RESEARCH ARTICLE

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A Role of Serum Interleukin-39 and Association with Small and Non-Small Cell Carcinoma in Lung Cancer Patients

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Abstract

Background: Lung cancer is the second most common malignancy globally and the leading cause of cancer-related deaths. Interleukin-39 (IL-39), a member of the IL-12 family secreted by B cells, acts as a pro-inflammatory cytokine and induces IL-23p19 expression in endothelial cells. Recent findings suggest reduced IL-39 expression in autoimmune thyroid disorders and breast cancer, indicating its possible role in disease progression. **Aim of Study:** To evaluate the role of IL-39 as an early prognostic biomarker in lung cancer. **Materials and Methods:** A case-control study was conducted between February and September 2024, involving 180 individuals aged 45–77. The cohort included 90 lung cancer patients (45 with small-cell carcinoma and 45 with non-small cell carcinoma) and 90 healthy controls. Blood samples were analyzed using ELISA to quantify IL-39 and additional tests, including CBC, liver enzymes (ALT, AST, ALP), and lipid profile (cholesterol, triglycerides). Statistical analysis was performed to assess correlations and diagnostic performance. **Results:** IL-39 levels were significantly lower in stage IV compared to stage III in both cancer types, with a greater reduction observed in small-cell carcinoma. Significant negative correlations were found between IL-39 and total cholesterol, NLR, ALT, AST, and ALP, while positive correlations were noted with hemoglobin and triglycerides. IL-39 demonstrated excellent diagnostic accuracy in small-cell carcinoma with a cut-off value of 3.26950 pg/mL (sensitivity 100%, specificity 100%, AUC 1.000). In non-small cell carcinoma, the cut-off value was 4.88700 pg/mL (sensitivity 63.5%, specificity 92.6%, AUC 0.689). **Conclusion:** IL-39 shows promise as a predictive and diagnostic biomarker in lung cancer, particularly in small-cell carcinoma, and may play a protective role in disease modulation through immune-related pathways.

Keywords: Lung cancer- small-cell carcinoma- non-small-cell carcinoma- IL-39

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Introduction

Lung carcinoma is a disease that is characterized by uncontrolled growth, unlimited proliferation, and metastases to distant sites. As stated by the "American Cancer Society" in 2020, it is presently the second most common cause of new cancer cases and the first most common cause of correlated deaths on a global scale. There is a protracted treatment period and an insidious advent of the disease [1]. In the context of accelerated economic development and the expansion of urbanization, air pollution is a global health issue. Lung cancer is linked to ambient particulate matter (PMs) from vehicles and industrial exhausts [2]. The incidence of lung cancer is increasing globally as a result of the increasing availability of tobacco and the industrialization of emerging countries. In addition, there have been theories that smoking cannabis, using electronic cigarettes, hot tobacco products, and COVID-19 enhance risk [3]. Radon is the second most prevalent cause of lung cancer in the industrialized world, resulting from naturally occurring subsurface uranium degradation [4]. Lung carcinogenesis has been associated with environmental exposures, including air pollution, arsenic, HIV, tuberculosis infection, and occupational hazards, including asbestos use [5].

According to the annual report of the Iraqi Cancer Register, the total of new cases cancer during the year 2022 was 39.068 Lung cancer is the third most prevalent form of cancer in Iraq and the most the first among males, there were 2853 lung cancer (1981 males and 872 females),

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while during the year 2023 was 43.062, the lung cancer is 3020 (2129 male and 981 female) [6].

Treatment is guided by the histologic classification of the majority of lung malignancies, which are non-small cell lung cancer (NSCLC; 84%) and small cell lung cancer (SCLC; 13%) [7]. The early detection of high-risk groups at a treatable and curable stage is facilitated by screening [8]. The frequency of annual chest X-ray screenings for lung cancer at clinics has decreased by 25% in lung cancer mortality among individuals tested annually, according to research published in accordance with Japan Radiographic Screening and Diagnosis guidelines [9].

Sputum analysis remains one of the most widely employed diagnostic techniques for establishing a definitive histological diagnosis of lung cancer. Bronchoscopy and cytological examination of multiple sputum samples are particularly valuable, as they assist in differentiating central tumors from lesions located in the peripheral bronchi [10].

