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RESEARCH

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FAM83A-AS1 predicts severe development of non-small cell lung cancer and adverse postoperative prognosis of thoracotomy

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Abstract

Background Thoracotomy is a common treatment for non-small cell lung cancer (NSCLC). However, the significant trauma from this procedure can limit patients' postoperative prognosis. Therefore, it's crucial to find an easily detected indicator that can predict the prognosis of NSCLC patients undergoing thoracotomy. FAM83A-AS1 was hypothesized as a predictor for the therapeutic effectiveness of thoracotomy. We evaluated its correlation with patient outcomes and its significance in predicting postoperative prognosis, with the aim of providing a reference to improve postoperative prognosis of thoracotomy.

Materials and methods The study enrolled patients with NSCLC who underwent thoracotomy, and tissue samples were collected during surgery. Blood samples were collected preoperatively and three days postoperatively. PCR was used to analyze plasma FAM83A-AS1 levels. The significance of these levels in the patients' postoperative prognosis was evaluated via logistic regression and ROC analyses, with a follow-up period of six months.

Results FAM83A-AS1 was significantly upregulated in NSCLC and correlated with severe progression in patients. Thoracotomy suppressed FAM83A-AS1 expression and reduced CA50, CEA, and CYFRA21-1 levels. Postoperative plasma levels of FAM83A-AS1 positively correlated with CA50, CEA, and CYFRA21-1. Patients with worse prognoses had higher plasma FAM83A-AS1 levels. FAM83A-AS1 was identified as a risk factor for poor postoperative outcomes in NSCLC patients undergoing thoracotomy and could be used to identify patients at risk of worse prognosis.

Conclusion An increase in FAM83A-AS1 in NSCL indicates severe disease development and can serve as a biomarker associated with thoracotomy, predicting a poor prognosis. It provides a potential indicator for patient outcomes.

Keywords Biomarker, Therapeutic target, Thoracotomy surgery, Prognosis, Tumor marker

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Background

Lung cancer is a major threat to human health, with the number of new cases and mortality rate ranking first among malignancies [1]. Over half of lung cancer patients have non-small cell lung cancer (NSCLC), often diagnosed in the advanced stages due to unnoticeable early symptoms [2]. Surgical treatment provides a comprehensive solution for NSCLC patients, and for those who qualify, it is commonly recommended to have surgery as soon as possible [3]. Traditional thoracotomy, which fully removes lesions and stabilizes disease conditions, is the earliest surgery for NSCLC and is considered the gold standard for its treatment [4]. However, it also has significant drawbacks. The surgical trauma from thoracotomy is relatively high, causing postoperative traumatic stress in patients. Moreover, the long-term chronic pain and the high occurrence of post-surgery complications limit its therapeutic efficiency and negatively affect the prognosis for NSCLC patients [5, 6]. Therefore, identifying effective biomarkers to predict therapeutic outcomes can help optimize treatment strategies and improve the postoperative recovery of patients.

The role of long non-coding RNAs (lncRNAs) in regulating cancer development has become increasingly evident with the advancement of molecular biology. Numerous studies have demonstrated the prognostic significance of lncRNAs in non-small cell lung cancer (NSCLC) through clinical trials. For instance, one study highlighted the predictive role of the downregulated TUG1 in NSCLC, in terms of tumor progression and patient prognosis [7]. Recent studies have pointed out the potential of lncRNA FAM83A-AS1 in NSCLC, showcasing its involvement in key tumor development processes such as immunity, necroptosis, and the tumor microenvironment [8–10]. FAM83A-AS1 was found to act as an oncogene in lung adenocarcinoma, promoting cell growth and metastasis by regulating the expression and function of target genes [11–14]. Further, bioinformatics studies identified FAM83A-AS1 as a potential prognostic biomarker for lung cancer, correlating with patient survival and disease progression [8, 15–20]. Consequently, FAM83A-AS1 is considered a therapeutic target for NSCLC, hypothesized to predict the postoperative prognosis of NSCLC patients undergoing thoracotomy.

