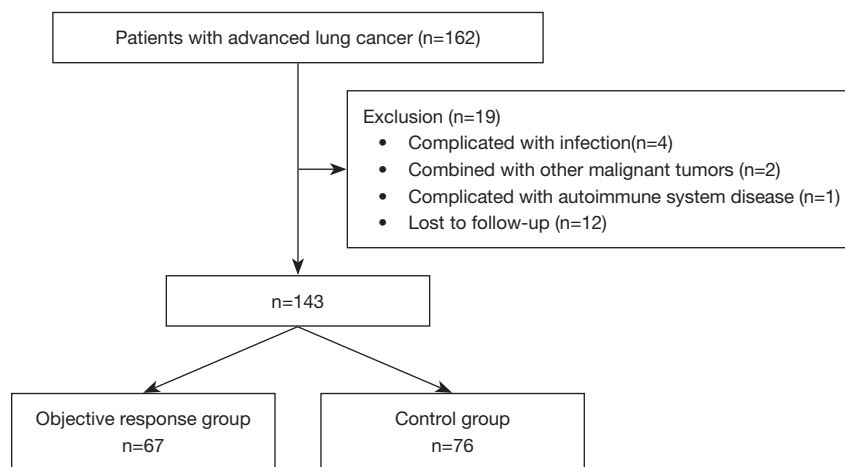


Figure 1 Inclusion flow chart for lung cancer patients.

an autoimmune system disease; (IV) had missing clinical data; and/or (V) were lost to follow-up.

This retrospective clinical study was conducted in accordance with the 2013 edition of the Declaration of Helsinki and was approved by the Ethics Committee of Fujian Medical University Xiamen Humanity Hospital (No. c20220048). The requirement for informed consent was waived. *Figure 1* provides a flow chart showing the process used to include the 143 patients with advanced lung cancer in this study.

Treatment methods

After the patients were admitted to the hospital, the relevant tests and examinations were performed. All the patients received Tislelizumab (200 mg/3 weeks, intravenously) for at least 4 cycles.

Efficacy evaluation

Before treatment, chest and abdomen electronic computed tomography, head magnetic resonance imaging, bone scanning, and other examinations were performed for the baseline evaluations. The efficacy of the immunotherapy was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST1.1). Efficacy was divided into CR, PR, SD, and PD. Patients with an efficacy evaluation of CR, PR, and SD continued to be treated according to the original plan, and patients with an efficacy evaluation of PD no longer received treatment. The OR rate was calculated

as follows: $OR = (CR + PR) / (CR + PR + SD + PD) \times 100\%$.

Detection of ctDNA

Before treatment, 5 mL of fasting elbow vein blood was extracted and plasma ctDNA levels were measured using a magnetic bead DNA extraction kit and fluorescence quantitative polymerase chain reaction. The kit was purchased from Beijing Qunxiao Keyuan Biotechnology Co., Ltd.

Statistical analysis

SPSS26.0 (IBM, Chicago, USA) was used to complete the data analysis of this study, and a P value <0.05 indicated that the difference was statistically significant. The measurement data of the 2 groups are expressed as the mean \pm standard deviation, and the differences between the 2 groups were analyzed by an independent samples *t*-test. The patient count data of the 2 groups are expressed as the number (percentage), and the chi-square test was used to analyze the differences between the 2 groups. The receiver operating characteristic (ROC) curve was used to analyze the value of the ctDNA in predicting the failure to achieve an OR after immunotherapy, and the optimal diagnostic threshold was calculated based on the weighted Youden index. A multivariate regression analysis was conducted to analyze the factors influencing the OR after immunotherapy in NSCLC patients. The R4.0.3 statistical software (Ross Ihaka Robert Gentleman, New Zealand) was used to

