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RESEARCH ARTICLE

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Diagnostic value of HSP90α and related markers in lung cancer

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Abstract

Purpose: To investigate the expression of heat shock protein 90α (HSP90α) in patients with lung cancer (LC) and the clinical value of HSP90α and other related markers in the diagnosis of LC.

Methods: Of 335 patients enrolled in the study cohort, 175 were screened for LC and 160 were healthy (HC). The plasma levels of HSP90α and related markers (CEA, NSE, CYFRA21-1 and ProGRP) were detected in all individuals in the cohort by enzyme-linked immunosorbent assay (ELISA). Groups were divided according to gender (male/female), age (≤60 years/>60 years), types of LC (small-cell carcinoma, squamous carcinoma and adenocarcinoma), staging (I, II, III and IV) and metastasis (metastasis and non-metastasis) separately. Wilcoxon Mann–Whitney test and Kruskal–Wallis test were used to compare statistical differences between two groups/among the multiple groups for each factor of HSP90α. The *r*-value and Kappa were used to compare HSP90α with related markers, and the receiver operating curve (ROC) was used to evaluate the efficacy of plasma HSP90α in predicting LC.

Results: No statistical difference was found in the plasma level of HSP90α among different age and gender groups ($p > 0.05$). In the group divided by LC type, staging and metastasis status, there were statistical differences among different groups in HSP90α level ($p < 0.05$). The levels of HSP90α, CEA, NSE, CYFRA21-1 and ProGRP in LC groups were significantly higher than HC ($p < 0.001$). R values of HSP90α correlated with other related markers in the diagnosis of LC ($p < 0.05$). Although HSP90α and other related markers did not fit the satisfactory conformance, in terms of the positive rate of diagnosis, it was statistically differences in the diagnostic positive rate between HSP90α and each marker ($p < 0.01$). ROC analysis showed that a plasma HSP90α cut-off point of 50.02 ng/ml had an optimal predictive value for LC.

Conclusions: HSP90α has significant clinical value in early screening and diagnosis of LC. The combined application of HSP90α and related markers can improve the positive rate of early diagnosis of LC effectively.

KEYWORDS
diagnosis, HSP90α, lung cancer, tumor markers

Zhimin Yuan, Longhao Wang and Songlin Hong contributed equally to this work.

1 | INTRODUCTION

Lung cancer (LC) is one of the malignant tumors with the highest morbidity and mortality that greatly threatens human health and life. According to the global cancer statistics report of 2018 published by Bray et al. LC remains the most common cancer (11.6% of the total cases) and the leading cause of death (18.4% of the total deaths) globally.[1] In China, the LC has the highest morbidity (57.26/1,000,000) and mortality (47.87/1,000,000) compared to other malignant tumors.[2] As there were no typical symptoms and/or discomfort in early LC, most were in the middle-late or terminal stage when being diagnosed. Therefore, it would be important to find more meaningful biomarkers in improving the early screening and diagnosis value of LC.

Heat shock proteins (HSPs), also known as stress proteins, are a group of proteins that are highly expressed by body cells after being stimulated by several physical and chemical factors.[3] HSP90α is actively secreted to the extracellular domain and plays a role by tumor cells when stress or malignant transformation occurs.[4,5] In 2009, Wang et al. found patients with liver cancer had a higher level of HSP90α in plasma, and the expression level correlated with the stage of liver cancer, which suggested HSP90α can be used as a tumor marker for early screening.[6] Previous studies of HSP90α mainly involved in liver cancer and colorectal cancer et al, while studies on the expression level of HSP90α on patients with LC were really rare, and the correlations between HSP90α and other tumor biomarkers were not well described.[7–11]

Based on the level of HSP90α and other related markers in blood from 175 patients with LC, the goals of this study were (i) to explore the expression level among different groups divided on age, gender, pathological types, staging and metastasis status respectively. (ii) to compare the diagnostic performance between HSP90α and other related markers. Here, we hypothesized that combined HSP90α with other tumor biomarkers such as CEA, NSE, CYFRA21-1 and ProGRP can effectively improve the early diagnosis rate of LC.