This study sought to validate the role of FAM83A-AS1 in the treatment of NSCLC. It did so by enrolling a group of NSCLC patients who underwent thoracotomy. By comparing the expression of FAM83A-AS1 before and after surgery, the study revealed how FAM83A-AS1 responds to thoracotomy in NSCLC. Additionally, the study evaluated the predictive significance of FAM83A-AS1 in the prognosis of NSCLC patients post-thoracotomy, potentially identifying a new biomarker.

Materials and methods

Study subjects

This study included 93 patients diagnosed with NSCLC who underwent thoracotomy at Zigong Fourth People's Hospital from January 2019 to December 2021. The inclusion criteria were as follows: (1) Patients diagnosed at TNM stages I-III; (2) Patients without surgical contraindications; (3) Patients with an estimated survival time of over 6 months; (4) Patients with complete clinical records and signed informed consent. Patients with other malignancies or those diagnosed with small-cell lung cancer were excluded. This study complied with the Helsinki Declaration and was approved by the Ethic Committee of Zigong Fourth People's Hospital.

Patients were monitored for six months after thoracotomy, either by phone or outpatient review. Adverse outcomes were defined as metastasis, recurrence, or death. No patients were lost to follow-up in this study. We compared the clinicopathological features between patients with good and adverse prognoses, and analyzed overall survival using the Kaplan-Meier curve. Postoperative adverse prognostic factors for NSCLC patients were evaluated using Cox regression analysis.

Sample collection

Blood samples were collected while fasting, before thoracotomy, and three days after the surgery. The samples were placed into anti-coagulation tubes and then centrifuged at 1500 g for 10 min to obtain plasma.

During surgery, tissue samples were collected, along with adjacent normal tissues about 2 cm from the lesion. These samples were frozen with liquid nitrogen and stored at -80 °C for later analysis.

Real-time quantitative PCR

Tissue and plasma samples were lysed using Trizol reagent (Invitrogen, USA), followed by total RNA extraction. The RNA's purity was assessed using NanoDrop 2000, selecting samples with an OD260/280 ratio between 1.8 and 2.2 for PCR analysis. The isolated RNA was converted to cDNA using the ImProm-II Reverse Transcription system (Promega, USA) and then amplified with the 7500 PCR system (Applied Biosystem, USA) using SYBR Green reagent (QIAGEN, USA). The relative expression of FAM83A-AS1 was calculated using the 2-ΔΔCT method, with β-actin serving as the internal reference.

Evaluation of tumor markers

Before and after surgery, tumor markers such as Carcinoma Antigen 50 (CA50), Carcinoembryonic Antigen (CEA), and Cytokeratin-19-Fragment (CYFRA21-1) were analyzed. The radioimmunoassay was used to assess

CA50 and CEA, while the electrochemical assay was used to detect CYFRA21-1.

Statistical analyses

To assess the changes in the levels of FAM83A-AS1 and tumor markers, a comparison of the differences between the two groups was conducted using the Student's t-test via GraphPad Prism 9.0 software. To assess the potential of FAM83A-AS1 in disease progression, we evaluated the correlation of FAM83A-AS1 with patients' clinicopathological features using the Pearson correlation analysis and the Chi-square test based on the average FAM83A-AS1 levels dividing patients into the low- and high-FAM83A-AS1 groups. To assess the predictive value of FAM83A-AS1 in the postoperative prognosis of NSCLC, we conducted logistic regression analysis and a receiver operating curve (ROC). We obtained the sensitivity and specificity by calculating the Youden index. A P value of less than 0.05 indicates statistical significance.