Table 1 Comparison of the clinical features of 2 groups

Category	Objective response group (n=67)	Control group (n=76)	t/ χ^2 value	P value
Age (years), mean \pm SD	58.82 \pm 11.76	59.38 \pm 12.61	0.274	0.785
Gender, n (%)			2.538	0.111
Male	49 (73.13)	46 (60.53)		
Female	18 (26.87)	30 (39.47)		
Body mass index (kg/m ²), mean \pm SD	25.45 \pm 2.43	25.39 \pm 2.65	0.118	0.906
History of smoking, n (%)	26 (38.81)	38 (50.00)	1.805	0.179
History of alcoholism, n (%)	21 (31.34)	36 (47.37)	3.815	0.051
Hypertension, n (%)	16 (23.88)	13 (17.11)	1.011	0.315
Diabetes, n (%)	7 (10.45)	11 (14.47)	0.525	0.469
Tumor site, n (%)			0.096	0.756
Left	37 (55.22)	40 (52.63)		
Right	30 (44.78)	36 (47.37)		
Type of pathology, n (%)			1.997	0.158
Adenocarcinoma	42 (62.69)	56 (73.68)		
Squamous cell carcinoma	25 (37.31)	20 (26.32)		
Tumor stage, n (%)			0.345	0.557
III stage	40 (59.70)	49 (64.47)		
IV stage	27 (40.30)	27 (35.53)		
Maximum diameter of primary tumor (cm), mean \pm SD	6.95 \pm 1.56	6.78 \pm 1.60	0.640	0.523
Pleural aggression, n (%)	14 (20.90)	18 (23.68)	0.159	0.690
Pleural effusion, n (%)	5 (7.46)	24 (31.58)	12.810	<0.001
Treatment, n (%)			11.699	0.001
Immunotherapy in combination with chemotherapy	43 (64.18)	27 (35.53)		
Immunotherapy	24 (35.82)	49 (64.47)		
CtDNA (ng/ μ L), mean \pm SD	2.96 \pm 1.13	4.16 \pm 1.24	6.010	<0.001
2-year mortality rate, n (%)	56 (83.58)	75 (98.68)	10.564	0.001

SD, standard deviation; ctDNA, circulating tumor DNA.

establish the prediction model. Kaplan-Meier was used to analyzed the survival between the two groups.

Results

Comparison of the clinical features of the 2 groups

Compared to the control group, the proportion of pleural effusion in the OR group was significantly decreased (7.46%

vs. 31.58%, $P<0.001$). Additionally, the proportion of patients treated with immunotherapy plus chemotherapy was significantly increased in the OR group compared to the control group (64.18% *vs.* 35.53%, $P=0.001$). CtDNA decreased significantly in the OR group compared to the control group (2.96 \pm 1.13 *vs.* 4.16 \pm 1.24 ng/ μ L, $P<0.001$). The 2-year mortality rate was significantly reduced in the OR group compared to the control group (83.58% *vs.* 98.68%, $P=0.001$; *Table 1, Figure 2*).

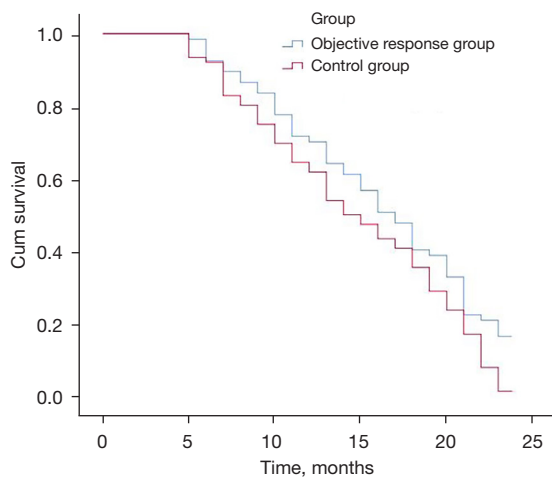


Figure 2 Comparison of 2 years survival between the two groups (Log Rank, Mantel-Cox, Chi-Square =4.970 and P=0.026).

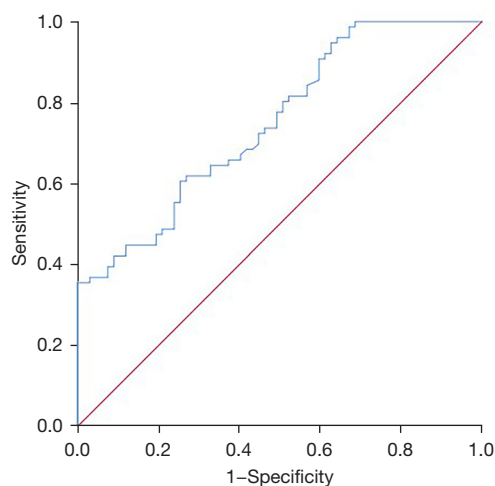


Figure 3 Value of ctDNA in predicting the failure to achieve an objective response after immunotherapy in NSCLC patients. ctDNA, circulating tumor DNA; NSCLC, non-small cell lung cancer.

Value of ctDNA in predicting failure to achieve an OR after immunotherapy in NSCLC patients

ctDNA was valuable in predicting that an OR would not be achieved after immunotherapy in the NSCLC patients. The area under the curve (AUC) of ctDNA in predicting that an OR would not be achieved after immunotherapy in the NSCLC patients was 0.750 (95% CI: 0.673–0.828, $P < 0.001$), the optimal diagnostic cut-off was 3.72 ng/ μ L, and the sensitivity and specificity were 0.618 and 0.731, respectively (Figure 3).

