

# Circulating tumor cell combined with artificial intelligence to establish a model for diagnosing the malignancy of pulmonary nodules

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## Research Article

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# Abstract

## Background

Exploring the clinical application value of combining circulating tumor cell (CTC) with artificial intelligence in predicting the pathological nature of pulmonary nodules. Constructing a prediction model based on factors related to lung cancer to provide reliable prediction criteria for clinical doctors to predict the pathological nature of pulmonary nodules, in order to guide clinical doctors in judging the benign and malignant nature and infiltration degree of pulmonary nodules (PN).

## Methods

This study included a total of 76 patients with PN who underwent surgical treatment. Based on preoperative imaging of the patients, an artificial intelligence imaging system called "United Imaging Intelligence" was used to classify the pulmonary nodules into three levels of "low risk", "medium risk", and "high risk", and the preoperative CTC level of the patients was recorded. Multiple logistic regression analysis was used to analyze the risk factors affecting the nature of the PN and to construct relevant column charts. Receiver operating characteristic (ROC) curves were used to analyze the diagnostic value of artificial intelligence and CTC levels for the nature of PN lesions.

## Results

The artificial intelligence model for grouping benign and malignant PN and the difference in CTC levels have statistical significance ( $P < 0.05$ ). The results of multifactor logistic regression analysis showed that artificial intelligence high-risk grouping, CTC level, and age are independent risk factors affecting the nature of PN ( $P < 0.05$ ). We also constructed a column chart to guide clinical doctors in treatment. The area under the curve (AUC) for the artificial intelligence risk grouping and CTC level diagnosis of malignant PN were 78.9% and 74.3%, respectively.

## Conclusion

Artificial intelligence model combined with CTC detection helps improve the accuracy of lung nodule characterization diagnosis and assists in guiding clinical decisions.

## Introduction

Lung cancer is one of the most common and deadly tumors in the world, seriously endangering human health and survival (1). The 5-year survival rate of early-stage lung cancer is about 85%, but it is often ignored due to the lack of corresponding clinical symptoms, leading to most lung cancer patients being diagnosed in the late stage and losing the opportunity for surgical cure (2, 3). Therefore, early diagnosis

and treatment is an important way to significantly increase patient survival. Developing new safe and efficient methods for accurately identifying patients with malignant pulmonary nodules (PN) has significant clinical significance.

With the continuous deepening of research in modern molecular biology, oncology, and other fields, more and more detection techniques (including non-invasive and invasive) are used to identify the benign and malignant nature of pulmonary nodules. Imaging examinations (such as low-dose CT (LDCT), positron emission tomography, etc.) and tumor marker detection are commonly used auxiliary screening methods in clinical practice. The popularity of LDCT has reduced the mortality rate of high-risk populations by 20% (5). However, the high false positive rate and overdiagnosis limit the diagnostic accuracy of LDCT screening. In a national lung screening trial, 25% of PN were determined to be benign after undergoing surgery (5, 6). Therefore, an accurate lung nodule automatic detection system would provide great assistance to clinicians. With the development of artificial intelligence, deep learning algorithms have shown significant advantages in the field of medical diagnosis, providing new opportunities for automatic intelligent diagnosis of medical images. The PN automatic detection model "United Imaging Intelligence" based on three-dimensional convolutional neural networks reduces the missed diagnosis rate of clinicians and improves diagnostic accuracy in clinical practice (7, 8).

Circulating tumor cell (CTCs) are one of the molecular markers analyzed in liquid biopsy. In the early stages of cancer, tumor cells can also be detected. CTC detection has gradually become a research hotspot in the diagnosis and treatment of malignant tumors due to its minimally invasive, high sensitivity, and high specificity advantages. In clinical practice, it has become an important means of non-invasive real-time monitoring of tumor progression (9, 10). Previous studies have shown that LDCT combined with CTC is a reliable method for early lung cancer screening (11).

This study aims to explore the value of CTC combined with artificial intelligence in the evaluation of benign and malignant PN, in order to provide a basis for clinical decision-making.