Results

FAM83A-AS1 was upregulated in NSCLC and was associated with patients' severity

In NSCLC patients, tumor tissues showed significant upregulation of FAM83A-AS1 compared to adjacent normal tissues (Fig. 1a). NSCLC patients were grouped based on the average FAM83A-AS1 expression in tissues. The low-FAM83A-AS1 group included 40 patients and the high-FAM83A-AS1 group consisted of 53 patients. There were significant differences in the TNM stage ($P=0.008$),

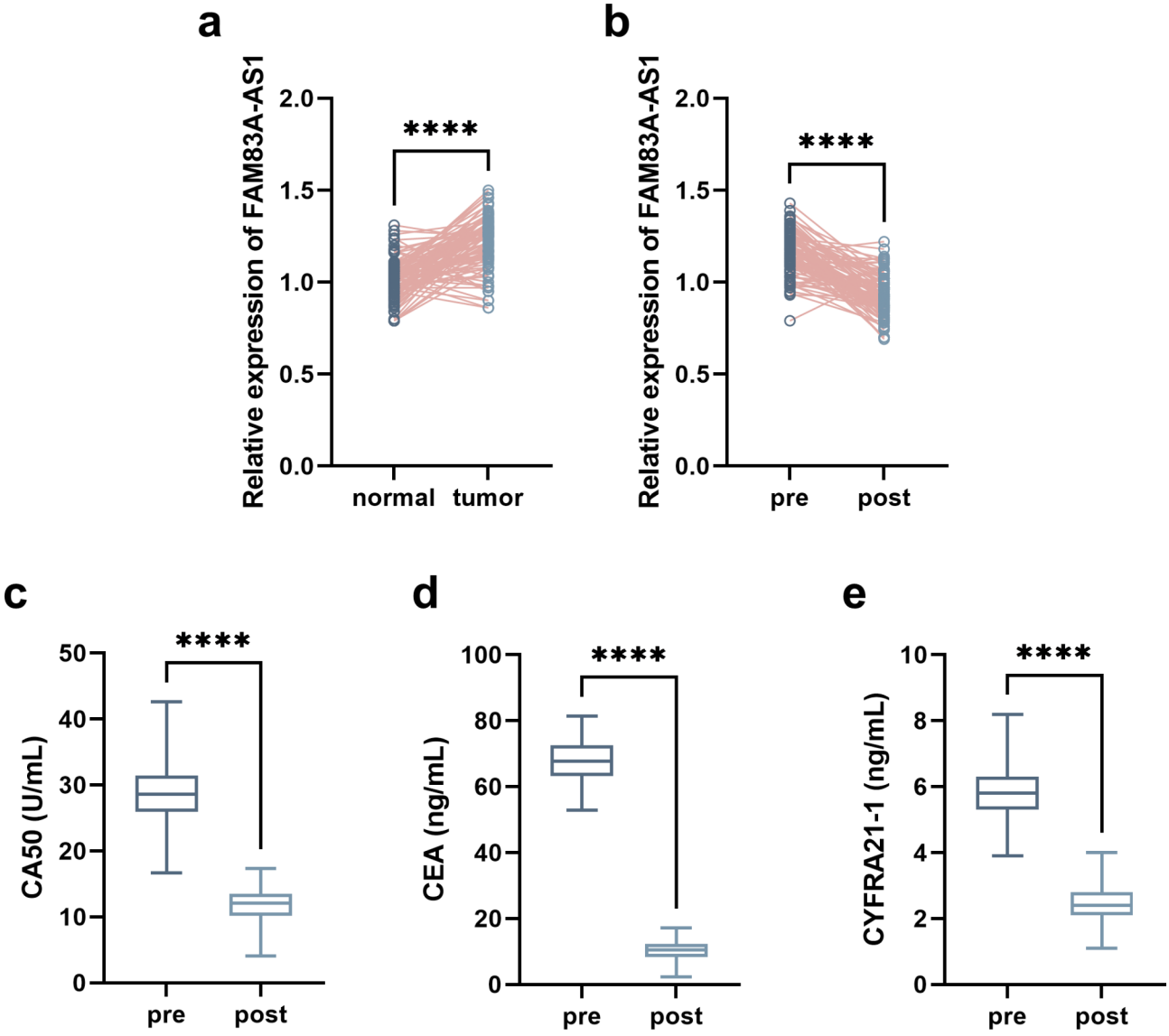

Fig. 1 This document illustrates the expression of FAM83A-AS1 in tissues (**a**) and plasma (**b**) before and after thoracotomy. It also shows the levels of CA50 (**c**), CEA (**d**), and CYFRA21-1 (**e**) before and after the procedure. The significant change is indicated by $^{****}P<0.0001$

