Computed tomography-guided cutting needle biopsy for lung nodules: when the biopsy-based benign results are real benign

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Research article

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Abstract

Background: Computed tomography (CT)-guided cutting needle biopsy (CNB) has been widely used for the diagnosis of lung nodules (LNs). The false-negative rate of CT-guided lung biopsy is reported to be up to 16%. The aim of this study was to determine the predictors of true-negative results in LNs with CNB-based benign results. Methods: From January 2011 to December 2015, 96 patients with CNB-based non-specific benign results were included in this study as the training group to detect predictors of true-negative results. From January 2016 to December 2018, an additional 57 patients were included as a validation group to test the reliability of the predictors. Results: In the training group, a total of 96 patients underwent CT-guided CNB for 96 LNs. The CNB-based results were true-negatives for 82 LNs and false-negatives for 14 LNs. The negative predictive value of the CNB-based benign results was 85.4% (82/96). Univariate and multivariate logistic regression analyses revealed that CNB-based chronic inflammation with fibroplasias (P = 0.013, hazard ratio = 0.110, 95% confidential interval = 0.019–0.625) was the independent predictor of true-negative results. The area under the receiver operator characteristic (ROC) curve was 0.697 (P = 0.019). In the validation group, biopsy results for 47 patients were true-negative and 10 were false-negative. When the predictor was used on the validation group, the area under the ROC curve was 0.759 (P = 0.011). Conclusions: Most of the CNB-based benign results were true-negatives, and CNB-based chronic inflammation with fibroplasias could be considered a predictor of true-negative results.

Background

Computed tomography (CT)-guided cutting needle biopsy (CNB) has been widely used for the diagnosis of lung masses or nodules due to its mini-invasive nature and high diagnostic accuracy [1-8]. CNB-based malignant results can be considered the final diagnosis as the rate of false-positives is extremely low (0–0.2%) [9]. A CNB-based specific benign diagnosis (e.g., tuberculosis, fungal infection, or benign tumors) can also be accepted as the final diagnosis [1-8], enabling patients with suspicious lung lesions to avoid unnecessary surgery.

However, the management of a CNB-based non-specific benign diagnosis (e.g., chronic inflammation) is challenging because this diagnosis cannot be considered the definite final diagnosis [1-8]. The false-negative rate of CT-guided lung biopsy was reported to be up to 16% [9]. At present, some studies have established some predictors of true- or false-negative findings from CNB-based non-specific benign results [9, 10]. However, no study has investigated true-negative findings in lung nodules (LNs) with CNB-based non-specific benign results.

In this study, we determined the predictors of true-negatives in LNs with CNB-based benign results.

Methods

This 2-center retrospective study was approved by our institutional review board. The requirement of informed consent was waived because of the retrospective nature.

Patients

From January 2011 to December 2015, a total of 141 patients with CNB-based benign results from LNs were collected. Among them, 96 patients with CNB-based non-specific benign results were included in this study as the training group that detected the predictors of true-negative results (Fig. 1). From January 2016 to December 2018, additional 57 patients were included as a validation group that tested the reliability of the predictors.

The decision for lung biopsy was made based on the recommendation of the management of LNs [11]. The inclusion criteria were: (a) patients with LN and (b) patients with CNB-based benign results. The exclusion criteria were: (a) CNB-based specific benign results; (b) patients with distant metastasis; and (c) lesions without a definite final diagnosis.

CT-guided CNB procedure

All procedures were performed by a chest radiologist with more than 5 years of biopsy experience. CNB was guided by a 16-detector CT (Philips, Cleveland, Ohio, USA). The tube voltage and current were 120 kV and 150 mA/s, respectively.

