Meta-analysis of Correlation between Peripheral Serum MIC-1 level and Lung Cancer

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Lung cancer (LC) is a common malignant tumor with high morbidity and mortality. The development of new molecular markers and the early diagnosis of LC and the exploration of emerging targeted therapies are of great significance. Therefore, this study systematically evaluates the correlation between peripheral serum MIC-1 levels and LC. Search PubMed, Web of Science, Medline and other databases, the search time is from the establishment of the database to July 2021. The LC group included LC patients, the Non-cancer group included patients with benign lung diseases (BLD), and the control group included healthy people. The serum MIC-1 levels of LC group and control group, LC group and Non-cancer group were compared respectively, and the correlation between serum MIC-1 and clinical characteristics of LC patients was evaluated and analyzed, and the ROC curve of MIC-1 in prediction of LC. Finally, 5 articles were included, including 1179 patients with LC, 109 patients with BLD, and 1020 healthy people. Meta-analysis results: the level of MIC-1 in LC group was overtop that in healthy group, and the difference was obvious [SMD=1.97, 95%CI (1.35, 2.59), $P<0.00001$]. The level of MIC-1 in LC group was overtop that in Non-cancer group, and the difference was obvious [SMD=382.97,95%CI (313.74, 452.19), $P<0.00001$]. The descriptive evaluation analyzes the correlation between MIC-1 and the clinical characteristics of LC group, and the results show that MIC-1 has a certain correlation with the stage of LC group. The AUC of serum MIC-1 in the identification of LC group and the control group was greater than 0.5. The AUC value of MIC-1 in the diagnosis of LC was 0.851-0.906, and the best sensitivity range was 63.50%-99.00%. The best specificity is in the range of 70.4%-95.80%. The Meta-analysis indicated that the serum MIC-1 level in LC group is overtop that in BLD and healthy people, and has a obvious correlation with LC stage staging; and the ROC curve shows that it has important significance in the diagnosis and prognosis of LC.

Keywords: Lung cancer; MIC-1; Peripheral serum; Correlation; Meta-analysis

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INTRODUCTION

For a long time, among all malignant tumors in the world, the morbidity and mortality of lung cancer (LC) have been among the top. It has become the highest death rate among all cancer types in the world [1]. According to a cancer statistics in the United States, there were 235,160 new LC patients in the United States in 2021, and the number of patients who died of LC was as high as 131,880, accounting for 21.7% of all cancer deaths in the region [2]. Studies have shown that smoking and asbestos exposure are two common factors that promote the progression of LC [3]. In histology, according to the cell size of LC morphology, LC can be divided into two types: Non-Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC). NSCLC patients account for about 85% of LC patients. Histologically, they can be divided into Lung Adenocarcinoma (LUAD), Lung Squamous Cell Carcinoma (LUSC), and Large Cell Lung Cancer (LCLC), which account for the largest number of 40%, 30%, and 10% [3,4]. Up to now, some emerging treatments for malignant tumors, such as neoadjuvant chemotherapy, immunotherapy, and molecular targeted therapy, have been proven to be

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effective methods for the treatment of NSCLC [3,5-9]. However, the study found that the current overall survival rate of NSCLC patients has dropped from 73% in stage IA to 15% in stage IV [10], and the prognosis is still not optimistic. The development of new molecular markers and the early diagnosis of LC and the exploration of emerging targeted therapies are of great significance.

Macrophage inhibitory cytokine 1 (MIC-1) is also known as growth differentiation factor 15 (GDF15) and placental transforming growth factor-β(PTGF-β. It belongs to the TGF-βfamily, is a secreted protein that can be autocrine or paracrine, and is the target of p53 (wild type) [11]. MIC-1 has an inhibitory effect on tumors [12], but studies have also shown that it has a promoting effect on advanced tumors [13]. Studies have shown [14-16] that MIC-1 levels are closely related to the benign and malignant lung tumors, the staging, grading and metastasis of LC. However, no systematic evaluation has been seen so far. Therefore, on the basis of meta-analysis, this study systematically evaluated the correlation between serum MIC-1 level and LC, in order to provide a reference for the diagnosis and treatment of LC in clinical progress.