## Materials and methods

### Study cohorts

This study included patients with PN who were treated at our hospital from January 2018 to July 2023. Inclusion criteria: 1. Patients with complete clinical data; 2. All patients underwent surgical treatment and had a clear pathological diagnosis; 3. Peripheral CTC detection using CellCollector (GILUPI CellCollector, GILUPI) was performed before surgery; 4. All patients underwent high-resolution CT examination before surgery, with nodule diameter  $\leq 3.0\text{cm}$ ; 5. CT images were analyzed for risk using the "United Imaging Intelligence" software. Exclusion criteria: 1. Unclear CT images; 2. Nodule diameter  $> 3.0\text{cm}$ ; 3. Clear surgical contraindications; 4. Evidence of distant metastasis. A total of 76 patients were included in this study.

We have collected complete clinical data of patients including gender, age, medical history, smoking history, and tumor markers (including carcinoembryonic antigen, neuron-specific enolase, cytokeratin 19 fragment, squamous cell carcinoma antigen).

This is a retrospective study conducted at Hebei Provincial People's Hospital. We waived the patients' informed consent. We ensured the confidentiality of patient information, and all procedures were in accordance with the Helsinki Declaration.

## Research methods

1. CTC detection is performed by collecting fasting elbow vein blood from patients on the morning of the day after admission, and examining peripheral blood CTCs using the CellCollector's circulating epithelial cell sampling probe. The sampling probe is inserted into the peripheral blood of the elbow vein through a 20G catheter, and the functional domain is exposed to the peripheral blood and placed in the body for 30 minutes. Tumor cells are captured by specifically binding to the EpCAM antigen on the surface of tumor cells.

2. Imaging examination: High-resolution CT (Siemens ForceCT) was used for CT examination. During scanning, the patient was instructed to hold their breath after inhaling, and the scanning range was from the upper edge of the thoracic inlet to the level of the adrenal gland. After scanning, we used the "United Imaging Intelligence" system to stratify the risk of pulmonary nodules, which were divided into three levels: "low risk," "medium risk," and "high risk."

## Statistical analyses

We used t-tests and chi-square tests to accurately describe the association between clinical characteristics and tumor malignancy in 76 patients. We used the "pROC" package in R software to plot ROC curves and calculate the area under the curve to evaluate the accuracy of the model. The "rms" package was used to perform univariate and multivariate logistic regression analyses on the patients, establish a prediction model, and construct column line charts to guide clinical decision-making. The analysis of differences in CTC counts among different infiltration groups was performed using GraphPad Prism. The R software version was 4.3.0, and the GraphPad software version was 9.4.1.

## Results

### Clinical features of the subject

We retrospectively analyzed 76 patients with PN who underwent surgery in our department, all of whom underwent CTC and high-resolution CT examinations in our hospital before surgery. Table 1 describes the clinical and pathological characteristics of the study subjects. After postoperative pathological diagnosis, 35 cases were benign lesions (including 16 cases diagnosed as Adenocarcinoma in situ) and 41 cases were lung adenocarcinoma (20 cases of minimally invasive adenocarcinoma and 21 cases of

invasive adenocarcinoma). The " United Imaging Intelligence " system identified 10 low-risk patients, 23 medium-risk patients, and 43 high-risk patients. The range of CTC counts was 0–5. There were no significant differences in gender, age, medical history, smoking history, and tumor marker counts between benign and malignant groups, lacking specificity.

Table 1

Association of Clinicopathological Characteristics in 76 PN patients. Abbreviations: CEA: carcinoembryonic antigen, NSE: neuron-specific enolase, CYFRA21-1: cytokeratin 19 fragment, SCC: squamous cell carcinoma antigen.