Table 1 Association of tissue FAM83A-AS1 with the clinicopathological features of patients

	Total	Low-FAM83A-AS1	High-FAM83A-AS1	*P*-value
Age				0.928
≤60	46	20	26	
>60	47	20	27	
Gender				0.786
Male	59	26	33	
Female	34	14	20	
TNM stage				0.008
I-II	63	33	30	
III	30	7	23	
Differentiation				0.011
Well-moderate	61	32	29	
Poor	32	8	24	
Tumor size				0.239
≤3	54	26	28	
>3	39	14	25	
Smoking				0.652
Yes	49	20	29	
No	44	20	24	
Invasion				0.001
Present	37	24	13	
Absent	56	16	40	
Lymph node metastasis				0.003
Present	33	21	12	
Absent	60	19	41	

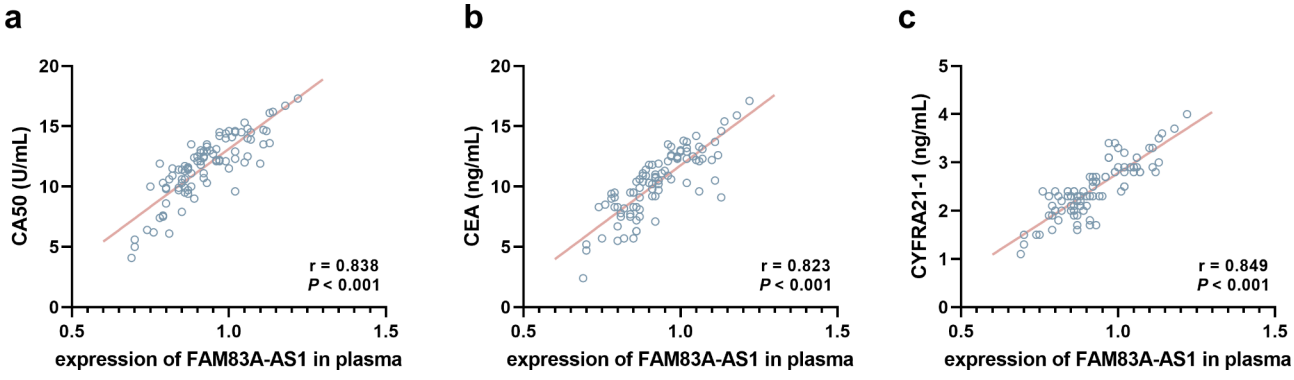

Fig. 2 This represents the correlation of postoperative plasma FAM83A-AS1 levels with CA50 (**a**), CEA (**b**), and CYFRA21-1 (**c**). $r > 0.8$ and $P < 0.001$ indicates the close association and the significant potential of FAM83A-AS1 in postoperative recovery of NSCLC patients

differentiation ($P=0.011$), invasion ($P=0.001$), and lymph node metastasis ($P=0.003$) between the two groups. These differences highlight the significant association of FAM83A-AS1 with clinicopathological features that are closely related to the severity of the disease (Table 1).

Thoracotomy reduced the expression of FAM83A-AS1 associated with tumor biomarkers

The expression of FAM83A-AS1 in plasma significantly decreased after thoracotomy compared to before the procedure (Fig. 1b). Similarly, the levels of CA50 (Fig. 1c), CEA (Fig. 1d), and CYFRA21-1 (Fig. 1e) also significantly decreased post-thoracotomy. Furthermore, postoperative plasma levels of FAM83A-AS1 had significant positive correlations with CA50 ($r=0.838$, Fig. 2a), CEA ($r=0.823$, Fig. 2b), and CYFRA21-1 ($r=0.849$, Fig. 2c).