MATERIALS AND METHODS

Search Strategy

Two researchers independently searched the literature, and searched the related literature in Pub Med, Embase, Web of knowledge and other databases through computers. The search terms are: "MIC-1", "GDF15" and "PTGF-β', "lung cancer". The search time is from the establishment of the database to July 2021.

Inclusion and Exclusion Criteria for Literature

Inclusion criteria: (1) The included documents are all published studies. (2) The research method is a cohort study. (3) Research subjects include LC patients and normal (or pneumonia, benign) controls. (4) Observation indicators include MIC-1 / GDF15/PTGF-β. (5) The language is English. Exclusion criteria: (1) Conference abstracts and review articles, duplicate documents, and unpublished documents. (2) Documents where relevant specific data cannot be obtained. (3) Documents whose grouping method does not meet the inclusion criteria designed in this study.

Data Extraction and Quality Evaluation

Two researchers jointly developed the search strategy and completed the inclusion of the literature independently. The controversial literature is up to the third researcher to decide whether to include it. Finally, integrate the material and data. Research screening process: preliminary screening of the retrieved literature by looking at the title and abstract of the literature, and then reading through the full text analysis for further screening, and finally determining the final inclusion criteria in strict accordance with the inclusion and exclusion criteria for literature. The quality of the included literature was independently evaluated by two researchers, and the evaluation standard used the Newcastle-Ottawa-Scale (NOS) scoring standard (evaluated in 3 dimensions, namely selection, comparability, and exposure). The total score of NOS is 9 points. The higher the score, the higher the quality of the literature. This study included literatures with scores ≥ 6 points.

Statistical Analysis

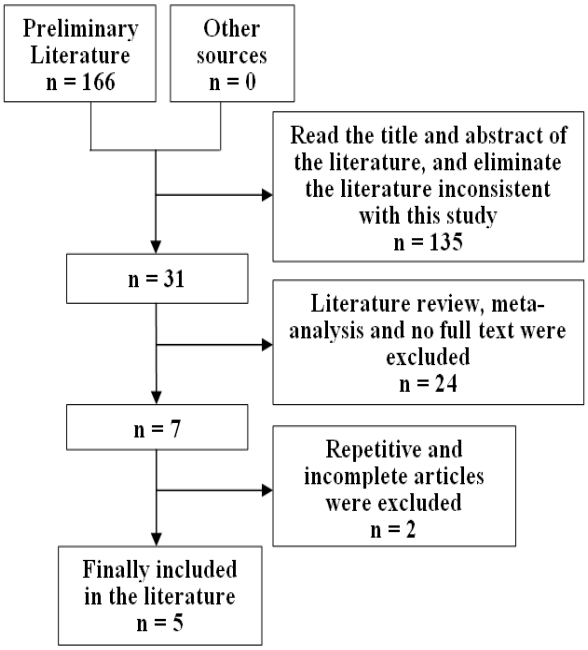
The research data used RevMan5.3 for Meta analysis. The fixed effects model (FEM) was selected for analysis, and the Z test was used to determine the heterogeneity of the results. $P > 0.1$ and $I^2 < 50\%$ indicate that there is no heterogeneity between the studies. If statistical heterogeneity exists and the source of heterogeneity cannot be eliminated, the random effects model (REM) analysis is used. Sensitivity analysis adopts the method of successively eliminating and recalculating the combined effect size of individual studies. The research data are continuous variables, and the results are expressed in terms of STD Mean Difference (SMD) and its 95%CI.

RESULTS AND DISCUSSION

The Results of Literature Search

A total of 166 articles were obtained in the preliminary examination. A total of 7 articles were screened through topic screening, abstract screening and duplicate literature screening. The full-text search of these 7 articles was further screened and finally 5 articles were included, including 1179 patients with LC, 109 patients with BLD, and 1020 healthy people. The literature search process is shown in Figure 1.

Figure 1
Document screening flow chart



The Basic Characteristics of the Included Studies and the Assessment of the Risk of Bias

The 5 articles included are all prospective cohort studies. The quality evaluation of each study is ≥7 points. The basic characteristics of each study are illustrated in Table 1.