All patients were placed in an appropriate position according to the location of LN. An 18G semi-automatic cutting needle (Wego, Weihai, China) was punctured into the lung parenchyma, after which an additional CT scan was performed to establish the needle tip location to move it accordingly. When the needle tip touched the target lesion, a specimen was obtained from the lesion. One

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Definitions

LN is defined as a round or oval lesion ≤ 3 cm that is completely surrounded by pulmonary parenchyma without other abnormalities [1-4]. CNB-based benign results can be divided into specific and non-specific benign results [10]. Specific benign results were defined as benign tumors or infectious diseases with identified pathogens. Non-specific benign results were defined as the presence of benign pathological features such as inflammatory cells or fibrosis that was insufficient to render a specific diagnosis.

CNB-based benign results were considered to be true-negatives if the lesions were benign upon final diagnosis. A final benign diagnosis could be made in 1 of the 3 ways: (a) surgery; (b) determination of a specific benign lesion upon pathological analysis of the lung biopsy sample; or (c) a decrease > 20% in lesion diameter, stability in size (without anticancer treatment) over a minimum of 2 years [10]. If lesions did not meet the criteria mentioned above, final diagnoses were listed as non-diagnostic lesions.

Statistical Analysis

The statistical analysis was performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were summarized as the mean ± standard deviation. Numeric data were analyzed using $\chi 2$ tests or Fisher exact probability tests. Predictors of true-negative findings were identified using univariate and multivariate logistic regression analyses. The covariates incorporated into the multivariate analysis were variables with $P < 0.1$ in the univariate analysis. Receiver operator characteristic (ROC) curves were created and areas under the curves were calculated. A p value < 0.05 was considered statistically significant.

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Results

Training group

In the training group, a total of 96 patients underwent CT-guided CNB for 96 LNs. All of the 96 LNs were diagnosed as CNB-based non-specific benign. The CNB-based results were true-negatives for 82 LNs and false-negatives for 14 LNs (Table 1). The negative predictive value (NPV) of the CNB-based benign results was 85.4% (82/96).

Complications

Pneumothorax and hemoptysis were found in 15 (15.6%) and 21 (22.9%) patients, respectively. Only five patients with pneumothorax underwent chest tube insertion and the remaining patients underwent conservative treatment.

True-negative LNs

Among the 82 true-negative LNs, 56 cases were confirmed by CT follow-up (Fig. 2) and 26 cases were confirmed by surgery. The 26 surgical diagnoses included inflammatory pseudo-tumors (n = 20), hamartoma (n = 3), granulomatous inflammation (n = 2), and bronchial cyst (n = 1).

False-negative LNs

Among the 14 false-negative LNs, 9 cases were confirmed by re-biopsy and 5 cases were confirmed by surgery. The final diagnoses of the 14 LNs included adenocarcinoma (n = 13) and squamous cells carcinoma (n = 1).

Re-biopsy and surgery

Patients underwent either re-biopsy (n = 14) or surgery (n = 33) after the initial CT-guided CNB (Table 2). The reasons for re-biopsy or surgery included increased size during follow-up (n = 4), abnormal tumor marker levels (n = 14), positron emission tomography (PET)-CT uptake (n = 20), and the patients' request (n = 9). False-negative LNs were found in all of the four cases with increased sizes, seven (50%) cases with abnormal tumor marker levels, and three (15%) cases with PET-CT uptake.

Predictor of true-negative

Univariate logistic analysis revealed that the predictors of true-negative results included younger age [P = 0.024, hazard ratio (HR) = 1.082, 95% confidence interval (CI) = 1.010–1.158], normal carcinoembryonic antigen (CEA) levels (P = 0.005, HR = 7.037, 95% CI = 1.782–27.784), normal squamous cell carcinoma antigen (SCC) levels (P = 0.01, HR = 22.091, 95% CI = 2.109–231.443), and CNB-based chronic inflammation with fibroplasias (P = 0.015, HR = 0.144, 95% CI = 0.030–0.684). Multivariate analysis revealed that the independent predictor of true-negative results was CNB-based chronic inflammation with fibroplasias (P = 0.013, HR = 0.110, 95% CI = 0.019–0.625, Table 3).

A ROC curve was established to test the predictive ability of CNB-based chronic inflammation with fibroplasias. The area under the ROC curve was 0.697 (P = 0.019, Fig. 3).