Interleukin-39 (IL-39) is a heterodimeric cytokine with a molecular weight of approximately 54 kDa. It consists of two subunits: IL-23p19, shared with IL-23, and EBI3 (Epstein-Barr virus-induced gene 3), which is also a component of IL-27 and IL-35. The IL-23p19 subunit belongs to the four-helix bundle family, similar in structure to cytokines such as IL-6 and granulocyte colony-stimulating factor (G-CSF) [11].

Pro-inflammatory cytokines cause matrix breakdown and plaque cell apoptosis, which destabilize atherosclerotic plaques. As a result, blood clots form, and the atherosclerotic plaque ruptures [12]. Decreased related IL-39 and hormone levels, the connection between SHBG and PCOS, and associated therapeutic approaches [13]. IL39's role in immunotherapy and oncology remains unexplored [14]. The studies found evidence for a positive association between lung cancer risk and white blood cell count, The neutrophil-to-lymphocyte ratio (NLR) is a simple blood-based metric that indicates a patient's inflammatory status; numerous studies have looked at how it relates to clinical response in non-small cell lung cancer (NSCLC) patients, and they've all come to the same conclusion: it has a negative association with outcome [15].

Cancer cells accumulate a significant amount of cholesterol by either upregulating cholesterol biosynthesis or enhancing cholesterol absorption to facilitate rapid cancer development [16]. Hyperlipidemia has been demonstrated to increase the risk of cancer; numerous malignancies are distinguished by fluctuations in blood cholesterol levels, whether they are elevated or depleted [17].

Serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are typically elevated in patients with chronic diseases; however, the AST/ALT ratio tends to decrease in such conditions [18]. Interestingly, individuals who developed cancer exhibited a higher baseline AST/ALT ratio compared to those who remained cancer-free. Moreover, cancer incidence was significantly greater among individuals in the highest quartile of the AST/ALT ratio distribution compared to those in the lowest quartile [19].

An elevated AST/ALT ratio has also been associated with an increased risk of all-cause mortality. Currently, the AST/ALT ratio is recognized as a valuable biomarker not only for liver diseases but also for various malignancies and cardiovascular disorders [20].

Materials and Methods

Patients and control groups

A local medical ethics council approved this study, and all participants gave their consent to share their personal information before the start of the study. This case-control research comprised 90 lung cancer samples, which were gathered from Imam Sadiq Hospital, Babylon Oncology Center (Babel, Iraq), and Karbala Health Al Hussain Oncology Center.

A Control group of 90 people appeared to be in good health. Patients were registered and provided with a file to record their data. Such as age, weight, gender, height, and so on, and their sex and age were equivalent to those of the patient groups. Patients with other chronic conditions, systemic immunological disease, heart disease, diabetes, and thyroid gland disease were excluded from the study.

Collection of data

The common situation for patients and Measuring the following factors in the blood of the participants such us Interleukin-39 /Melsin company/China by ELISA and the effect of leukocyte, neutrophils, lymphocytes, neutrophil-to-lymphocyte ratio (NLR), hemoglobin, platelets, Total Cholesterol kit Triglyceride kit/BIOLABO France Linear company /Spain, by ichroma alkaline phosphatase (Alp). Biolabo /France alanine aminotransferase (ALT), aspartate aminotransferase (AST) Cobas /Roche and albumin by BCG method/Biomaghreb/Tunisia

Statistical analysis

All data are expressed in the form of means ± standard deviations. The computer facilities of Microsoft Excel 2013 and SPSS 25 were employed to analyze statistical information. The statistical significance threshold was set at p-value ≤ 0.05. To gauge how closely the parameters were correlated, Pearson's correlation coefficient was used. In this, results were used two-way t-test to compare the differences among groups. Also, the receiver operating characteristic -area under the curve was used for diagnosis of patients with lung cancer (small cell and non-small) by novel markers such as IL-39

Results

Ninety people participated in this research, with 36 of "small cell carcinoma" and 54 of "non-small cell carcinoma". The average age of the participants was 64.500 years. , 90 samples of healthy people. There was substantial variation between the groups (P.05). When compared to "small-cell carcinoma" and "non-small-cell carcinoma" patients and healthy people, when "non-small cell carcinoma" stage four was higher than stage three, Table (1) illustrates the increased serum level of IL-39 in patients in the lung cancer group, especially