2 | MATERIALS AND METHODS

2.1 | Patients and methods

A total of 335 individuals were screened at the Physical Examination Center of Shaanxi Provincial Cancer Hospital from December 2017 to December 2019, all of whom underwent serological testing for HSP90α and related markers (optional testing). Screening found that 175 of 335 patients were diagnosed with LC and classified as lung cancer group (LC) according to inclusion criteria; 160 healthy people were tested at the same time and were included in the group of healthy controls (HC). The inclusion criteria for LC patients were as follows: (i) have a pathological diagnosis; (ii) TNM staging; (iii) patient has the HSP90α test result before treatment; (iv) no tumors other than LC and (v) no use HSP90α related inhibitors before. HC exclusion criteria included any of the following: (i) inflammation and/or other diseases related to inflammation; (ii) any other tumors and (iii) use HSP90α related inhibitors. Clinicopathological variables such as gender, age, pathological types, tumor stage and metastasis status were collected from the database of Shaanxi Provincial Cancer Hospital. Groups were divided according to the gender (male/female), age (≤60 years/>60 years), types of LC (small-cell carcinoma (SCLC), lung squamous cell carcinoma (LUSC) and lung adenocarcinoma (LUAD)), staging (I, II, III and IV) and metastasis (metastasis and non-metastasis) separately. The staging of LC were classified according to American Joint Committee on Cancer classification (AJCC 7th edition, 2010). This study was approved by the ethics committee and review committee of Shaanxi Provincial Cancer Hospital. For this type of study, informed consent is not required.

2.2 | Testing of blood samples

Peripheral blood samples were collected into 2 ml EDTA-K2 anticoagulant tubes for the detection of HSP90α and other related markers. Plasma were separated from the whole blood cells by centrifugation at 1006.2*g* for 10 min, then stored the plasma at −20°C until use. Plasma HSP90α was measured with a commercially ELISA Kit (Progy Biotechnology Development Co. Ltd). Briefly, samples were added to the 96-well microplate pre-coated with HRP labeled monoclonal antibody to HSP90α, then incubated at 37°C for 1 h. The reaction was visualized by adding 50 μl chromogen 3,3,5,5-tetramethylbenzidine (TMB) solution A and 50 μl chromogen TMB solution B to each well and incubated for 20 min at 37°C. Finally, the reaction was stopped by adding with 50 μl stop solution to each well. The optical density was measured at 450 nm and referenced to 620 nm on Rayto RT-6100 Micro-plate Spectrophotometer (Rayto Co. Ltd). The standard curve was generated by plotting the logarithm of average O.D. obtained for each of the six standard samples on the vertical (*Y*) axis versus the logarithm of corresponding concentrations on the horizontal (*X*) axis. The absorbance of samples was calculated with the method of substitution in the standard curve. Double logarithmic curve fitting was recommended, and the coefficient of correlation (R^2) was required to be greater than 0.980. A commercially available ELISA kit was used for the quantitative assessment of plasma HSP90α concentrations according to the manufacturer's recommendations.

The levels of serum CEA, NSE, CYFRA21-1 and ProGRP were tested with a commercially available ELISA kit (Roche Life Science) following the manufacturer's recommendations using Cobas E411 automatic analyzer (Roche Diagnostics).

2.3 | Statistical methods

All data are presented as the mean ± standard deviation (SD). Wilcoxon Mann–Whitney test and Kruskal–Wallis test were used to compare statistical differences between two groups/among the

multiple groups for each factor of HSP90α. In addition, the correlation coefficient r and kappa value were calculated to compare the differences between HSP90α and various markers separately in LC. The receiver operating curve (ROC) was used to evaluate the efficacy of plasma HSP90α in predicting LC. The application SPSS 21.0 was used for all statistical comparisons and the significant statistical level was set at the threshold of $p < 0.05$. The paired comparison of ROC curves and the box plot of HSP90α expression in types of LC and staging were plotted by GraphPad Prism 9.0 software (GraphPad Software, Inc.).