Validation group

Clinical data of the patients in the validation group (n = 57) were used to test the predictive ability of the predictor. There were no significant differences in baseline data between the training and validation groups. The biopsy results for 47 patients were true-negative and 10 were false-negative. CNB-based chronic inflammation with fibroplasias was tested by the validation group, and the area under the ROC curve was 0.759 (P = 0.011, Fig. 4).

Discussion

This study determined the predictors of true-negative results for LNs with CNB-based benign results. First of all, the NPV in the training group of this study was 85.4%, which is within the range demonstrated by previous studies regarding CT-guided CNB for lung lesions (78–90%) [9, 10, 12]. This NPV value may indicate that most CNB-guided benign results are reliable. Among the 82 cases with true-negative results, 56 cases (68.2%) were confirmed by CT follow-up. This result indicates that CT follow-up is a reasonable management for LNs with CNB-based benign results.

A multi-center study of the malignant risk of CNB-based non-diagnostic results revealed that granulomatous inflammation, abscess, and organizing pneumonia were predictors of true-negative results [13]. In this study, we also found that all of the six cases with CNB-based granulomatous inflammation were true-negatives. However, CNB-based granulomatous inflammation was not a significant predictor of true-negative results in this study. This finding may be associated with the limited sample size of cases with CNB-based granulomatous inflammation.

Our study found that CNB-based chronic inflammation with fibroplasias was an independent predictor of true-negative results. The true-negative group had a significantly higher rate of cases with CNB-based chronic inflammation with fibroplasias than the false-negative group (54.9% vs. 7.1%, respectively; P = 0.001). Similarly, Liu et al. [12] also found that CNB-based chronic inflammation with fibroplasias is a predictor of true-negative results. Chronic inflammation with fibroplasias is considered a first step to the formation of organizing pneumonia or granulomatous inflammation [12, 14, 15]. Therefore, it is reasonable that CNB-based chronic inflammation with fibroplasias may indicate a true-negative result.

Abnormal tumor marker levels were not found to be associated with false-negative results, although univariate logistic analysis demonstrated that abnormal CEA and SCC levels were predictors of false-negative results. Also previous studies did not find any tumor marker level to be associated with false-negatives from CNB-based benign results [9, 10, 12].

Kim et al. [10] found that partial-solid lesions were a risk factor for false-negative CNB-based benign results (HR = 3.95, P = 0.022). Many studies suggest that regular CT follow-up is the predominant management of partial-solid LNs [16, 17]. Therefore, only two cases with partial-solid LNs were included in the training group.

A ROC curve was generated to test the predictive ability of CNB-based chronic inflammation with fibroplasias, with an area under the ROC curve of 0.697 (P = 0.019). An additional validation group with 57 cases tested this predictive factor again and demonstrated that the area under the ROC curve was 0.759 (P = 0.011). These results may indicate an impressive predictive ability of CNB-based chronic inflammation with fibroplasias.

The present study had some limitations. First, the major limitation of this study was the retrospective design, which led to selection bias. Second, there is no unified criterion for the quantity of biopsy specimens that need to be collected. Instead, we collected biopsy specimens in accordance with our experience. Although the sample number was not associated with true-negative results, it may have otherwise biased our findings. Third, the PET-CT data were incomplete.

Conclusions

In conclusion, although further clinical researches are needed, our study indicated that most of the CNB-based benign results were true-negatives. CNB-based chronic inflammation with fibroplasias could be considered as the predictor of true-negative results.

Abbreviations

CEA: carcinoembryonic antigen

CNB: cutting needle biopsy;

CT: computed tomography;

LN: lung nodule;

NPV: negative predictive value;

NSE: neuron-specific enolase;

PET: positron emission tomography;

ROC: receiver operator characteristic

SCC: squamous cell carcinoma antigen.

Declarations

Ethics approval and consent to participate: This retrospective study was approved by institutional review board of Xuzhou Central Hospital. The consent to participate was waived due to the retrospective nature. Only the relevant patient provided informed consent for publication of the images in Fig. 2.