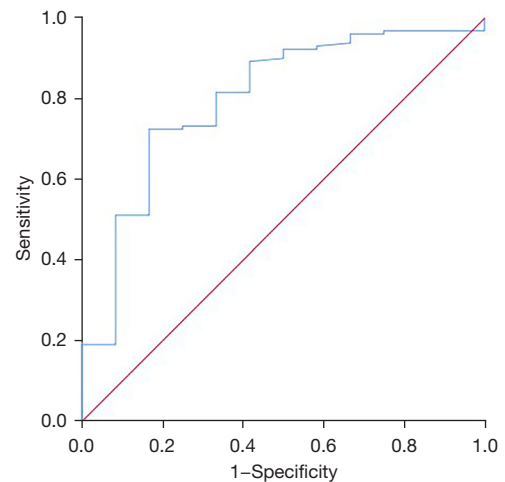


Figure 4 Value of ctDNA in predicting death within 2 years of immunotherapy in patients with non-small cell lung cancer. ctDNA, circulating tumor DNA.

Value of ctDNA in predicting death within 2 years of immunotherapy in NSCLC patients

ctDNA was valuable in predicting death within 2 years of immunotherapy in NSCLC patients, and had an AUC of 0.800 (95% CI: 0.666–0.935, $P = 0.001$). The best diagnostic cut-off was 2.87 ng/ μ L with sensitivity and specificity value of 0.725 and 0.833, respectively (Figure 4).

Analysis of influencing factors of OR in NSCLC patients after immunotherapy

The absence of pleural effusion, immunotherapy in combination with chemotherapy, and ctDNA < 3.72 ng/mL were influencing factors of OR after immunotherapy in NSCLC patients (b value =1.152, 1.124 and 1.482, $P = 0.045$, 0.004 and < 0.001 ; Table 2).

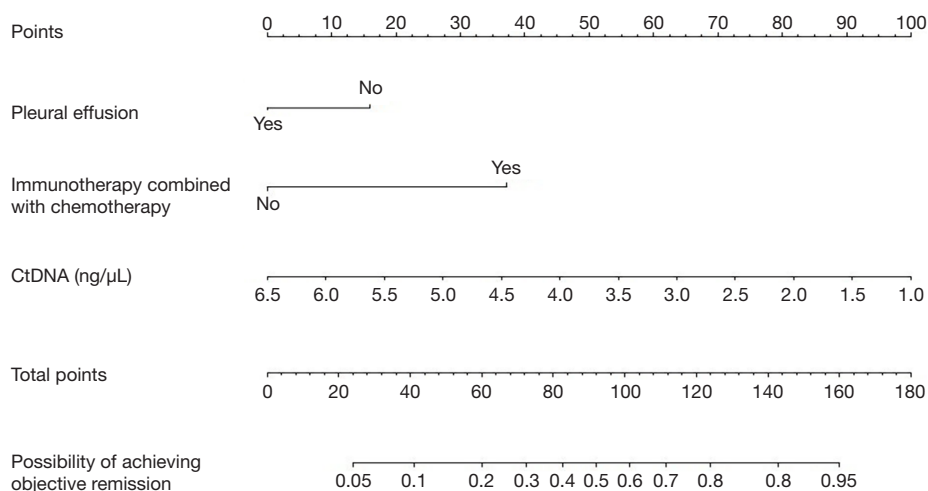
Establishment and verification of a predictive model of OR in patients with NSCLC after immunotherapy

The R4.0.3 statistical software (Ross Ihaka Robert Gentleman) was used to randomly divide the data set into the training set and validation set. The sample size of the training set was 72 and that of the validation set was 71. Pleural effusion, immunotherapy in combination with chemotherapy, and ctDNA were the factors included in the predictive model. We made a nomogram and drew a ROC curve. The area under the ROC curve of the training set

Table 2 Analysis of factors influencing objective remission after immunotherapy in NSCLC patients

Variables	B value	Standard error	Wald value	P value	Relative risk (95% CI)
Smoking history	-0.541	0.401	1.821	0.177	0.582 (0.266–1.277)
Pathology type	-0.845	0.449	3.537	0.060	0.430 (0.178–1.036)
Absence of pleural effusion	1.152	0.575	4.013	0.045	3.164 (1.025–9.765)
Immunotherapy in combination with chemotherapy	1.124	0.395	8.107	0.004	3.076 (1.419–6.666)
CtDNA <3.72 ng/ μ L	1.482	0.409	13.132	<0.001	4.403 (1.975–9.817)
Constant	-5.163	1.063	23.567	<0.001	0.006

NSCLC, non-small cell lung cancer; ctDNA, circulating tumor DNA.

**Figure 5** Nomogram of objective response after immunotherapy in non-small cell lung cancer patients. ctDNA, circulating tumor DNA.

was 0.850 (95% CI: 0.760–0.940) and that of the verification set was 0.732 (95% CI: 0.616–0.847). The model was tested by the Hosmer-Lemeshow Goodness-of-Fit test in the validation set, and had a chi-square value of 14.227, and a P value of 0.076, which indicated that the model was valuable and credible (Figures 5,6).