3 | RESULTS

3.1 | Heat shock protein 90α in lung cancer and healthy control group

A total number of 335 cases were enrolled in this study, including 175 (125 males, 50 females, and age ranging from 31 to 86 years old) cases with LC and 160 HC (121 males, 39 females, and age ranging from 26 to 68 years old). No significant difference in sex ($p = 0.228$) and age ($p = 0.104$) were observed between LC and HC ($p > 0.05$), and the levels of HSP90α were significantly higher in LC than in HC ($p < 0.001$). As shown in Table 1.

3.2 | Level of HSP90α in clinical parameter groups

There was no significant difference in HSP90α observed between male and female subjects ($p = 0.943$) and between different age groups ($p = 0.701$). As shown in Figure 1, for different types of LC, plasma levels of HSP90α were higher in SCLC groups than LUAD group ($p < 0.05$), and there were no statistically significant differences between the other two groups ($p > 0.05$). And plasma levels of HSP90α in I, II, III and IV stage LC patients were all significantly higher than HC ($p < 0.05$). HSP90α were significant difference in I, II, III and IV stage LC patients ($p = 0.024$; <0.05). Comparison between different stages showed, there were no significant statistical differences between phases I, II and III ($p > 0.05$), the plasma levels of HSP90α in late-stage LC patients (TNM stage III + IV) were significantly higher than in patients with early-stage LC (TNM stage I + II, $p < 0.001$; Table 2 and Figure 2). As can be seen from Table 2, patients with lymph node and/or distant metastasis status had higher plasma levels of HSP90α compared with patients with non-metastatic status ($p < 0.001$).

3.3 | Comparison of consistency and correlation between HSP90α and CEA, NSE, CYFRA21-1, ProGRP

The levels of HSP90α, CEA, NSE, CYFRA21-1 and ProGRP in LC groups were significantly higher than HC ($p < 0.001$). As shown in Figure 3, pearson correlation analysis was used to compare the correlation coefficient r and p values, and Kappa method was used to compare the consistency of HSP90α, CEA, NSE, CYFRA21-1 and ProGRP. In diagnosis of LC, plasma HSP90α levels were positively correlated with the serum levels of CEA ($r = 0.297$; $p < 0.001$), NSE ($r = 0.247$; $p = 0.001$), CYFRA21-1 ($r = 0.322$; $p < 0.001$) and ProGRP ($r = 0.176$; $p = 0.019$), which showed that HSP90α and various markers were correlated in LC diagnosis ($p < 0.05$). The diagnosis results of HSP90α and CEA (Kappa = 0.151, $p = 0.001$), NSE (Kappa = 0.233, $p < 0.001$), CYFRA21-1 (Kappa = 0.331, $p < 0.001$) and ProGRP (Kappa = 0.053, $p = 0.360$), which was poor consistency, respectively. The diagnosis positive rate of HSP90α and CEA (73.9%, 26.1%), NSE (75.8%, 24.2%), CYFRA21-1 (80.7%, 19.3%) and ProGRP (85.4%, 14.6%), which was significantly higher than various markers, and the difference is statistically significant, respectively ($p < 0.001$). As shown in Table 3.

3.4 | Receiver operating curvecurve analysis of HSP90α and other markers

As shown in Figure 4, the results revealed that the area under the ROC curve of HSP90α for LC was 0.794 and the optimal cut-off level was 50.02 ng/ml, which provided an 88.1% sensitivity and a 69.7% specificity. In addition, our study found that the ability of plasma HSP90α for predicting LC is superior to NSE, CYFRA21-1 and ProGRP, but lower than CEA. The results revealed that the area under the ROC curve of HSP90α for I stage LC was 0.696 and the optimal cut-off level was 50.34 ng/ml, which provided a 57.1% sensitivity and 88.7% specificity ($p = 0.049$ <0.05).

