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Research Article

Regression–Based Diagnostic Models for Early Lung Cancer Integrating Conventional Indicators with Tumor Markers

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Abstract

The aim of this research was to develop a lung cancer diagnostic and predictive model that integrates traditional laboratory indicators with tumor markers. This model is intended to facilitate early screening and assist in the process of identifying or detecting lung cancer through a cost-effective, rapid, and convenient approach, ultimately enhancing the early detection rate of lung cancer. A retrospective study was conducted on 66 patients diagnosed with lung cancer and 159 patients with benign pulmonary conditions. Data including general clinical information, conventional laboratory test results, and tumor marker levels were collected. Data analysis was conducted using SPSS 26.0 (Statistical Product and Service Solutions 26.0). The lung cancer diagnosis and prediction model is created using a composite index established through binary logistic regression. The combined diagnostic prediction models, incorporating both traditional indicators and tumor markers, demonstrated a greater area under the curve (AUC) when compared to the diagnostic prediction model based solely on tumor markers and their combination testing. The values of cut-off point, AUC, accuracy, sensitivity, specificity, positive and negative detection rate and accuracy rate are 0.1805, 0.959, 86.67%, 0.955, 0.830, 95.45%, 83.02% and 89.33 respectively and it is shown that the combined diagnostic model display notable efficacy and clinical relevance in aiding the early diagnosis of lung cancer.

Keywords

Combined Detection, Early Lung Cancer, Tumor Markers, Binary Logistic Regression

1. Introduction

Lung cancer stands as the primary cause of cancer-related deaths [1], characterized by a low survival rate of only 19.4% over five years [2]. However, patients diagnosed with early-stage lung cancer exhibit a greater five-year overall survival rate of approximately 80% [3, 4]. During the initial phases of lung cancer, symptoms are often not apparent in most patients, leading to delayed diagnosis and a higher likelihood of advanced-stage or metastatic disease at the time of diagnosis. Consequently, early detection plays a crucial role in enhancing the diagnostic rates of lung cancer and decreasing mortality associated with the disease.

While lung biopsy remains the preferred diagnostic method for lung cancer, it is an invasive procedure carrying inherent risks. Despite this, imaging technologies like computed to-

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mography (CT) have demonstrated efficacy when conducting screenings for individuals at high risk of lung cancer, there was a 20% decrease in lung cancer mortality among those who underwent CT screening [5, 6]. Despite this benefit, CT scans present challenges such as low specificity and high costs for lung cancer detection, along with potential harm from repeated exposure to radiation [7, 8]. In contrast, utilizing biomarkers in peripheral blood for cancer prediction offers a method that is easily accessible, does not require any invasive procedures, and has gained widespread acceptance. During the progression of cancer, tumor markers are substances that are either released by tumor cells or are produced as a result of the interplay between tumors and the host's cells. Variations in their presence or levels [9, 10] can indicate the presence of tumors, playing a crucial role in lung cancer screening, diagnosis, and treatment assessment. Nevertheless, the ability of tumor markers to detect early-stage lung cancer is not optimal, as indicated by the sensitivity rates reported in studies [11, 12]. Additionally, no individual serum tumor marker is exclusively reliable for lung cancer detection [13, 14]. Enhancing the early diagnosis rates of lung cancer has become a focal point of research, with investigations focusing on combining traditional biological markers present in the peripheral blood, including tumor markers, can be used as indicators.

Hence, this research employs binary logistic regression to develop a comprehensive diagnostic model for lung cancer. This model integrates clinical data, encompassing various laboratory parameters and tumor markers. The aim is to offer a more convenient, rapid, and cost-effective approach for the purposes of detecting and identifying lung cancer at its earliest stages. In addition, clinical screening and diagnostic procedures are essential, ultimately enhancing the early detection rates of the disease.