Table 1. Comparisons of Parameters for the Patients Groups and the Control Group

Parameters		Patients Groups		healthy group (3)	p-value
		Small cell ca. (1) Mean±SD	Non-small cell ca (2) Mean ± SD	Mean ± SD	
Male/Female		24/21	24 /21	68/22	
male %		53	53	75.5	
female%		47	47	24.5	
Age(year)		64.111 ± 7.640	62.652 ± 7.211	60.177 ± 5.762	A 2. 011
					B 0. 486
Hb g/dL		11.201±1.660	11.723±2.705	13.958±2.93	A 2. 51E-07
					B 2. 63E-08
	Total	7.845±2.848	7.509±3.418	6.310±1.569	A 0. 069
	$10^3/\mu l$				B 0. 060
	NEUT.	10.084±5.235	6.935±3.241	2.664±1.282	A 1. 64E-05
	$10^3/\mu l$				B 0. 003
WBC	LYM.	2.527±0.984	1.974±4.288	2.205±0.812	A 0. 352
	$10^3/\mu l$				B 0. 515
	N/L	4.125 ±5.91	3.630±1.126	3.615±1.577	A 1. 9E-06
					B 0. 007
PLT $10^3/\mu l$		299.20±75.01	291.02 ±93.33	217.62±52.54	A 0. 000
					B 0. 000
		2.464 ± 0.264	1.931 ± 0.469	1.382±0.861	A 0. 000
TG (mmol/l)					B 0. 005
		5.333 ± 0.802	4.070 ± 0.803	4.990 ± 0.861	A 0. 002
TC (mmol/l)					B 0. 000
		0.480 ± 0.288	0.346 ± 0.291	0.610±0.320	A 0. 003
HDL.C (mmol/l)					B 0. 005
		3.702± 0.581	2.868± 0.585	2.950±0.603	A 0. 002
LDL.C (mmol/l)					B 0. 000
		1.121± 0.160	0.878± 0.203	0.692± 0.141	A 0. 000
VLDL.C (mmol/l)					B 0. 004
ALT (IU/L)		32.50 ±4.412	22.75±3.828	12.00±4.280	A 0. 000
					B 0. 007
AST (IU/L)		49.50±15.351	31.25± 8.235	18.11±6.222	A 4. 07E-06
					B 0.001
AST/ALT		2.424±2.232	1.790±1.067	1.592±0.651	A 0.137
					B 0.387
ALP (IU/L)		255.888±47.379	224.259±64.692	88.422±22.83	A4.54E-12
					B 1.41E-11
Interleukin-39 Pg/ml		2.242±0.461	4.270± 0.472	5.512± 0.507	A 2.05E-23
					B 4.86E-15

Data represented as Mean ± SD, standard deviation; Hb, hemoglobin; WBC, White blood cell; LYM, lymphocyte; NEUT, neutrophil; N/L, neutrophil/ Lymphocyte; PLT, Platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; A, p-value (small cell ca. +healthy); B, p-value (non -small cell ca.+healt)

in small cell carcinoma patients, compared to the non-small cell carcinoma patient subgroups, compared to the healthy group. Also, triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and white blood cells (WBC).

Interleukin-39 biomarker exhibited excellent diagnostic efficiency (sensitivity: 1.000%, specificity: 1.000%), (AUC 1.000) (95% CI: 1.000-1.000; p<0.000), and the AUC determined best cut-off value (3.26950 pg/mL) gives the best value in "small-cell carcinoma" patients as shown in Figure 2 and Table 4. While Interleukin-39 biomarkers have poor diagnostic efficiency for non-small

Table 2. Comparisons of (Intreleukine-39) Parameters of the Small and Non-Small Cell ca. (stage 4, 3)