Consent for publication: The relevant patient provided informed consent for publication of the images in Fig. 2. The obtained consent was written.

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

Competing interests: None.

Funding: None

Authors' contributions: XL designed this study, TW and XL performed the CT-guided biopsy procedure, HH, HTY and YZ collected the patients' data; YFWY and XMX analyzed these data; HH wrote and revised this paper; Final manuscript was approved by all authors.

Acknowledgments: None

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Tables

Table 1. Comparison of baseline data between true and false negatives in training group.

	True negative	False negative	P value
Patients number	82	14	
Age (year)	56.3 ± 12.8	64.7 ± 5.3	< 0.001
Sex (male/female)	47/35	7/7	0.610
Smoker	34	5	0.686
Imaging feature			
Size (mm)	18.5 ± 5.8	18.6 ± 5.2	0.989
Solid/Sub-solid	81/1	13/1	0.272
Spiculation	38	9	0.214
Pleural retraction sign	32	7	0.440
Cavity	7	1	1.000
Calcification	15	0	0.179
Enlarged hilar or mediastinal lymph nodule (≥ 10 mm)	16	5	0.315
Emphysema	17	3	1.000
Uptake in PET-CT (SUVmax ≥ 2.5)	18 (n = 35)*	3 (n = 8)*	0.750
Nodule location			
Right lung/Left lung	41/41	7/7	1.000
Upper lobe/Non-upper lobe	39/43	6/8	0.744
Details of biopsy procedure			
Lesion - pleura distance (mm)	15.5 ± 14.6	19.5 ± 14.5	0.340
Needle - pleura angle (degrees)	69.0 ± 19.3	64.4 ± 24.5	0.420
Number of specimen	1.6 ± 0.7	1.3 ± 0.5	0.154
Pneumothorax	12	3	0.803
Hemoptysis	16	5	0.315
Tumor marker			
Abnormal CEA (normal: 0-5 ug/L)	6	5	0.009
Abnormal Cyfra21-1 (normal: 0-3.3 ng/ml)	7	2	0.852
Abnormal SCC (normal: 0-2.5 ug/L)	1	3	0.009
Abnormal NSE (normal: 0-16.3 ng/ml)	2	0	1.000
Pathological feature of biopsy			

Chronic inflammation with fibroplasia	45	1	0.001
Chronic inflammation with alveolar epithelial hyperplasia	14	3	0.987
Granulomatous inflammation	8	0	0.599

CEA: Carcinoembryonic antigen; CT: Computed tomography; NSE: Neuron-specific enolase; PET: Positron emission tomography; SCC: Squamous cell carcinoma antigen; SUV: Standardized uptake value.

*: Thirty-five and 8 patients underwent PET-CT examination in true- and false-negative groups, respectively.

Table 2. Reasons of re-biopsy or surgery in training group.

	Number
Re-biopsy	14
Surgery	33
Reasons	
Increased size during follow-up	4
Abnormal tumor marker level	14
PET-CT uptake	20
Patients’ requirement	9

PET: Positron emission tomography; CT: Computed tomography.

Table 3. Predictors of true negatives.

Variables	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Age	1.082	1.010 – 1.158	0.024	1.078	0.995 – 1.169	0.066
Abnormal CEA	7.037	1.782 – 27.784	0.005	4.228	0.697 – 25.635	0.117
Abnormal SCC	22.091	2.109 – 231.443	0.01	13.060	0.801 – 212.880	0.071
Chronic inflammation with fibroplasia	0.144	0.030 - 0.684	0.015	0.110	0.019 - 0.625	*0.013*

CI: confident interval; CEA: Carcinoembryonic antigen; SCC: Squamous cell carcinoma antigen.

Table 4. Comparison of baseline data between training and validation group.