|                          |             | Benign disease          | LUAD                    | P-value |
|--------------------------|-------------|-------------------------|-------------------------|---------|
|                          |             | 35                      | 41                      |         |
| Gender (%)               | Female      | 17 (48.57)              | 26 (63.41)              | 0.285   |
|                          | male        | 18 (51.43)              | 15 (36.59)              |         |
| Age (median [IQR])       |             | 57.000 [46.500, 63.500] | 60.000 [54.000, 65.000] | 0.1201  |
| History (%)              | No          | 29 (82.86)              | 35 (85.37)              | 1       |
|                          | Yes         | 6 (17.14)               | 6 (14.63)               |         |
| Smoke (%)                | No          | 25 (71.43)              | 34 (82.93)              | 0.3561  |
|                          | Yes         | 10 (28.57)              | 7 (17.07)               |         |
| CEA (median [IQR])       |             | 1.870 [1.345, 2.675]    | 2.520 [1.420, 3.690]    | 0.2168  |
| NSE (median [IQR])       |             | 10.530 [9.285, 14.215]  | 12.130 [10.730, 13.530] | 0.1927  |
| CYFRA21-1 (median [IQR]) |             | 1.810 [1.440, 2.665]    | 1.840 [1.330, 2.350]    | 0.4314  |
| SCC (median [IQR])       |             | 0.971 [0.750, 1.362]    | 0.981 [0.747, 1.348]    | 0.7904  |
| CTC (median [IQR])       |             | 0.000 [0.000, 1.000]    | 1.000 [1.000, 2.000]    | 0.0001  |
| Position (%)             | Left        | 18 (51.43)              | 12 (29.27)              | 0.0828  |
|                          | Right       | 17 (48.57)              | 29 (70.73)              |         |
| Risk (%)                 | Low Risk    | 9 (25.71)               | 1 (2.44)                | 0.0004  |
|                          | Medium risk | 14 (40.00)              | 9 (21.95)               |         |
|                          | High Risk   | 12 (34.29)              | 31 (75.61)              |         |

## CTC and artificial intelligence predict the nature of PN

There were significant differences ( $P < 0.001$ ) in CTC counts and " United Imaging Intelligence " model between benign and malignant groups (Table 1). ROC curves were used to evaluate the specificity of CTC counts and " United Imaging Intelligence " model in the diagnosis of PN. As expected, the AUCs of both were as high as 74.3% and 78.9%, respectively (Fig. 1). These results indicate that CTC and " United

Imaging Intelligence " model are effective predictive indicators of benign and malignant PN. In fact, "United Imaging Intelligence" software has been widely used in our clinical practice for pulmonary nodule screening, helping clinicians make judgments.

## **CTC counts differ in lung adenocarcinoma with different degrees of invasion**

CTC mainly comes from tumor lesions, and tumor cells from primary or metastatic lesions detach into the blood and participate in the occurrence and metastasis of tumors. Therefore, we investigated the differences in CTC counts between in situ adenocarcinoma, microinvasive adenocarcinoma, and invasive adenocarcinoma. It was found that there was a significant difference in CTC counts between different degrees of invasion (Fig. 2) after calculation.

## **Logistic regression analysis**

Logistic regression analysis was performed by stratifying clinical information, CTC and "United Imaging Intelligence" model, and the predictors of  $P < 0.1$  in univariate analysis (age, nodule location, CTC and "United Imaging Intelligence" model) were included in multivariate analysis, and we found that age, CTC and "United Imaging Intelligence" high risk were independent predictors of benign and malignant diagnosis of pulmonary nodules (Table 2). In the multivariate analysis, the P value for intermediate risk was 0.537, and we further analyzed the risk grade and the degree of tumor invasion, and no significant differences were seen (Fig. 2). However, the higher degree of infiltration, the higher risk group, the lower risk proportion and the increased risk proportion.

Table 2  
Univariate and Multivariate logistic regression analysis

|                    | Univariate logistic Analysis |             |         | Multivariate logistic Analysis |             |         |
|--------------------|------------------------------|-------------|---------|--------------------------------|-------------|---------|
| Characteristics    | OR                           | 95%CI       | P-value | OR                             | 95%CI       | P-value |
| Age                | 1.04                         | 0.99–1.09   | 0.081   | 1.06                           | 1-1.13      | 0.045   |
| CEA                | 1.17                         | 0.86–1.59   | 0.327   | NA                             | NA          | NA      |
| CTC                | 2.5                          | 1.45–4.33   | 0.001   | 2.2                            | 1.15–4.21   | 0.018   |
| CYFRA21-1          | 1.01                         | 0.77–1.33   | 0.929   | NA                             | NA          | NA      |
| Gender             | 0.54                         | 0.22–1.36   | 0.195   | NA                             | NA          | NA      |
| History            | 0.83                         | 0.24–2.85   | 0.765   | NA                             | NA          | NA      |
| NSE                | 1.1                          | 0.92–1.31   | 0.293   | NA                             | NA          | NA      |
| Position           | 2.56                         | 1-6.58      | 0.051   | 2.11                           | 0.65–6.82   | 0.213   |
| Risk               |                              |             |         |                                |             |         |
| Medium vs Low Risk | 5.79                         | 0.62–53.76  | 0.123   | 2.12                           | 0.19–23.21  | 0.537   |
| High vs Low Risk   | 23.25                        | 2.65-203.77 | 0.004   | 14.37                          | 1.44-143.88 | 0.023   |
| SCC                | 0.71                         | 0.34–1.48   | 0.362   | NA                             | NA          | NA      |
| Smoke1             | 0.51                         | 0.17–1.54   | 0.235   | NA                             | NA          | NA      |