3.5 | Combined diagnosis of HSP90α and markers in LC

The combination of HSP90α, NSE and ProGRP showed better performance (AUC = 0.930, sensitivity 98.75% and specificity 82.76%), significantly improved the diagnostic ability than NSE and ProGRP (AUC = 0.901, sensitivity 89.38% and specificity 86.21%) in the SCLC group (Figure 5a, Table 4). The combination of HSP90α

TABLE 1 Age, sex and HSP90α in lung cancer and healthy control

Variables	All ($n = 335$)	HC ($n = 160$)	LC ($n = 175$)	p value
Age	60.5 ± 8.6	59.7 ± 6.9	61.2 ± 9.8	0.104
Male sex, *N* (%)	255 (76.1)	121 (75.6)	125 (71.4)	0.228
HSP90α ng/ml	54.57 ± 12.14	38.03 ± 12.87	89.53 ± 8.20	<0.001***

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

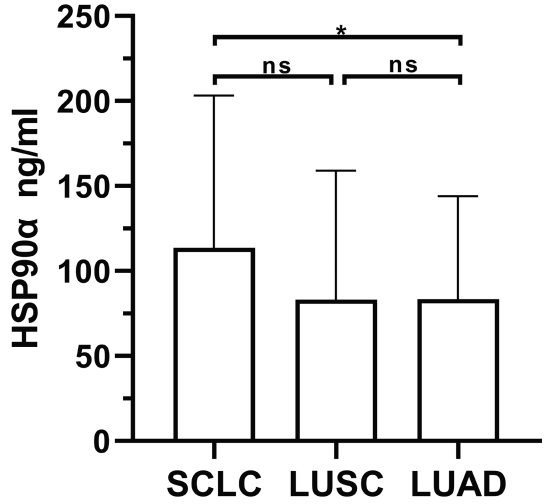

FIGURE 1 Levels of plasma HSP90α in the different types of LC groups. (LC, lung cancer; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; SCLC, small-cell lung cancer)

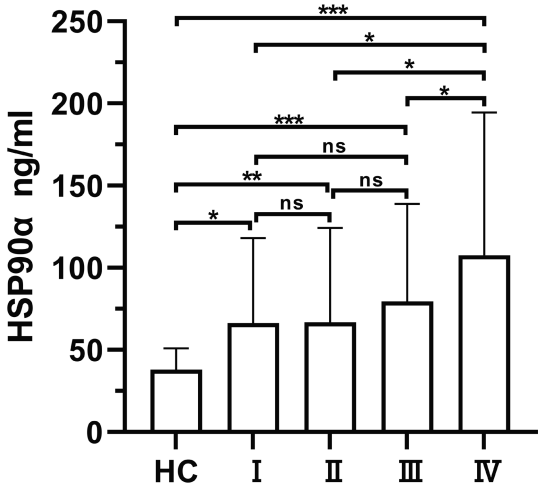

FIGURE 2 Levels of plasma HSP90α in the staging groups and healthy controls (HC) group

TABLE 2 Level of HSP90α in gender, age, classified, staging and metastasis groups

Variables	N	HSP90 α ng/ml	p value
Sex			
Male	125	87.36 ± 70.87	0.943
Female	50	94.94 ± 81.58	
Age			
≤60 years	71	99.19 ± 87.58	0.701
>60 years	104	82.58 ± 62.54	
Pathological type			0.116
SCLC	29	113.54 ± 89.71	–
LUSC	56	83.14 ± 76.00	0.104
LUAD	90	83.53 ± 60.55	0.043*
Staging			
I	14	66.28 ± 51.79	0.024*
II	22	66.84 ± 57.47	
III	60	79.44 ± 59.32	
IV	79	107.63 ± 86.84	
Metastasis			
Yes	96	105.00 ± 82.22	0.015*
No	79	75.69 ± 62.68	

Abbreviations: LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; SCLC, small-cell lung cancer.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

and CYFRA21-1 showed better performance (AUC = 0.818, sensitivity 87.50% and specificity 69.64%), significantly improved the diagnostic ability than CYFRA21-1 (AUC = 0.715, sensitivity 69.64% and specificity 65.00%) in the LUSC group (Figure 5b, Table 4). The combination of HSP90α and CEA showed better performance (AUC = 0.996, sensitivity 95.63% and specificity 99.97%), significantly improved the diagnostic ability than CEA (AUC = 0.991, sensitivity 97.78% and specificity 95.00%) in the LUAD group (Figure 5c, Table 4). We found that the combination of HSP90α and specificity markers significantly improved the diagnostic ability of all types of LC.