	Training group	Validation group	P value
Patients number	96	57	
Age (year)	57.5 ± 12.3	58.2 ± 10.6	0.750
Sex (male/female)	54/42	33/24	0.843
Smoker	39	29	0.217
Imaging feature			
Size (mm)	18.6 ± 5.7	17.8 ± 6.0	0.434
Solid/Sub-solid	94/2	55/2	0.992
Spiculation	47	29	0.818
Pleural retraction sign	39	20	0.496
Cavity	8	7	0.427
Calcification	15	3	0.054
Enlarged hilar or mediastinal lymph nodule (≥ 10 mm)	21	9	0.359
Emphysema	20	14	0.592
Nodule location			
Right lung/Left lung	48/48	32/25	0.462
Upper lobe/Non-upper lobe	45/51	28/29	0.788
Details of biopsy procedure			
Lesion - pleura distance (mm)	16.1 ± 14.6	17.5 ± 13.8	0.558
Needle - pleura angle (degrees)	68.3 ± 20.1	67.2 ± 19.4	0.733
Number of specimen	1.5 ± 0.7	1.4 ± 0.5	0.381
Pneumothorax	15	8	0.790
Hemoptysis	21	14	0.702
Tumor marker			
Abnormal CEA (normal: 0-5 ug/L)	11	7	0.879
Abnormal Cyfra21-1 (normal: 0-3.3 ng/ml)	9	7	0.570
Abnormal SCC (normal: 0-2.5 ug/L)	4	2	1.000
Abnormal NSE (normal: 0-16.3 ng/ml)	2	2	0.992
Pathological feature of biopsy			
Chronic inflammation with fibroplasia	46	30	0.948

Chronic inflammation with alveolar epithelial hyperplasia	17	13	0.442
Granulomatous inflammation	8	1	0.198
True negative/False negative	82/14	47/10	0.626

CEA: Carcinoembryonic antigen; SCC: Squamous cell carcinoma antigen; NSE: Neuron-specific enolase.