FAM83A-AS1 predicted the adverse postoperative prognosis of NSCLC patients receiving thoracotomy

According to a six-month follow-up survey, enrolled patients were divided into two groups: a good-prognosis group of 49 patients and an adverse-prognosis group of 44 patients. Patients in the adverse-prognosis group had higher postoperative plasma FAM83A-AS1 levels than those in the good prognosis group (Fig. 3a). A logistic regression analysis identified FAM83A-AS1 (OR=6.441,

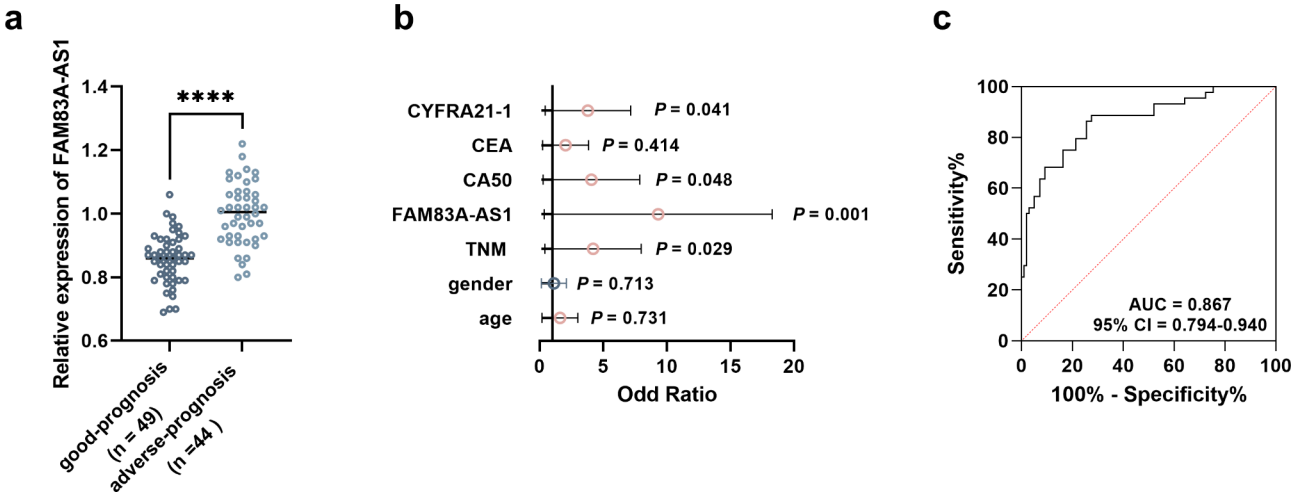

Fig. 3 This document discusses the levels of postoperative plasma FAM83A-AS1 in NSCLC patients with different prognoses (**a**). $^{****}P < 0.0001$ indicates significant dysregulation. It also explores the significance of FAM83A-AS1 in predicting patients' postoperative prognosis (**b**, $P < 0.05$) and in distinguishing patients with adverse prognosis (**c**, AUC > 0.8)

95% CI=2.142–19.369) as a risk factor for adverse postoperative prognosis in NSCLC patients who underwent thoracotomy. Other risk factors included TNM stage (OR=3.079, 95% CI=1.124–8.436), CA50 (OR=2.898, 95% CI=1.009–8.320), and CYFRA21-1 (OR=2.807, 95% CI=1.045–7.543, Fig. 3b and Table S1). ROC analysis confirmed that FAM83A-AS1 could distinguish between NSCLC patients with adverse prognoses and those with good prognoses, with a sensitivity of 88.64% and a specificity of 71.43% (Fig. 3c).

Discussion

FAM83A-AS1, previously identified as a tumor promoter in NSCLC, has been found to mediate tumor cell growth, metastasis, and regulate tumor progression [11, 12]. This study confirmed the dysregulation of FAM83A-AS1 in the tumor tissues of NSCLC patients compared to the normal tissues distant from the lesion. Furthermore, patients with increasing FAM83A-AS1 majorly showed poor differentiation, advanced TNM stages, presence of invasion and lymph node metastasis, which correlate with the severe development of NSCLC. Hence, an increase in FAM83A-AS1 was hypothesized to possess close association with the severity of NSCLC, aligning with its reported role as a tumor promoter. The potential involvement and regulatory impact of FAM83A-AS1 in NSCLC suggest it could serve as a therapeutic target.