2. Materials and Methods

2.1. Clinical Sample Collection

Between April 2019 and February 2024, data on the overall clinical features (such as age and gender) and laboratory indicators (encompassing tumor markers, liver and kidney function tests, electrolytes, blood counts, and coagulation profiles) of individuals diagnosed with either lung cancer or benign lung conditions at the Second Affiliated Hospital of Zunyi Medical University were gathered through retrospective analysis. Following the application of specific inclusion and exclusion criteria, 868 cases were scrutinized, with 225 cases meeting the criteria for further follow-up analysis. Among these, 66 cases were individuals diagnosed with lung cancer, all verified through pathological biopsy, while the remaining 159 cases were patients with benign lung conditions. The category of subjects is segregated into distinct comparison groups: the lung cancer and benign lung disease group consisting of 225 cases, where the lung cancer group is represented by symbol 1 and another group is represented by symbol 0. Based on these two comparison groups, we will establish a comprehensive indicator screening and diagnostic prediction model to detect early-stage lung cancer and benign lung disease patients.

2.2. Inclusion and Exclusion Criteria

Inclusion criteria for early lung cancer cases were as follows: inclusion criteria limited to patients with a definitive lung cancer diagnosis, confirmed via pathological biopsy. Exclusion criteria encompassed patients with other cancers, a past history of cancer, those who had undergone prior treatment, and cases with incomplete data. The benign lung disease group comprised solely of cases with a confirmed benign lung condition, excluding those with a past history of lung or other cancers, suspected lung cancer, or incomplete data.

2.3. Statistical Analysis

Utilizing SPSS 26.0, statistical evaluations and visual representations were performed. Measures that followed a normal distribution were presented as X ±SD and described as the median and interquartile range when a normal distribution were not met. To compare the normally distributed measurement data across different groups, statistical description of independent samples was utilized. In all analyses, a significance level of $P<0.05$ was considered statistically significant. The receiver operating characteristic (ROC) curve was plotted, and the area under the curve (AUC) was calculated to compare the diagnostic prediction models.

3. Model Building Strategies

Regression analysis is a versatile research methodology [15, 16] that offers valuable insights across various study contexts. It can be used to explore relationships between an outcome and multiple independent variables, as well as to assess how effectively an outcome can be forecasted based on a specific set of independent variables. Logistic regression stands out as an effective and robust method for evaluating the influence of a group of independent variables on a dichotomous outcome. outcome by assessing the individual contribution of each independent variable. The fundamental formula for multiple linear regression involving several independent α variables is,

$$\hat{Y} = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_i X_i \quad (1)$$

Where $\hat{Y}$ is the estimated continuous outcome, X_i denotes independent variable, β_i is estimated coefficient. Identifying the contributions of independent variables in logistic regression starts with the subsequent equation.

$$P\left(\hat{Y}_i\right)=\frac{e^{\beta_0+\beta_1X_1+\beta_2X_2+\ldots+\beta_iX_i}}{1+e^{\beta_0+\beta_1X_1+\beta_2X_2+\ldots+\beta_iX_i}} \quad (2)$$

Precisely, a binary outcome represented as a probability should be within the range of 0 to 1. To address this issue, the logit scale resolves it by transforming the initial linear regression equation mathematically to produce the logit, which is the natural logarithm of the odds of belonging to one outcome category ($\hat{Y}$) compared to the other category ($1-\hat{Y}$).

$$\ln\left(\hat{Y}/1-\hat{Y}\right)=\beta_0+\beta_1X_1+\beta_2X_2+\ldots+\beta_iX_i. \quad (3)$$

Coefficients in formula (3) are solved using maximum likelihood estimation. In our experimental analysis (P<0.05), the independent variables will be selected based on the following three scenarios: 1) the combination of three traditional tumor markers (P<0.05); 2) the combination of all clinical indicators with statistically significant differences (P<0.05); 3) the combination of all clinical indicators. After obtaining the integrated detection probabilities of the aforementioned combination of indicators, the optimal cut-off point will be determined using the Youden index.