## Establishment of nomograms

Multifactorial logistic regression analysis identified age, CTC, and " United Imaging Intelligence " model as independent predictive factors for the nature of PN. We further constructed a column chart of the multifactorial logistic regression analysis model. We divided the study cohort into training and validation cohorts in a ratio of 3:1. By constructing a column chart of the training cohort data, we verified its accuracy using ROC curves, calibration curves, and DCA curves (Fig. 3). The area under the AUC curve was 86.4%, and the calibration curve showed good consistency between the predicted and actual results, both indicating high accuracy of the column chart. DCA provides insight into the range of predicted risks, and the results show that the model provides patients with high value. ROC curves, calibration curves, and DCA based on the training set all showed good performance (Fig. S1).

## Discussion

In recent years, the incidence and mortality rate of lung malignant tumors have ranked first in the world. Studies have shown that the 5-year recurrence rate after surgery for early-stage lung cancer is only 10%, and early detection of lung cancer with surgical treatment is the key to treating lung cancer (12). Early-stage lung cancer has no specific clinical manifestations, and its initial manifestation may only be

isolated nodules in the lungs. Isolated nodules can be classified into solid nodules and subsolid nodules based on the different solid components within the PN. Solid nodules refer to nodules with a density that can block the small bronchi and blood vessels inside, while subsolid nodules refer to nodules with unclear or indistinct boundaries, and the density within the nodules cannot block the small bronchi and blood vessels inside (13, 14).

Studies have shown that compared to non-small cell lung cancer with subsolid nodules on imaging, lung lesions with pure solid nodules have a higher rate of lymph node metastasis and malignancy, and a worse prognosis (15, 16). Therefore, in clinical practice, solid PN require early and rapid diagnosis to avoid delaying the patient's condition. However, the judgment of imaging features is related to the experience of radiologists and thoracic surgeons, so the interpretation of imaging results may vary among doctors of different levels, and the imaging features of solid PN with a diameter  $\leq 1$  cm may not be obvious (17, 18). Therefore, having a unified diagnostic criteria and the ability to accurately identify small PN is an important prerequisite for screening early-stage lung cancer. Therefore, in this study, in the analysis of imaging features, the United Imaging Intelligence was used to uniformly identify the size and related morphology of PN in patients (19). However, relying solely on CT imaging features cannot completely differentiate between benign and malignant PN. Previous studies have shown that combining imaging features with more sensitive molecular markers can increase the positive diagnostic rate of lung cancer (20–22).

Related studies have shown that some tumor markers in serum can also assist in the diagnosis of lung cancer. However, traditional tumor markers such as CEA, NSE, and CA199 have low specificity and sensitivity in the diagnosis of early-stage lung cancer (22–25). In recent years, the emergence of liquid biopsy techniques represented by CTCs has provided new ideas for the early diagnosis of lung cancer. CTCs refer to tumor cells that detach from primary or metastatic lesions and enter the blood. CTCs are extremely rare in peripheral blood, and specific CTC markers are key to improving the detection rate of CTCs. Folate receptor positivity, as a specific marker of CTCs, has high sensitivity and specificity and can be highly expressed in tumor cells. Folate receptors are expressed very low in fallopian tubes, renal tubules, alveolar wall cells, choroid plexus, and uterus, and are not expressed in blood cells. The expression of folate receptors in lung cancer cells exceeds 78%, and folate receptors can recognize active CTCs, unaffected by the transformation of epithelial cells into mesenchymal cells. In this study, the CellCollector (GILUPI CellCollector, GILUPI) in vivo detection method was used to detect peripheral CTCs before surgery. Immunofluorescence staining was performed for CTC evaluation and PD-L expression analysis. In addition, CTCs captured by the CellCollector sampling probe were isolated and subjected to whole genome amplification and quality assessment. Qualified CTCs underwent NGS to determine copy number variations (CNV). In 2010, the American Joint Committee on Cancer (AJCC) Cancer Staging Manual proposed that CTCs could become a new indicator to help pathologists stage cancer, and CTCs have begun to be used in clinical practice to better formulate treatment plans for lung cancer patients (26–28). Previously, some people attempted to combine CTC evaluation with established screening methods, focusing on improving its specificity by combining low-dose CT screening plans with subsequent CTC evaluation. CTC counting evaluation was performed on patients