4 | DISCUSSION

Heat shock protein 90α is one type of homologous hypotype molecular chaperone protein encoded by the gene HSP90AA1.[12] Cheng et al.[13] demonstrated that HSP90α is present in the cytoplasm and can be secreted by tumor cells. The extracellular HSP90α participates in the invasion and metastasis of malignant tumor cells,[14,15] it can promote metastasis and invasion of the tumor cells via activating plasma fibrinolysin. HSP90α can promote and induce the growth of tumor cells, angiogenesis, cell proliferation, metastasis and local invasion.[16,17]

Rong et al.[18] explored the significance of HSP90α as a potential biomarker in liver cancer in their study. Sourbier et al.[19] have even systematically summarized the up-regulation of HSP90α in cancer cells, tissues and serum of liver cancer patients, and its close correlation with the occurrence, development and outcome. And McDowell et al.[20] found that in the of detection proteomic HSP90α and HSP90β, at least 10 of 17 human tumors had one significantly up-regulated HSP90 hypotype or HSP90 synergistic partner in 2009. These studies suggested that HSP90α maybe also a potential biomarker in LC. Zhang et al.[21] found the diagnostic value of HSP90α for peripheral LC in bronchoalveolar lavage fluid. The same results were also obtained in our study, the results of plasma level of HSP90α also had a higher level compared with HC in LC patients, even in early-stage patients, and not affected by the gender and age. In addition, the area under the ROC curve of HSP90α for I stage LC was 0.696, the optimal cut-off level of 50.34 ng/ml is higher the total cut-off level, the specificity of 88.7% was also significantly higher