4. Results

4.1. Examination of The Overall Clinical Traits of Subjects

Within the comparison group of lung cancer and benign lung disease, an elevated risk of lung cancer was linked to three tumor markers (Carcinoembryonic antigen [CEA], squamous cell carcinoma antigen [SCC], cytokeratin-19 fragment [CYFRA21-1], neuron-specific enolase [NSE], and pro-gastrin-releasing peptide [proGRP]). Another conventional indicators as follows: Age, WBC (White Blood Cell Count), Neut# (Neutrophil Count), Lymph# (Lymphocyte Count), Mono# (Monocyte Count), Eos# (Eosinophil Count), Baso# (Basophil Count), RBC (Red Blood Cell Count), HGB (Hemoglobin), HCT (Hematocrit), MCV (Mean Corpuscular Volume), MCH (Mean Corpuscular Hemoglobin), MCHC (Mean Corpuscular Hemoglobin Concentration), RDW (Red Cell Distribution Width), PLT (Platelet Count), PCT (Plateletcrit), PLT (Platelet Count), PDW (Platelet Distribution Width), MPV (Mean Platelet Volume), ESR (Erythrocyte Sedimentation Rate), ALT (Alanine Aminotransferase), AST (Aspartate Aminotransferase), AST/ALT (Ratio of Aspartate Aminotransferase to Alanine Aminotransferase), GGT (Gamma-Glutamyl Transferase), TBIL (Total Bilirubin), DBIL (Direct Bilirubin), IBIL (Indirect Bilirubin), TBA (Total Bile Acids), TP (Total Protein), ALB (Albumin), GLB (Globulin), A/G (Albumin to Globulin Ratio), PA (Prealbumin), Urea (Urea Nitrogen), Cr (Creatinine), GLU (Glucose), PT-INR (Prothrombin Time - International Normalized Ratio), PT (Prothrombin Time), PT% (Prothrombin Activity), APTT (Activated Partial Thromboplastin Time), Fbg (Fibrinogen), TT (Thrombin Time), PTR (Prothrombin Time Ratio). First of all, a normality test and statistical descriptive analysis were conducted on the traditional indicators and tumor markers of the patients. It was found that the normal distribution was considered to be statistically significant (P<0.05). Therefore, it decide to use the median (the upper and lower quartiles) to represent the range of values for each serum tumor marker, as shown in Table 1.

Table 1. *Comparisons of Detection Results of Three Serum Tumor Markers and Other Conventional Indicators.*

No	Indicators	Group 1: *n*=99		Group 0: *n*=126		*P* value
		[*M*(*P*$_{25}$, *P*$_{75}$)]	Mean	[*M*(*P*$_{25}$, *P*$_{75}$)]	Mean	
1	Age	63.5 (54, 69.25)	61.89	63 (49, 72)	60.49	0.742
2	WBC	6.06 (5.38, 7.42)	6.97	6.82 (5.32, 8.97)	7.85	0.099
3	Neut#	3.88 (3.21, 4.88)	4.68	4.63 (3.25, 6.68)	5.70	0.03
4	Lymph#	1.46 (1.2, 1.95)	1.56	1.25 (0.91, 1.66)	1.35	0.009
5	Mono#	0.42 (0.35, 0.56)	0.53	0.5 (0.38, 0.7)	0.58	0.018
6	Eos#	0.12 (0.06, 0.21)	0.19	0.07 (0, 0.15)	0.22	0.003
7	Baso#	0.04 (0, 0.06)	0.04	0 (0, 0.05)	0.03	0.009
8	RBC	4.49 (4.17, 4.81)	4.47	4.31 (3.86, 4.73)	4.25	0.024
9	HGB	136 (122.75, 149.25)	135.69	128 (116, 141)	126.36	0.001
10	HCT	0.41 (0.38, 0.44)	0.41	0.38 (0.35, 0.42)	0.38	0.002