Table 1
Basic characteristics of various studies

Author	years	Research object	Group	Sample size	Gender (male/female)	Age (year)	MIC-1(pg/mL)	Quality evaluation (points)
Liu [17]	2016	NSCLC	LC group	152	89/63	58.8±8.2	1325.0±848.0	8
		Benign lung disease	Non-cancer group	48	20/28	53.2±10.1	848.0±183.0	
		Health	Control group	105	59/46	55.4±9.3	367.0±207.0	
Wang (1) [18]	2017	LC	LC group (Training group)	350	218/132	60(27-85)	1388.05±874.38	9
		Health	Control group (Training group)	350	162/188	59(20-80)	388.79±408.02	
Wang (2) [18]	2017	LC	LC group (Verification Group)	411	267/144	60(28-87)	1434.0±950.33	
		Benign lung disease	Non-cancer group (Verification Group)	78	4/74	57(26-75)	1035.16±718.86	
		Health	Control group (Verification Group)	389	205/184	58(19-78)	393.65±347.62	
Xu [19]	2020	NSCLC	NSCLC	296	--	26-77	1582.31±473.01	8
		Health	Control group	240	--	37-68	507.71±107.64	
Molfino [20]	2021	LC	LC group	34	27/7	67.97 ± 12.03	6.74±0.32	7
		Health	Control group	30	13/17	58.53 ± 11.85	6.38±0.50	
Deng [21]	2021	LC	LC group	88	62/26	62.1 ±9.7	1395.44±237.91	7
		Pneumonia	Non-cancer group	31	21/10	62.3 ±11.5	1050.41±203.88	
		Health	Control group	41	20/21	48.4 ±5.1	564.36±166.88	

Meta Analysis

The level of MIC-1 in healthy controls and LC patients

A total of 5 studies were included, and the study data was statistically heterogeneous (P<0.1 and I^2>50%), so the random effects model was adopted. Meta-analysis results: the level of MIC-1 in LC group was overtop that in healthy group, and the difference was obvious [SMD=1.97, 95%CI (1.35, 2.59), P<0.00001] (Figure 2). In order to find the source of heterogeneity, each study was excluded one by one, and it was found that Deng [21] and Xu [19] were the sources of heterogeneity. After excluding these two studies, the direction of the meta-analysis results did not change. The level of

MIC-1 in LC group was still obviously overtop that in healthy group [SMD=1.42,95%CI(1.32,1.53), P <0.00001] (Figure 3).

Figure 2
The level of MIC-1 in the control group and LC patients

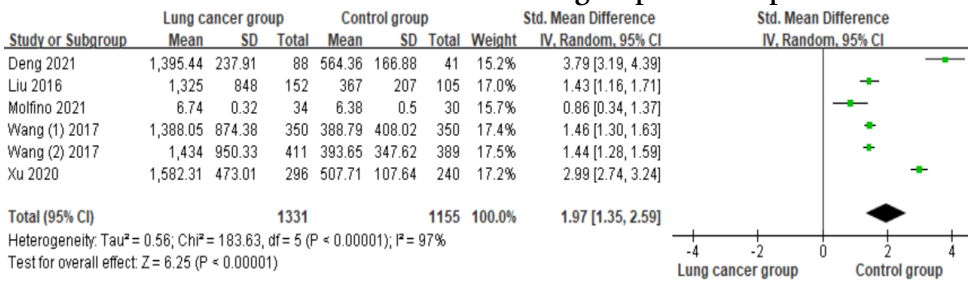
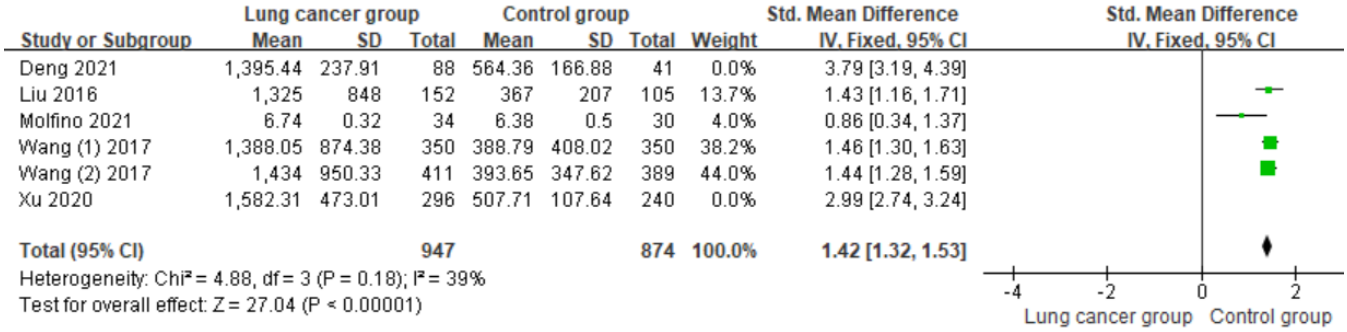