Figures

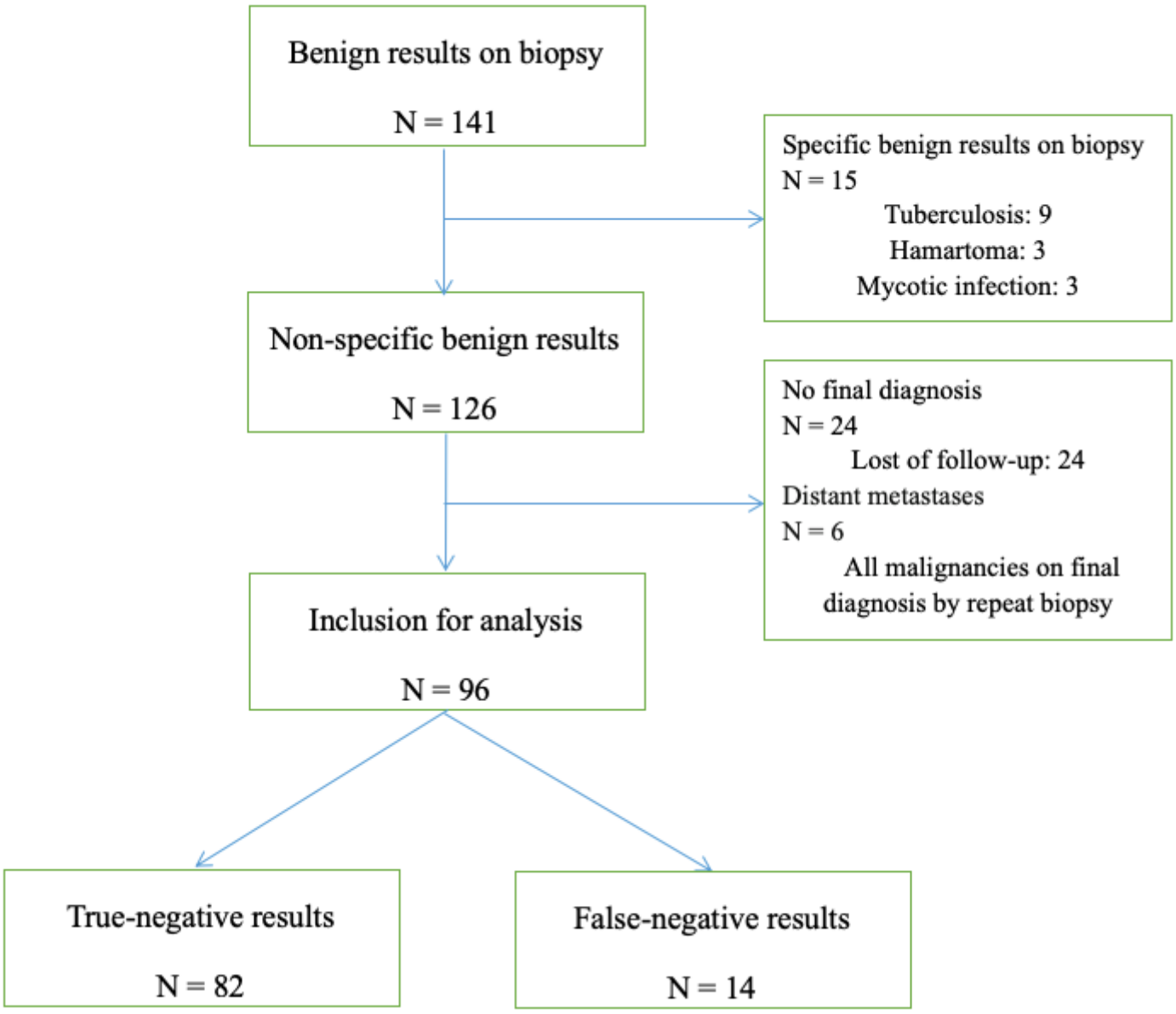

Figure 1

A flowchart of training group in this study.

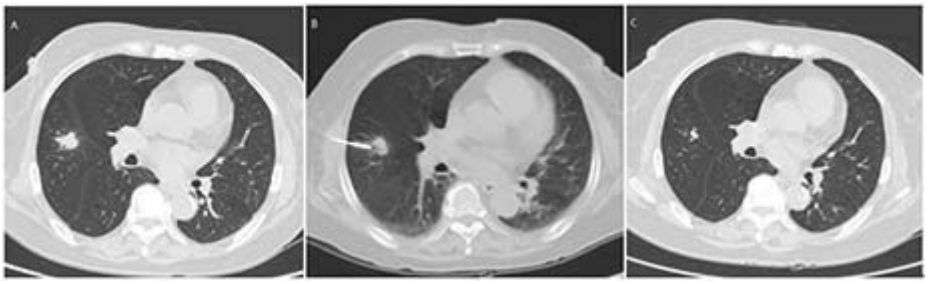

Figure 2

A LN which was presented with CNB-based chronic inflammation with fibroplasias. (A) A lN located in right middle lobe. (B) The procedure of the lung biopsy. (C) The lesion was significant resolved after 10 months.