No	Indicators	Group 1: n=99		Group 0: n=126		P value
		[$M(P_{25}, P_{75})$]	Mean	[$M(P_{25}, P_{75})$]	Mean	
11	MCV	90.8 (87.3, 93.5)	90.39	90 (86, 93.4)	89.28	0.281
12	MCH	30.7 (29.5, 31.63)	30.4	30.2 (28.8, 31.3)	29.88	0.046
13	MCHC	337 (328.75, 344)	336.14	334 (325, 346)	334.55	0.635
14	RDW	13 (12.48, 13.4)	13.09	13.4 (12.7, 14.5)	13.78	0.001
15	PLT	237 (200, 281.25)	244.44	239 (184, 307)	256.00	0.813
16	PCT	0.26 (0.24, 0.3)	0.29	0.26 (0.22, 0.32)	0.28	0.621
17	PLT	33 (26.75, 40.85)	34.11	30.8 (24, 38.1)	31.95	0.177
18	PDW	12.85 (11.7, 15.18)	13.7	12.7 (10.7, 14.6)	13.18	0.228
19	MPV	11 (10.3, 12)	11.17	10.8 (10, 11.6)	10.92	0.209
20	ESR	16 (7, 35.75)	24.75	26 (12, 57)	36.46	0.009
21	ALT	20.5 (14, 27.25)	24.29	17 (11, 26)	34.99	0.104
22	AST	25 (22.75, 29.25)	27.28	23 (19, 34)	40.09	0.317
23	AST/ALT	1.23 (0.9, 1.69)	1.36	1.45 (1, 2)	1.64	0.033
24	GGT	23 (15.75, 39)	33.66	26 (17, 45)	38.47	0.274
25	TBIL	9.7 (7.08, 13.65)	10.99	10.5 (7.7, 13.5)	11.41	0.425
26	DBIL	2.3 (1.88, 3.3)	2.62	2.4 (1.8, 3.3)	2.98	0.654
27	IBIL	7.5 (5.5, 10.2)	8.37	8 (5.8, 10.6)	8.43	0.414
28	TBA	3.84 (2.52, 5.88)	5.16	3.56 (2.13, 7.18)	5.70	0.715
29	TP	68.45 (62.83, 72.1)	67.57	67.7 (63.4, 72.1)	67.35	0.777
30	ALB	39.05 (35.4, 42.6)	38.41	37.5 (34, 41.1)	37.08	0.074
31	GLB	29.25 (26.83, 31.9)	29.16	30 (26.5, 33.7)	30.27	0.27
32	A/G	1.37 (1.19, 1.53)	1.35	1.28 (1.09, 1.49)	1.28	0.086
33	PA	212 (179.75, 259)	217	192 (144, 238)	190.76	0.008
34	Urea	5.2 (4.06, 6.78)	5.41	4.57 (3.79, 6.17)	5.30	0.16
35	Cr	69 (58, 83)	70.72	71 (58, 87)	73.99	0.362
36	GLU	5.6 (4.88, 6.6)	5.99	5.62 (4.88, 7.68)	6.98	0.34
37	PT-INR	0.94 (0.91, 0.99)	0.95	0.94 (0.87, 1.01)	0.96	0.466
38	PT	11.5 (10.8, 12.4)	11.48	10.8 (10, 12.1)	11.09	0.003
39	PT%	111.6 (102, 120.25)	112.28	111.3 (96.7, 126.5)	111.33	0.996
40	APTT	29.5 (26.38, 35.33)	30.85	28 (26.1, 32.1)	29.59	0.114
41	Fbg	3.12 (2.8, 3.84)	3.5	3.45 (2.81, 4.79)	4.03	0.054
42	TT	17.35 (16.68, 18)	17.38	17.5 (16.8, 18.9)	18.12	0.093
43	PTR	0.95 (0.92, 0.99)	0.96	0.94 (0.87, 1)	0.96	0.227
44	SCC	0.75 (0.58, 1)	1.25	0.8 (0.6, 1.1)	1.68	0.615
45	proGRP	33.55 (27.5, 44.55)	63.32	33.9 (26, 45.5)	36.57	0.776
46	CEA	2.45 (1.47, 5.62)	16.2	1.85 (1.19, 2.61)	2.28	0.002
47	NSE	17.21 (12.77, 26.45)	20.31	14.1 (11.39, 20.2)	18.01	0.007

No	Indicators	Group 1: n=99		Group 0: n=126		P value
		[$M(P_{25}, P_{75})$]	Mean	[$M(P_{25}, P_{75})$]	Mean	
48	CYFRA21-1	3.49 (2.43, 5.27)	5.99	2.36 (1.72, 3.3)	3.04	0.000
49	Smoking	-	-	-	-	0.015

4.2. Establishment and Evaluation of Diagnostic Model

For our experimental investigation, we will choose independent variables according to three specific scenarios: 1) three conventional tumor markers (P<0.05 in Table 1); 2) all clinical indicators with statistically significant variances (P<0.05 in Table 1); 3) all clinical indicators. Based on the calculation of the integrated detection probabilities from the specified set of indicators, we will establish the optimal cut-off using the Youden index.