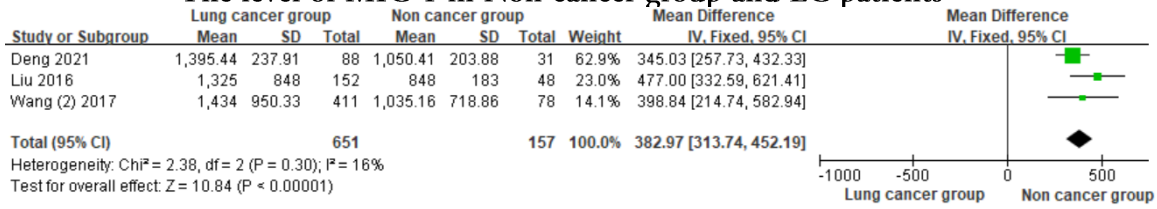
Figure 3
The level of MIC-1 in the control group and LC patients (excluding heterogeneity)



The level of MIC-1 in Non-cancer group and LC group

A total of 3 studies were included, and there was no statistical heterogeneity in the study data (P>0.1 and I^2<50%), so the fixed-effects model was used. Meta-analysis results: the level of MIC-1 in LC group was overtop that in Non-cancer group, and the difference was obvious [SMD=382.97, 95%CI (313.74,452.19), P<0.00001] (Figure 4).

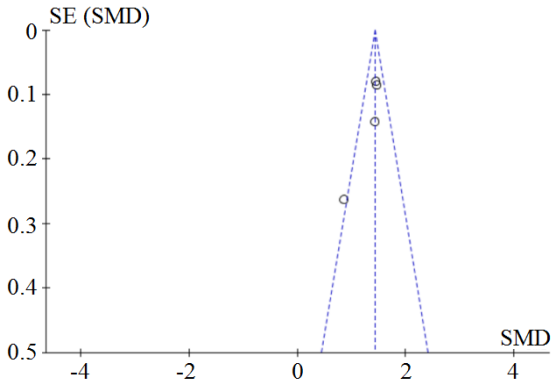
Figure 4
The level of MIC-1 in Non-cancer group and LC patients



Bias risk assessment

After excluding heterogeneity, the control group and the MIC-1 level of LC group were included in the study for funnel plot analysis. The results show that there is a study that intersects the oblique funnel, so this study may have a certain risk of bias, as shown in Figure 5. The small number of included studies may be the reason why this study has a certain risk of bias.

Figure 5
Funnel chart



The Correlation between MIC-1 and the Clinical Features of LC

The correlation between MIC-1 and gender of LC patients

Among the included studies, two studies reported the correlation between gender and MIC-1 level. Deng [21] believed that the MIC-1 levels of LC patients of different genders were not obviously different (P>0.05), while Liu [17] believed that The proportion of women in high-level MIC-1 (≥1465 pg/mL) was overtop that of men (P<0.05).

The correlation between MIC-1 and the age of LC patients

In the included studies, two studies reported the correlation between age and MIC-1 level. Deng [21] study showed that the MIC-1 level of LC patients of different ages (<60 years old and ≥60 years old) was not obviously different (P > 0.05). The research of Liu [17] also concluded that the proportions of different ages (<60 years and ≥60 years) in different levels of MIC-1 (<1465 pg/mL and ≥1465 pg/mL) were not obviously different (P>0.05).

The correlation between MIC-1 and smoking history of LC patients

In the included studies, 2 studies reported the correlation between smoking history and the level of MIC-1. The study of Liu [17] concluded that there were different levels of MIC-1 (<1465 pg/mL and ≥1465 pg/mL) There was no obvious difference in the proportion of smoking history (P>0.05). The study of Deng [21] also showed that the MIC-1 level of LC patients with different smoking history (<20 years and ≥20 years) was not obviously different (P>0.05).