with confirmed pulmonary "ground-glass" nodules and healthy controls. Only some patients with nodules had CTCs in their blood. Subsequent molecular analysis revealed that these CTCs had a "malignant tendency" (29). However, their study did not establish a model to predict the pathological nature of the nodules, and there was a lack of unified diagnostic criteria. We retrospectively evaluated the diagnostic efficacy of liquid biopsy combined with artificial intelligence in 76 suspected lung cancer patients, and the results showed that this predictive model had better predictive performance.

This study is based on the construction of a predictive model for PN using imaging AI and CTCs, and it has been confirmed to have good accuracy, stability, and applicability through internal and external validation, providing reference for clinical decision-making.

## **Declarations**

### **Acknowledgements**

Not applicable.

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### **Availability of data and materials**

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

### **Authors' contributions**

RD, LL, DG and XX completed the main design and conception of the study. ZQ, ZX, and XW complete the collection of clinical data. LL and LW complete the collection of CTC data. ZH and ZX collected the pathological data of patients. ZQ and EN integrate the data. RD, LL, and CS analyze and interpret the data. LW processes the data graphics. RD and CS drafted the first draft of the article, and DG and XX made final revisions to the article. All authors have read and approved the final manuscript.

### **Ethics approval and consent to participate**

This study was approved by the Ethics Committee of Hebei General Hospital (no. 2023125). Retrospective information was recorded by the Hebei General Hospital Medical Record System, which dispensed with the requirement for informed patient consent.

### **Patient consent for publication**

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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## Figures