Discussion

With a 5-year survival rate of <5%, the mortality rate of patients with advanced NSCLC is extremely high (1). The emergence of immunotherapy in recent years has brought hope to patients with advanced NSCLC, but immunotherapy also has a number of issues, such as its high costs and ineffectiveness in some patients (7-9). To better predict the efficacy of immunotherapy in patients with advanced NSCLC, we designed this study and found

that the absence of pleural effusion, immunotherapy in combination with chemotherapy, and ctDNA <3.72 ng/ μ L were valuable factors of objective remission after immunotherapy in NSCLC patients (P=0.045, 0.004 and <0.001). CtDNA was valuable in predicting the efficacy of immunotherapy in NSCLC patients, and the prediction model constructed according to the relevant risk factors was also valuable in predicting objective remission after immunotherapy in NSCLC patients.

ctDNA, also known as circulating tumor cell DNA, refers to the presence of a small number of tumor cell necrosis secretion of DNA fragments in the blood. CtDNA can be used for the early diagnosis of some cancers and to guide the treatment and evaluate the prognosis of malignant tumor patients (21-24). At present, ctDNA is also used in the diagnosis and treatment of lung cancer patients. A study confirmed that ctDNA can be used for the early

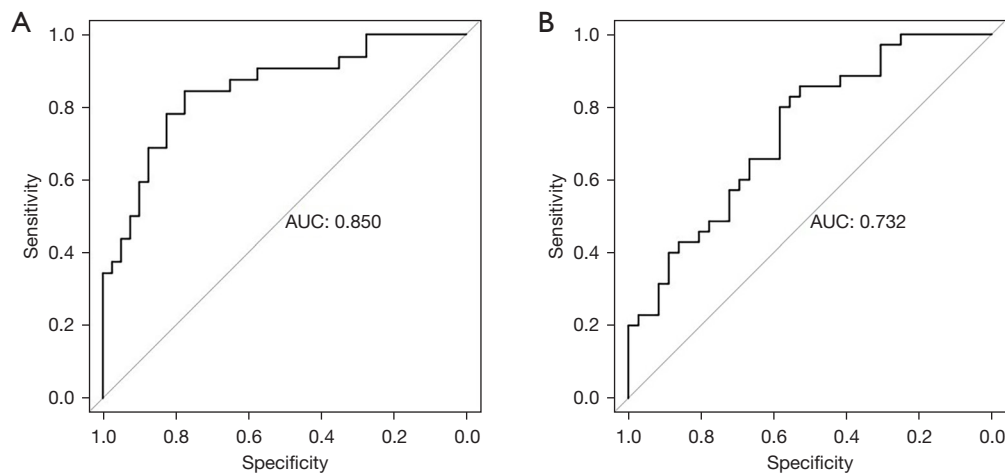


Figure 6 The value of the model in predicting which non-small cell lung cancer patients would achieve an objective response after immunotherapy. (A) shows the training set, and (B) shows the validation set. AUC, area under the curve.

diagnosis of lung cancer patients (25). ctDNA is an also emerging biomarker in NSCLC. A previous study showed that ctDNA was a good predictor of chemotherapy efficacy in patients with advanced NSCLC, and decreased ctDNA was associated with longer progression-free survival (26). Moreover, another study suggested that failure to detect ctDNA after treatment may be associated with a better prognosis (27). A study of NSCLC patients receiving neoadjuvant chemotherapy and immunotherapy also confirmed that preoperative ctDNA was associated with the treatment response in lung cancer patients (17).

ctDNA is a cell-free extracellular DNA found in body fluids such as blood, synovial fluid, and cerebrospinal fluid. The ctDNA has a short half-life, and thus can accurately reflect the current situation of tumors, and represents a promising new biological index (27). Thus, ctDNA could be used to guide immunotherapy in NSCLC patients.

Limitations

This was a retrospective clinical study, and it did not dynamically monitor ctDNA levels. Moreover, we failed to study the mutant molecules of ctDNA in this retrospective study.

Conclusions

More and more scholars have begun to study the role of various biological indicators in different diseases (28-33). This study showed that ctDNA level was valuable

in predicting the efficacy of immunotherapy in NSCLC patients, and ctDNA may be used to guide immunotherapy in NSCLC patients and thus improve patient outcomes. The dynamic monitoring of ctDNA levels may also be helpful, which needs to be explored in future research.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-379/rc>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-379/coif>). The 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. This retrospective clinical study was conducted in accordance with the 2013 edition of the Declaration of Helsinki and was approved by the Ethics Committee of Fujian Medical University Xiamen Humanity Hospital (No. c20220048). The requirement for informed consent was waived.

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