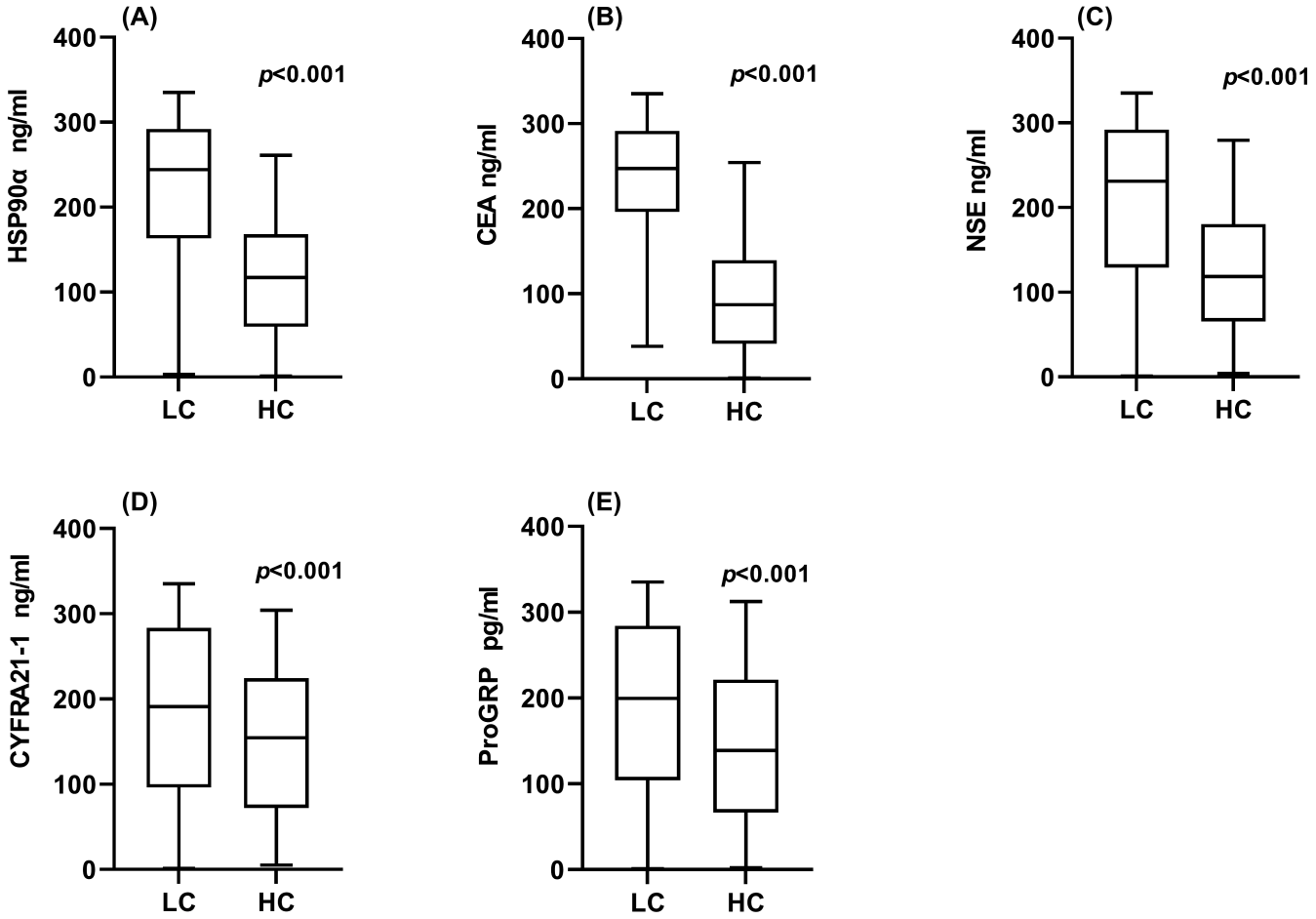

FIGURE 3 Comparison of HSP90α, NSE, ProGRP, CYFRA21-1 and CEA in lung cancer (LC) and healthy controls (HC) group

TABLE 3 Correlation and consistency between HSP90α and related markers in lung cancer

Index	*R* with HSP90α	*p* value	Kappa with HSP90α	*p* value
CEA	0.297	<0.001***	0.151	0.001***
NSE	0.247	0.001***	0.233	<0.001***
CYFRA21-1	0.322	<0.001***	0.331	<0.001***
ProGRP	0.176	0.019*	0.053	0.360

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

than the total specificity. These results suggested that HSP90α has a diagnostic value in early LC screening and clinical diagnosis.

As we all know, SCLC was much more malignant in LC, grow faster, easy to develop lymph nodes and hematogenous metastasis and a poor prognosis. The expression of HSP90α in SCLC was higher than in other pathology subtypes, which indicated HSP90α can be used as an auxiliary indicator for the identification of the pathology subtypes of LC. The result indicated that HSP90α was correlated with SCLC, a high malignancy tumor. In the study of Shi et al.,[22] the plasma level of HSP90α was found to be associated with the staging of the tumor, therapeutic response, preoperative and postoperative of the surgery, disease progression in patients with LC. Our study also found that its expression was positively correlated with stage and pathology subtypes of LC. Cheng et al. reported the abnormally elevated of HSP90α indicates poor prognosis or metastasis in patients with breast cancer,[23,24] our study also showed a significant increase of HSP90α levels in patients with lymph node and/or distant metastasis which is consistent with previous studies.[10,25–27] This showed that HSP90α can promote the invasion and migration of tumor cell.

Heat shock protein 90α was considered to have differences in correlation with various markers in the diagnosis of LC by comparison ($p < 0.05$). In the consistency comparison of HSP90α with CEA, NSE, CYFRA21-1 and ProGRP, it can be found the consistency of HSP90α with each marker is not satisfactory. Therefore, we further discussed that the ROC curve analysis was performed to determine the value of HSP90α for predicting LC. The results revealed that the AUC of HSP90α for predicting LC was 0.794 and the optimal cut-off