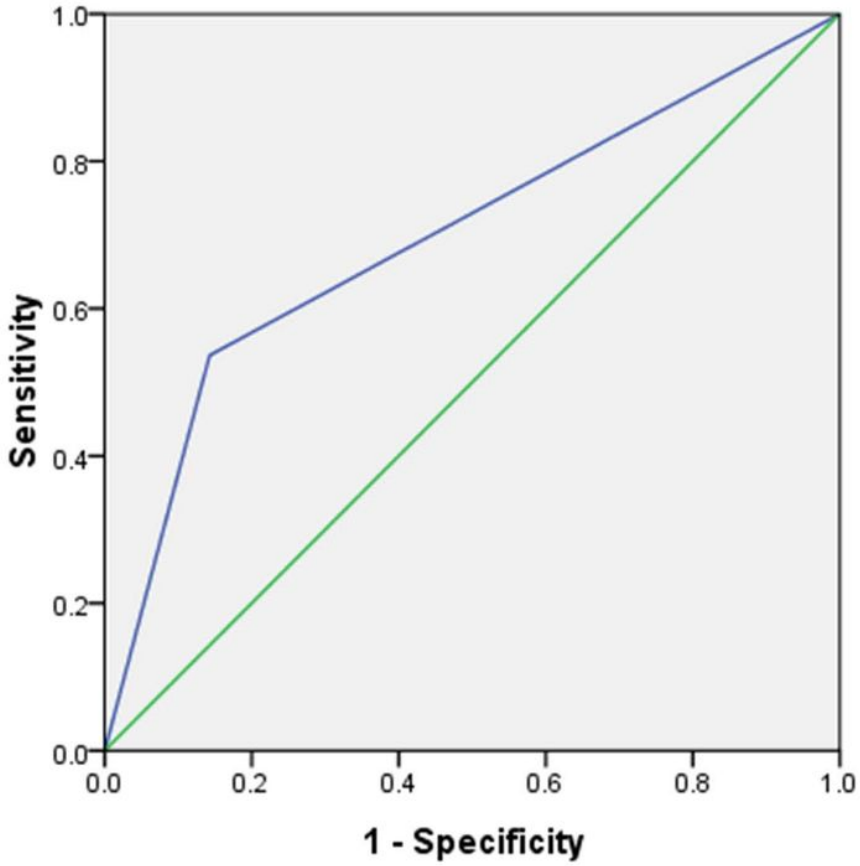

Figure 3

The ROC curve generated using the predictor from training group.

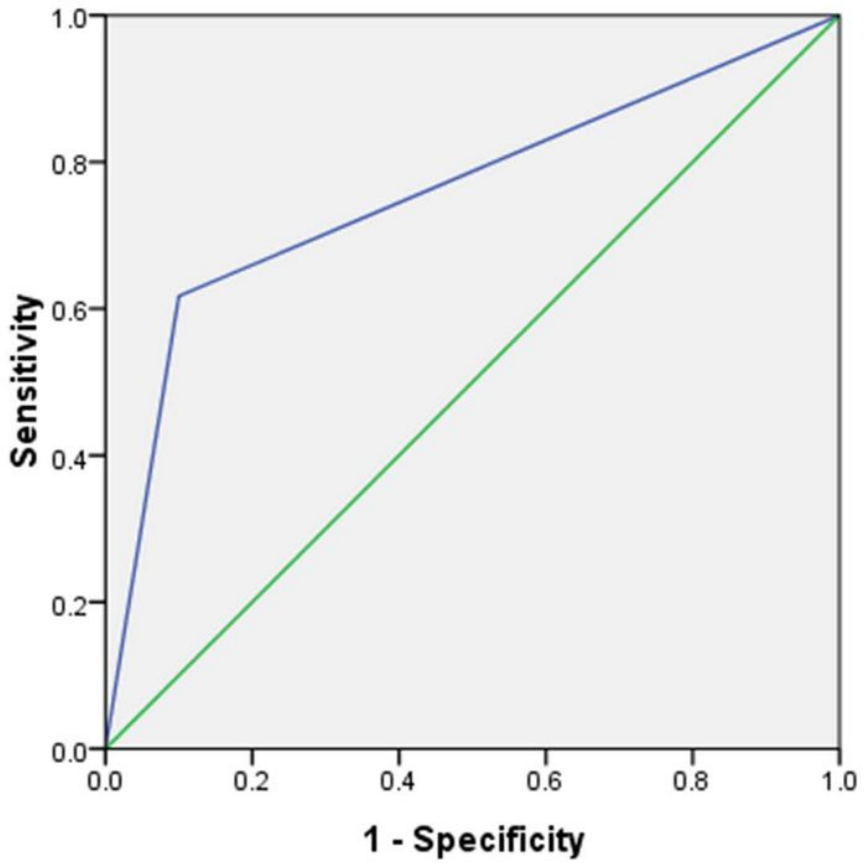

Figure 4

The ROC curve generated using the predictor from validation group.