In the group comprising patients with lung cancer and benign lung disease, a diagnostic prediction model was created using three indicators. The model achieved an area under the curve (AUC) value of 0.703. The diagnostic model demonstrated a sensitivity of 45.5% and a specificity of 85.5% in the detection of lung cancer and benign lung disease. Additionally, the Youden index for the model was calculated to be 0.310. If all the indicators in Table 1 that meet the condition of P<0.05 are selected as combined indicators, a diagnostic model was developed utilizing a set of 28 indicators, in which include WBC, Neut#, Lymph#, Mono#, Eos#, Baso#, RBC, HGB, HCT, MCH, RDW, ESR, AST/ALT, PA, PT, CEA, NSE and CYFRA21-1, respectively. The diagnostic model achieved an area under the curve (AUC) value of 0.859. It demonstrated a sensitivity of 0.894 and a specificity of 0.742 in detecting the condition. Furthermore, the Youden index for the model was calculated to be 0.636. The combined diagnostic models involving 28 indicators exhibited a superior AUC compared to the model relying solely on three tumor markers.

More importantly, all indicators in Table 1 are selected as combined detection index, the diagnostic model achieved an AUC value of 0.959, indicating its strong performance. It exhibited a sensitivity of 0.955 and a specificity of 0.830 in accurately identifying the condition. The calculated Youden index for the model was 0.785, suggesting its effectiveness. Notably, the AUC of the combined diagnostic models surpassed that of the model utilizing 28 indicators alone. The diagnostic prediction model, which integrates traditional laboratory indicators with tumor markers, demonstrates superior performance in diagnosing lung cancer compared to the model solely relying on tumor markers and 28 indicators that include conventional indicators, tumor markers and meet the condition of P<0.05.

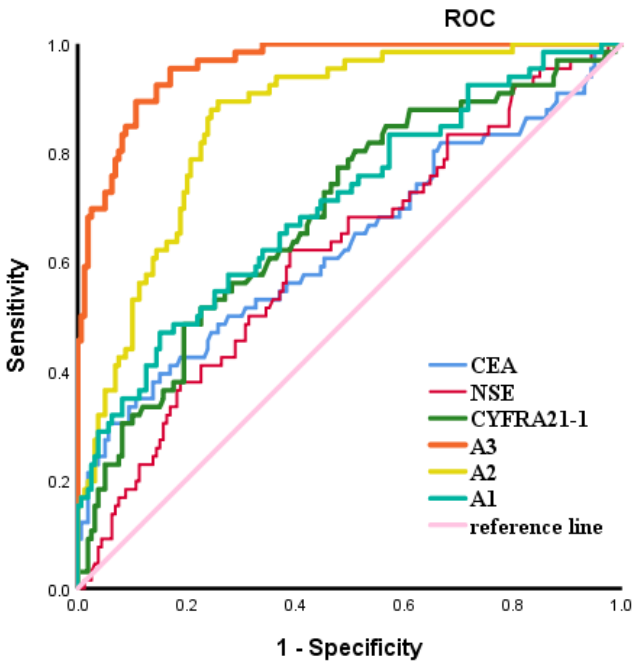

Figure 1. *ROC curve of diagnostic models using individual indicators and different combination approaches.*