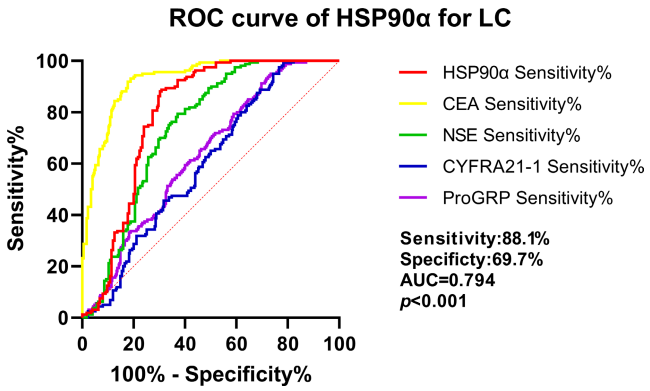

FIGURE 4 The receiver operating curve (ROC) curve analysis of the diagnosis efficiency of HSP90α and various markers in lung cancer (LC) patients

level was 50.02 ng/ml, the sensitivity and specificity were 88.1% and 69.7%, respectively.[6] We found that the optimal cut-off value was lower than the clinical reference value. The ROC curve analysis the diagnosis efficiency of HSP90α and various markers in LC patients, the ability of plasma HSP90α for predicting LC is superior to NSE, CYFRA21-1 and ProGRP, but lower than CEA. The combination of HSP90α and specificity markers (NSE, ProGRP, CYFRA21-1 and CEA) significantly improved the diagnostic ability of all types of LC. Therefore, while reducing the clinical reference value of HSP90α and combining various markers, the diagnosis rate of LC may be effectively improved.

In 2009, Luo et al.[6] identified the regulatory mechanism by which tumor cells can specifically secrete HSP90α, and revealed the role of extracellular HSP90α in tumors. Then in targeted therapy of some tumors, HSP90α inhibitors have been developed and used as targeted therapy in clinical cases. The aim is to reduce plasma HSP90α expression in stages. Multiple clinical studies confirmed that HSP90α inhibitors had specificity and pleiotropic effect obviously for the treatment of malignant tumors.[28,29] At present, most studies suggest that HSP90α inhibitors are mainly binding sites acting on the C or N termini of the structural-functional regions in HSP90α, thus represses the activity of extracellular HSP90α to inhibit tumor growth, proliferation, and metastasis.[30] But this targeted therapy in turn reduces serum HSP90α expression. This may introduce errors in the Serological test of HSP90α as a diagnostic marker. So the LC patients using HSP90α inhibitors were excluded from the tracing of cases in this study.

Mechanistic studies suggest that HSP90α may play an important role in tumor metabolism and apoptosis. Ghosh et al.[31] found that the HSP90α carboxyl-terminal inhibitors played an important role in cell apoptosis and metastasis by blocking the complex activity of HSP90α/Aha1 and pc3-mm cells. It can be interfered with the invasion and metastasis of pancreatic ductal adenocarcinoma by regulating HSP90α/uPA mmp-2 protein hydrolysis axis.[32] In this study, patients with lymph node and/or distant metastasis status had higher plasma levels of HSP90α. This suggests that the overexpression of HSP90α in plasma at different stages may be a