The correlation betweenMIC-1 and pathological tissue of LC patients

In the included studies, 3 studies reported the correlation between tumor recurrence/metastasis and the level of MIC-1. The research of Liu [17] concluded that the proportions of squamous cell carcinoma and adenocarcinoma in different levels of MIC-1 (<1465 pg/mL and ≥1465 pg/mL) were not obviously different (P>0.05). The research of Deng [21] also showed that the MIC-1 level of patients with LUAD/LUSC/SCLC was not obvious (P>0.05). Wang [18] research showed that the MIC-1 levels of SCLC and NSCLC, LUAD, LUSC and other pathological types were not obviously different (P>0.05).

The correlation between MIC-1 and T staging of LC patients

Three studies included in the study reported the correlation between T stage and MIC-1 level in patients with LC. Liu [17] researched that the proportion of T1-2/T3-4 in different levels of MIC-1 (<1465 pg/mL and ≥1465 pg/mL) was obviously different (P<0.05). The study of Deng [21] also showed that the MIC-1 levels of LC patients in T1/T2/T3 stages were also obviously different (P<0.05). Wang [18] study showed that the MIC-1 level of T1-2/T3-4 patients in the training group was obviously different (P<0.05); while the MIC-1 level of T1-2/T3-4 patients in the verification group was compared , The difference is not obvious (P>0.05).

The correlation between MIC-1 and N stage of LC patients

Among the included studies, 3 studies reported the correlation between the N stage of LC patients and the level of MIC-1. Liu [17] researched that the difference in the proportion of N0/N1/N2 in different levels of MIC-1 (<1465 pg/mL and ≥1465 pg/mL) was not obvious (P>0.05). The study of Deng [21] also showed that the MIC-1 level of LC group with N0-2/N3 staging was not obviously different (P>0.05). Wang [18] research showed that the MIC-1 level of N0/N1-3 patients in the training group and the verification group was not obviously different (P>0.05).

The correlation between MIC-1 and stage staging of LC patients

In the included studies, 3 studies reported the correlation between the stage staging of LC patients and the level of MIC-1. Liu [17] researched that different levels of MIC-1 (<1465 pg/mL and ≥1465 pg/mL) had obvious differences in the proportion of stageI/stageII (P<0.05). The study of Deng [21] also showed that the MIC-1 level of stageIII/stageIV of LC patients was also obviously different (P<0.05). Wang [18] research showed that the MIC-1 level of stageI / stageII/ stageIII / stageIV patients in the training group and the verification group was obviously different (P<0.05).

ROC Curve

The ROC curve parameters of serum MIC-1 in the identification of LC and control groups are as follows (see Table 2), and the AUC in the table is greater than 0.5. The AUC range of MIC-1 in the diagnosis of LC patients is 0.851-0.906, the best sensitivity is 63.50%-99.00%, and the best specificity is 70.4%-95.80%. The ROC curve AUC value of MIC-1 combined with CEA in the diagnosis of LC is 0.93, 95% CI is 0.873-0.988, sensitivity is 77.00%, and specificity is 95.80%.

Table 2
ROC curve parameters of serum MIC-1 for diagnosis of LC

Author	Serum index	AUC	95%CI	Cutoff value	Sensitivity	Specificity
Liu [17]	MIC-1	0.9	0.80–0.94	1000 pg/ml	99.00%	70.40%
Xu [19]	MIC-1	0.906	0.842-0.971	1000pg/mL	63.50%	95.00%
	MIC-1 combined with CEA	0.93	0.873-0.988	/	77.00%	95.80%
Deng [21]	MIC-1	0.851	0.776～0.926	/	78.20%	71.00%

Discussion

Surgical treatment is usually the main treatment for early LC, and systemic treatment is the main treatment for late LC. Precision treatment is the prerequisite for the treatment of advanced LC [22]. For advanced LC patients with positive driver genes such as EGFR mutations, ALK rearrangements, and ROS1 mutations, the use of corresponding targeted drugs can obviously improve the patients' median progression-free survival and overall survival, and there are fewer drug-related adverse reactions. However, due to the low mutation rate of common genes in LUSC, the mutation rate of EGFR gene is less than 5%, and the incidence of ALK fusion gene is less than 3%, which limits the application of targeted drugs in LUSC. In addition, LUSC is highly malignant and easy to invade and metastasize. Therefore, it is necessary to explore new targets to guide the clinical treatment of LUSC. For advanced LUSC with negative driver genes, the first-line treatment often chooses platinum-containing dual-drug chemotherapy. The first-line platinum-containing dual-drug chemotherapy regimen is usually paclitaxel or gemcitabine combined with platinum drugs, and its effective rate is about 54%, however, the median survival time of most patients does not exceed 10 months [23]. Tumor markers can diagnose and predict the patient's condition, which is of great significance to the diagnosis and treatment of cancer.