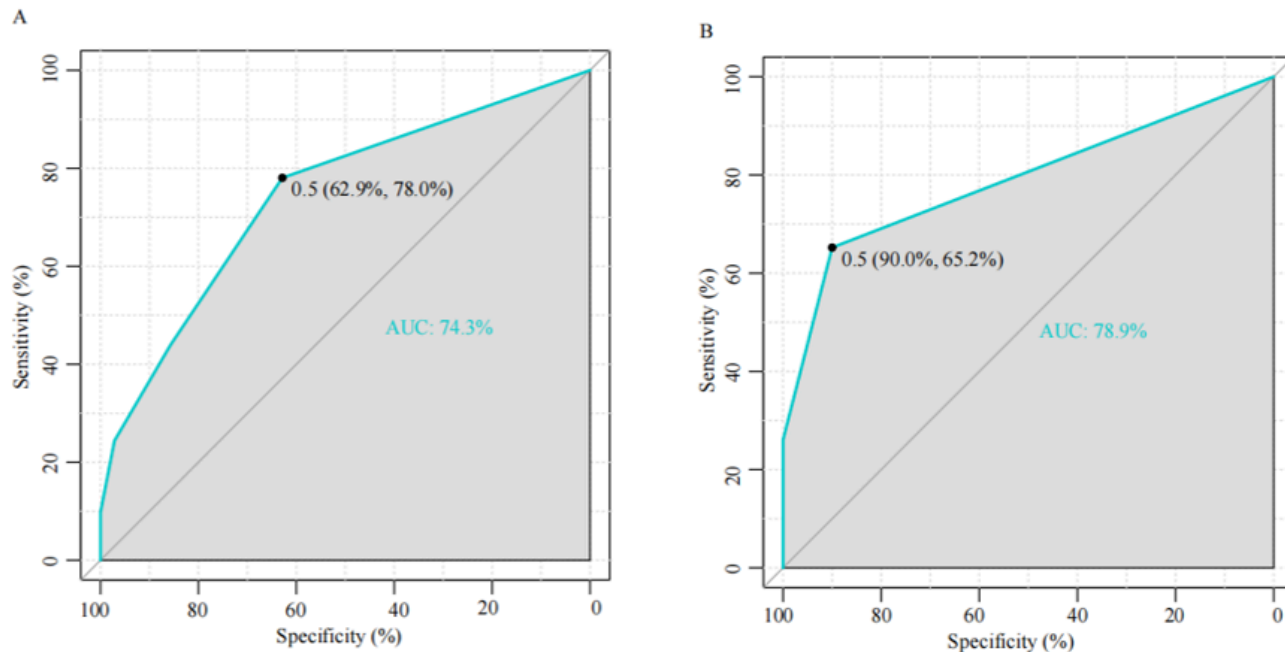


**Figure 1**

A and B, The receiver-operating characteristic (ROC) curve showed the CTC and AI risk group in the nature of pulmonary nodule. AUC, area under the curve.

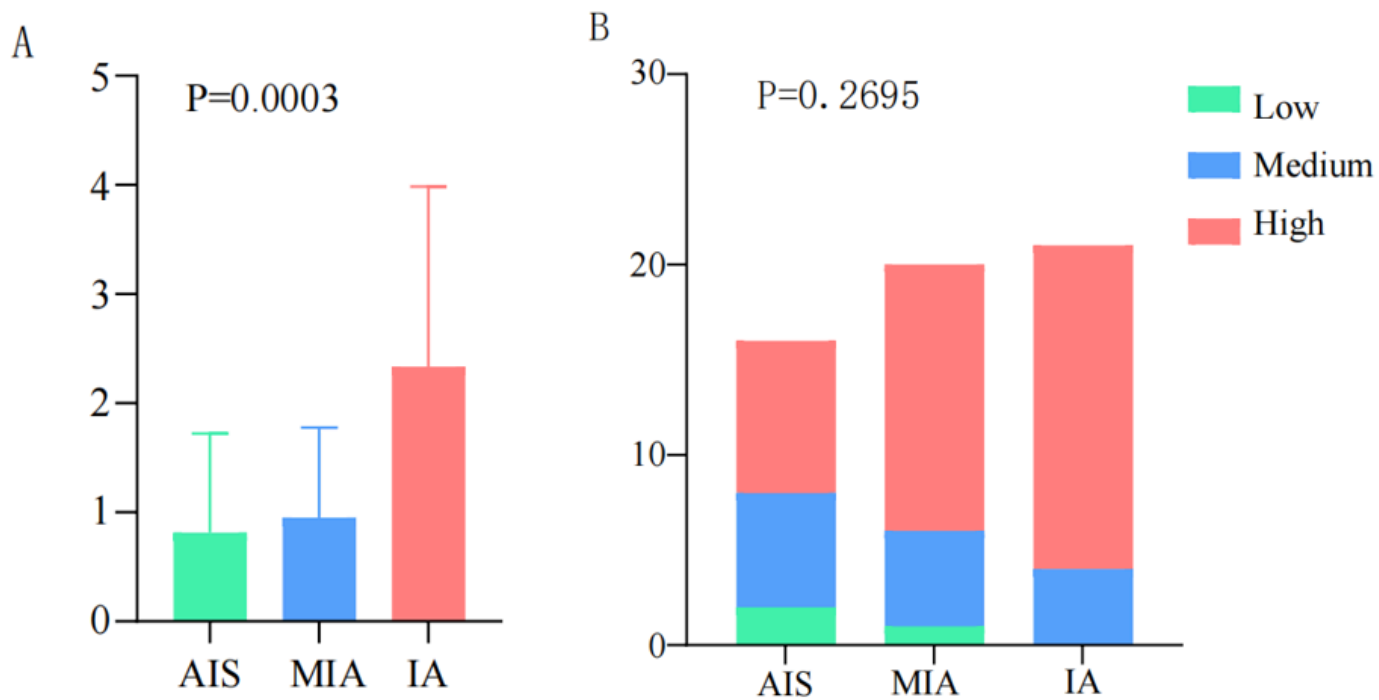


**Figure 2**

A Differences in CTC count for different degrees of invasion of LUAD. B Risk group of LUAD with different degrees of invasion.