Thoracotomy is a curative treatment for NSCLC, but it can be limited by the significant trauma it causes [21]. Predicting prognosis can greatly improve the long-term survival of NSCLC patients undergoing thoracotomy. Given the proven significance of FAM83A-AS1 in NSCLC, particularly its regulation of cell metastasis and epithelial-mesenchymal transition, it is hypothesized to be associated with patients' postoperative outcomes [22]. As expected, thoracotomy lowered the plasma FAM83A-AS1 levels in NSCLC patients and also reduced tumor biomarkers, including CA50, CEA, and CYFRA21-1. These biomarkers are closely linked with tumor metastasis and recurrence [23–26]. Thoracotomy is typically performed on patients without distant metastasis, and the tumor markers released by cancer cells are mainly present in the lesion. Thoracotomy can significantly reduce the tumor load and therefore decrease the levels of FAM83A-AS1 and the contents of these markers. The significant reduction in these markers suggests the complete removal of tumor tissues [27, 28]. Conversely, when tumor recurrence occurs post-surgery, the levels of these markers would increase and can be used as diagnostic indicators. The postoperative plasma level of FAM83A-AS1 in the study subjects showed a positive correlation with CA50, CEA, and CYFRA21-1, indicating it might be associated with postoperative recurrence or other adverse development in NSCLC patients.

Patients were monitored for six months after thoracotomy, with nearly half experiencing adverse outcomes such as recurrence and metastasis. Previous research has shown the prognostic significance of FAM83A-AS1 in pancreatic cancer, linking it with cadherin binding and immune infiltration [29]. Its prognostic potential in NSCLC has been noted in several studies, but not thoroughly investigated [10, 17, 20]. In this study, patients with adverse prognoses had higher plasma FAM83A-AS1 levels. FAM83A-AS1 was also identified as a risk factor for adverse prognosis in NSCLC patients who underwent thoracotomy. It showed significant efficiency in distinguishing between patients with different outcomes. Therefore, FAM83A-AS1 holds great potential

for predicting patient outcomes and evaluating the therapeutic efficiency of thoracotomy. Serum FAM83A-AS1 level can be considered as an index in monitoring disease progression and postoperative recovery of patients with NSCLC, especially for patients receiving thoracotomy.

While this study has revealed the clinical significance of FAM83A-AS1 in evaluating the therapeutic efficiency of thoracotomy, there are still many aspects that require further exploration in future studies. The regulatory effect and mechanism of FAM83A-AS1 have been extensively discussed in previous studies, suggesting that the inhibitory effect of thoracotomy on FAM83A-AS1 might underlie its role as a therapeutic target. However, evidence is still needed to determine whether thoracotomy can also regulate the downstream targets of FAM83A-AS1. With the development of bioinformatics and molecular biology, omics analyses have become an effective means in cancer research. Multiomics analyses could provide more information deepening the understanding of biomarkers in tumor progression from different perspectives, such as immune [30]. More importantly, bioinformatic analyses could dig out more candidates for various human cancers not limited to NSCLC [31]. Such information could provide additional indicators and aid in improving therapeutic effectiveness of human cancers.

Conclusion

An increase in FAM83A-AS1 levels is linked to severe development of NSCLC and influences the therapeutic efficiency of thoracotomy. The postoperative plasma FAM83A-AS1 level also correlates with recurrence in NSCLC patients who undergo thoracotomy, serving as an adverse prognostic indicator for their postoperative prognosis.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13019-024-03235-3.

Supplementary Material 1

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Not applicable.

Author contributions
L.C. Z and L.Q. Q designed the research study. F. T, Y.M L, L.C. Z, L.Q. Q and C.C. X performed the research and analyzed the data. L.C. Z and L.Q. Q wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was approved by The Ethics Committee of Zigong Fourth People's Hospital and followed the principles outlined in the Declaration of Helsinki. In addition, informed consent has been obtained from the participants involved.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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