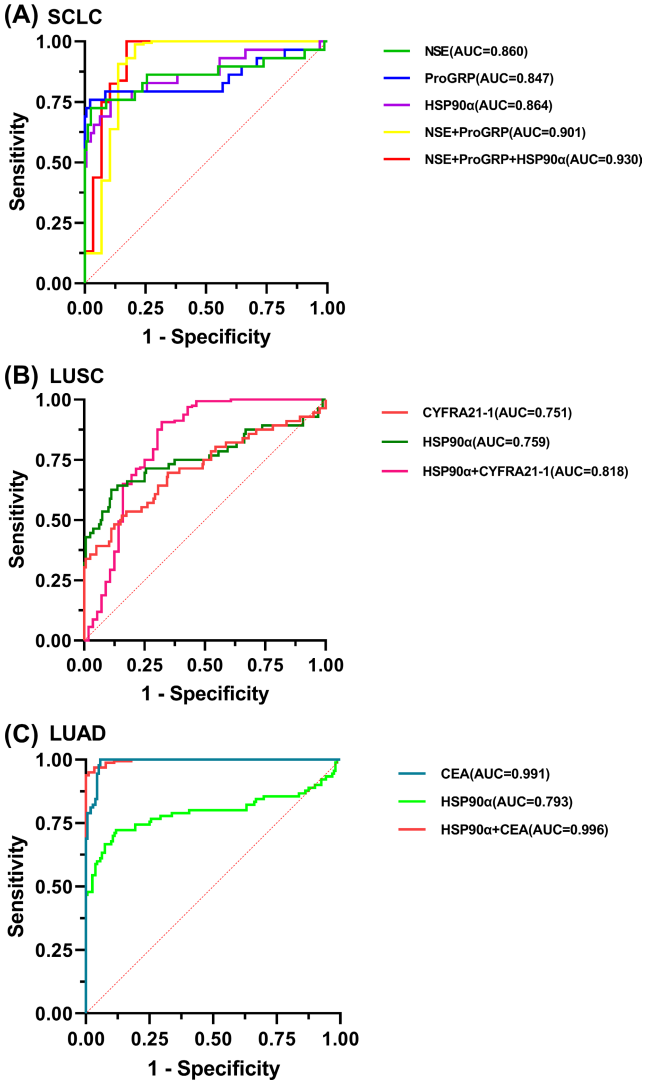

FIGURE 5 The receiver operating curve (ROC) curve analysis of the diagnostic efficiency of HSP90α and specificity markers (NSE, ProGRP, CYFRA21-1and CEA) in various types of lung cancer (LC) patients. a The ROC curve analysis of the diagnosis efficiency of HSP90α, NSE and ProGRP for SCLC. b The ROC curve analysis the diagnosis efficiency of HSP90α and CYFRA21-1 for LUSC. c The ROC curve analysis the diagnosis efficiency of HSP90α and CEA for LUAD

marker for distant metastasis of LC. Of course, further research is needed.

This study excluded other factors and proved the important value of plasma HSP90α in the diagnosis of LC in the whole cycle, but there are still some deficiencies in this study. First of all, the amount of data in this study is small, especially for early-stage tumors. This may be because early screening in developing countries is not sound enough and citizens do not attach importance to the early detection of cancer diseases. In addition, the data of this study came from a single-center, and insufficient data may have an impact on the research results. In the future, multi-center early screening and systematic study of medical record tracking will be more helpful to prove whether HSP can be used as a basis for early diagnosis of LC.

TABLE 4 Main parameters of ROC curve analysis results

Variables	AUC	95%CI	Sensitivity (%)	Specificity (%)	Cut-off	*p* value
SCLC						
NSE	0.860	0.758–0.963	75.86	91.25	10.67	<0.001***
ProGRP	0.847	0.737–0.956	79.31	91.25	33.61	<0.001***
HSP90α	0.864	0.774–0.955	75.86	89.38	51.78	<0.001***
NSE + ProGRP	0.901	0.812–0.990	89.38	86.21		<0.001***
NSE + ProGRP + HSP90α	0.930	0.861–1.000	98.75	82.76		<0.001***
LUSC						
CYFRA21-1	0.715	0.627–0.803	69.64	65.00	4.28	<0.001***
HSP90α	0.759	0.671–0.848	71.43	74.38	44.42	<0.001***
CYFRA21-1 + HSP90α	0.818	0.739–0.897	87.50	69.64		<0.001***
LUAD						
CEA	0.991	0.983–0.998	97.78	95.00	8.82	<0.001***
HSP90α	0.793	0.721–0.864	71.11	88.75	50.50	<0.001***
CEA + HSP90α	0.996	0.992–1.000	95.63	99.97		

Abbreviations: LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; SCLC, small-cell carcinoma.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

5 | CONCLUSION

In conclusion, HSP90α has a significant diagnostic value in the classification, staging and metastasis of LC. As a potential tumor biomarker, HSP90α has important clinical significance in the early screening, diagnosis, treatment and prognosis evaluation of LC. Combined HSP90α with other tumor biomarkers such as CEA, NSE, CYFRA21-1 and ProGRP can improve the diagnosis rate of LC effectively.

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CONFLICT OF INTEREST

All authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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