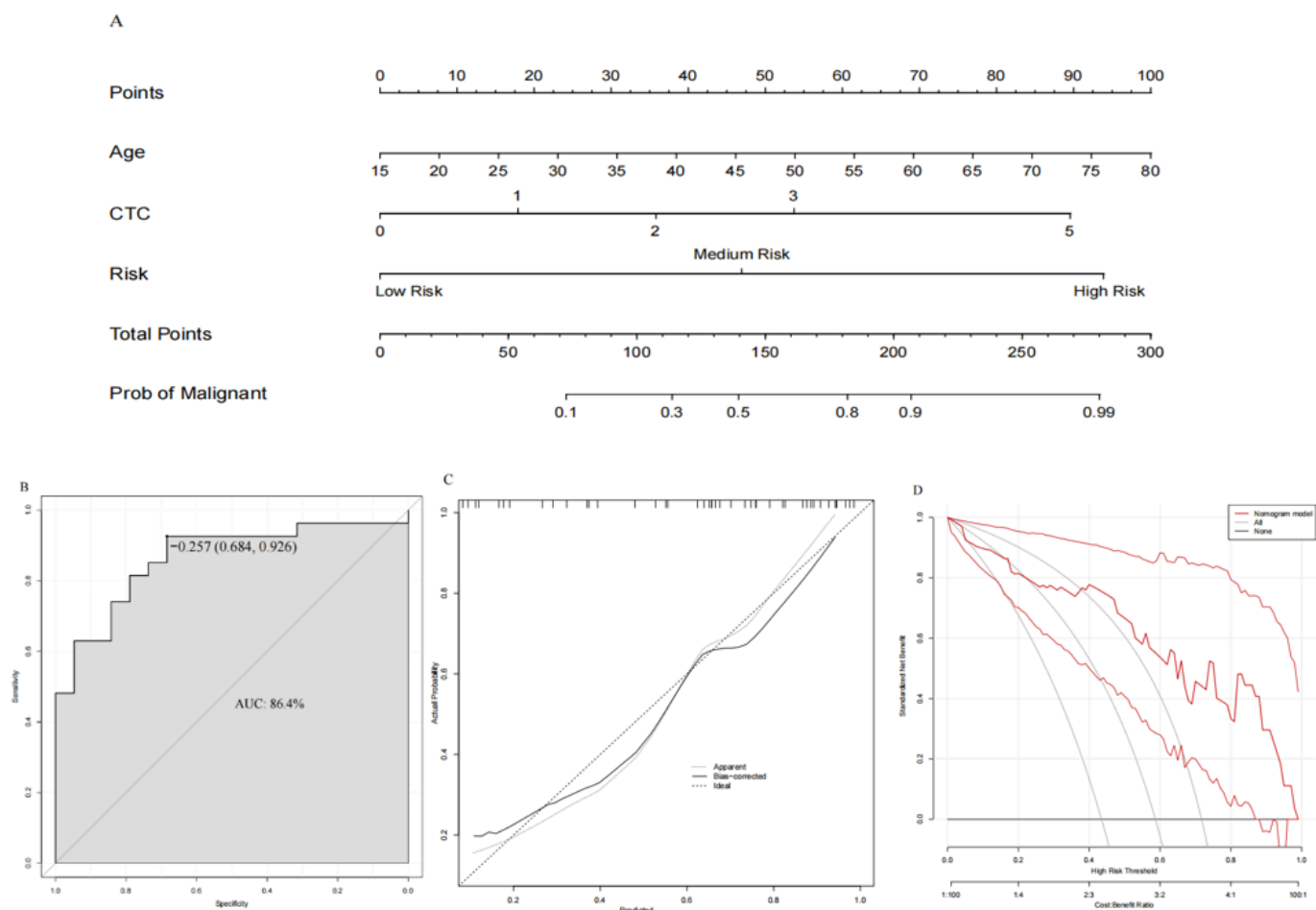


**Figure 3**

Construction of Nomogram based on the training set. A The nomogram for the diagnostic models of pulmonary nodules. B, C, D ROC curves, Calibration plots and Decision Curve Analysis for the nomogram.

## Supplementary Files

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