ROC curves are shown in Figure 1. Obviously, the combined detection ability of all indicators is higher than other methods. Table 2 (these indicators had significant differences (P<0.05)) presents a detailed comparisons of different approaches in detecting lung cancer and benign lung disease patients, while those indicators (P>0.05) is not analyzed in Table 1. Between the early-stage lung cancer and benign lung disease group, 28 indicators were associated with early-stage lung cancer. Furthermore, there were notable differences in the levels of these 28 indicators between patients with early-stage lung cancer and those with benign lung disease. The model achieved an AUC of 0.859 (refer to A2 in Table 2), with sensitivity and specificity rates of 0.894 and 0.742, respectively, and a Youden index of 0.636 (as shown in Table 2). The model exhibit a good diagnostic effectiveness in distinguishing participants who had early-stage lung cancer as well as those with benign lung disease. However, if all clinical indicators are taken into consideration as a combined indicator to establish a diagnostic model (without considering P<0.05), it is found that the ROC, sensitivity, positive

detection rate and accuracy of the model are the highest.

Table 2. *Comparisons between individual indicators and different combination approaches.*

Different Methods	AUC	Cut-Off	Sensitivity (%)	Specificity (%)	Youden index	Negative Rate (%)	Positive Rate (%)	Accuracy (%)
CEA	0.685	4.400	0.303	0.943	0.246	94.34	30.3	75.56
CYFRA21-1	0.775	2.410	0.773	0.522	0.295	52.2	77.27	59.56
SCC	0.528	2.950	0.091	0.943	0.034	94.34	9.01	69.33
A1	0.703	0.2965	0.455	0.855	0.310	85.53	45.45	73.77
A2	0.859	0.2532	0.894	0.742	0.636	74.21	89.39	78.67
A3	0.959	0.1805	0.955	0.830	0.785	83.02	95.45	86.67

A1: Combined method using three tumor markers. A2: Combined method using 28 indicators (P<0.05). A3: Combined method using all conventional indicators and three tumor markers.

5. Discussion

The objective of the study is to create a diagnostic model for accurately detecting lung cancer and is pivotal in understanding the disease's onset and progression [17]. In this research, three diagnostic models which includes the combination of three tumor markers (P<0.05), all laboratory indicators (P<0.05) and all indicators (without considering P<0.05), were created by integrating traditional laboratory indicators and serum tumor markers through binary logistic regression. Especially, risk assessment capabilities using all laboratory indicators (A3) surpassed those of the model solely based on tumor markers, the combination of three tumor markers (A1) and the combination of all laboratory indicators (A2) (in Table 2). In this study, the age, SCC and proGRP of tumor markers distribution among cases of individuals diagnosed with lung cancer and those with benign lung disease showed no significant difference in the risk of lung cancer as presented in Table 1. Consequently, age SCC and proGRP were not factored into the creation of the diagnosis model for distinguishing between lung cancer and benign lung disease. However, this exclusion of age does not imply that age is irrelevant in identifying benign and malignant lung diseases. Future verification will involve expanding the sample size for more comprehensive validation. Furthermore, smoking [18, 19] can also have a significant impact on the differences between patients with early-stage lung cancer and those with benign lung disease (as shown in Table 1. In fact, a large number of studies use multiple serum markers to establish a diagnostic model for early lung cancer currently, and these markers have statistical significance (P<0.05). This study, however, utilized all serum markers (include both P<0.05 and P>0.05) to establish the diagnostic model and found that the diagnostic results were superior to other methods.

6. Conclusions

Utilizing binary logistic regression method in this study, the diagnostic model for lung cancer that integrates conventional laboratory indicators with tumor markers demonstrates superior diagnostic efficacy. This approach holds far-reaching importance for early adjunctive diagnosis of lung cancer.

Author Contributions

Shufang Zhou: Conceptualization, Data curation, Resources, Investigation, Writing-original draft, Writing-review & editing, Validation

Xiaojun Ge: Methodology, constructive viewpoints and suggestions

Zhifang Yang: Supervision, Writing - review & editing

Fei Zeng: Supervision, Writing - review & editing, Data curation

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Data Availability Statement

1. The data is available from the corresponding author upon reasonable request.
2. The data supporting the outcome of this research work has been reported in this manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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Biography

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Research Field

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Zhifang Yang: Clinical laboratory testing, medical statistical Analysis, probability statistics in medicine
Fei Zeng: Clinical laboratory testing, medical statistical Analysis, probability statistics in medicine