Tarfiei et al. [24] study showed that MIC-1 played a tumor suppressor or promotion effect in the process of carcinogenesis. The level of MIC-1 induces cytotoxicity, apoptosis and MAPK inhibition of A549 cells. MIC-1 plays a dual role in the level of TGFBR2 in the process of carcinogenesis. Zhao et al. [25] found that the level of GDF15 was obviously up-regulated in non-small cell LC tissues. However, clinically, serum is easier to detect than tissue cells, and serum MIC-1 has become an important indicator of tumor screening because of its involvement in the process of tumorigenesis and its proliferation and apoptosis. At present, there have been clinical reports on the application of this indicator to LC, but no systematic evaluation has been seen. In view of this, this study systematically evaluated the correlation between serum MIC-1 level and LC. The results of the Meta-analysis indicated that the MIC-1 of LC patients and healthy controls were compared, and five studies were included. Among them, Wang [18] reported that the level of MIC-1 in the training group and LC patients was overtop that in the healthy control group, and the difference was obvious. However, there is heterogeneity among the studies. In order to find the source of heterogeneity, each study was excluded one by one. It was found that Deng[21] and Xu[19] were the source of their heterogeneity. After excluding these two studies, the direction of the meta-analysis results did not change. It can be seen that the results of LC patients with higher MIC-1 level than healthy controls are more reliable. Non-cancer group includes patients with benign lung tumors and pneumonia. The level of MIC-1 in LC patients is overtop that in the Non-cancer group, with obvious differences and no statistical heterogeneity. It can be seen that the ranking of MIC-1 serum levels is likely to be LC> BLD> healthy people, but the serum MIC-1 levels in LC, BLD, and healthy people have not been compared in this study. Clear segmentation range, which needs further experimental research. After excluding heterogeneity, the control group and LC patients' MIC-1 level were correlated into the study for funnel plot analysis. The results show that there is a study that intersects the oblique funnel, so this study may have a certain risk of bias. The small number of included studies may be the reason why this study has a certain risk of bias.

In the study of the correlation between MIC-1 and the clinical characteristics of LC patients, only descriptive analysis and evaluation can be performed due to the few included studies and inconsistent grouping methods. Two studies included in the study reported the correlation between gender and the level of MIC-1. Deng [21] believed that the MIC-1 level of LC patients of different genders was not obviously different, while Liu [17] reported that women with high levels of MIC-1 The proportion is overtop that of men. It can be seen that the correlation between gender and MIC-1 level needs more experimental studies to further verify whether the two are related. Studies by Deng [21] and Liu [17] both show that MIC-1 is not obviously correlated with age, smoking history, and pathological type. The studies of Liu [17], Deng [21], and Wang [18] all showed that the MIC-1 level is not obviously correlated with the N stage of LC patients, but hasa obvious correlation with the stage of LC patients. Studies by Liu [17], Deng [21] and Wang [18] (training group) have shown that MIC-1 level is obviously correlated with the T stage of LC patients, while Wang [18]

verification group shows that MIC-1 level is associated with LC There is no obvious correlation between the T stage of the patient. It can be seen that the correlation between T stage and MIC-1 level in LC patients still needs to be included in more high-quality studies for meta-analysis to better evaluate the correlation between T stage and MIC-1 level in LC patients.

The AUC of serum MIC-1 in the identification of LC group and the control group was greater than 0.5, and the range of the AUC value of MIC-1 in the diagnosis of LC was 0.851-0.906. This shows that serum MIC-1 is of great significance in the diagnosis and prognosis of LC.

CONCLUSSION

To sum up, the MIC-1 level in LC patients is overtop that in benign lung diseases and healthy people. It has a obvious correlation with LC stage staging, and is of great significance in the diagnosis and prognosis of LC.

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