Parameters		A small cell ca.		Non-small cell ca		p-value
		Stage 4	Stage 3	Stage 4	Stage 3	
Total number		20	25	20	25	
Age(year)		66.421± 6.500	62.188± 5.980	62.251±8.881	62.932±9.920	A 0. 188
						B 0. 857
						C 0. 251
						D 0. 810
Hb g/dL		11.144±1.812	11.663±1.075	11.675±2.122	11.753±1.762	A 0. 511
						B 0. 919
						C 0. 572
						D 0. 873
	Total	8.957±1.993	6.827±3.033	7.560 ±3.624	8.106±3.087	A 0. 091
	10^3/µl					B 0. 731
						C 0. 324
						D 0. 303
	NEUT.	15.328±4.521	6.727±1.902	8.658±1.320	5.505±1.016	A 0. 001
WBC	10^3/µl					B 1. 13E-06
						C 0. 007
						D 0. 071
	LYM.	3.114±0.393	1.736±0.700	2.141±0.5583	1.846±0.415	A 6 .88E-05
	10^3/µl					B 0. 143
						C 0. 000
						D 0. 64809
	N/L	4.966±1.458	3.593±1.607	4.191±0.776	3.181±1.181	A 0. 082
						B 0. 063
						C 0. 229
						D 0. 648
PLT 10^3/µl		322.000±88.821	285.727±82.896	273.416±0.588	306.666±74.385	A 0. 402
100-450						B 0. 409
						C 0. 326
						D 0. 482
		2.812±0.369	2.245± 0.297	2.150±0.485	1.746± 0.515	A 0. 021
TG (mmol/l)						B 0. 142
						C 1. 21E-05
						D 0. 004
		6.242±0.977	4.918± 0.770	4.125±0.744	3.980± 1.039	A 0. 112
TC(mmol/l)						B 0. 583
						C 1. 53E-09
						D 0. 010
		0.580±0.276	0.423±0.300	0.297±0.268	0.370±0.3911	A 0. 710
HDL.C(mmol/l)						B 0. 557
						C 0. 001
						D 0. 55
		4.97 0±0.684	3.422±0.539	2.899±0.521	2.781± 0.727	A 0. 114
LDL.C(mmol/l)						B 0. 583
						C 1. 53E-09
						D 0. 010
		1.282±0.167	1.847±0.135	0.950 ±0.220	0.813± 0.234	A 0. 024

Data represented as Mean ± SD, standard deviation; Hb, hemoglobin; WBC, Wight blood cell; LYM, lymphocyte; NEUT, neutrophil; N/L, neutrophil/ Lymphocyte; PLT, Platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; A, p-value of small cell ca. (stage 4+stage 3); B, p-value of non-small cell ca. (stage 4+stage 3); C, p-value (stage 4 of small and non-small cell ca.); D, p-value (stage3 of small and non-small cell ca.

Table 2. Continued

Parameters	A small cell ca.		Non-small cell ca		p-value
	Stage 4	Stage 3	Stage 4	Stage 3	
VLDL.C(mmol/l)					B 0. 597
					C 1. 21E-05
					D 0. 004
ALT(IU/L)	32.142±6.221	32.818±9.624	29.416±9.210	15.600±5.785	A 0. 951
					B 0. 049
					C 0. 803
					D 0. 020
AST (IU/L)	58.285±11.554	43.626±8.666	42.166±10.336	22.338±6.987	A 0. 091
					B 0. 002
					C 0. 020
					D 0. 015
AST/ALT	3.642±3.199	1.649±0.795	2.085±1.513	1.555±0.425	A 0. 153
					B 0. 261
					C 0. 268
					D 0. 725
ALP (IU/L)	275.857±50.926	243.181±42.466	230.083±90.150	219.600±36.529	A 0. 184
					B 0. 710
					C 0. 175
					D 0. 153S
Interleukin-39 Pg/ml	1.879±0.327	2.472±0.384	3.923±0.366	4.547±0.350	A 0. 003
					B 0. 000
					C 5 .56E-09
					D 5. 17E-12

Data represented as Mean ± SD, standard deviation; Hb, hemoglobin; WBC, Wight blood cell; LYM, lymphocyte; NEUT, neutrophil; N/L, neutrophil/ Lymphocyte; PLT, Platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; A, p-value of small cell ca. (stage 4+stage 3); B, p-value of non-small cell ca. (stage 4+stage 3); C, p-value (stage 4 of small and non-small cell ca.); D, p-value (stage3 of small and non-small cell ca.

Table 3. Correlation between (interleukin-39) and Studied Parameters Infected of Lung cancer

Parameters	r	p.value
Age (year)	0.4	0.02
BMI kg/m^2	0.483	0.02
LDL-C (mg/dL)	-0.526	0.01
VLDL-C (mg/dL)	-0.769	0.0001
HDL-C (mg/dL)	0.094	0.1
TC (mg/dL)	-0.526	0.0004
TG (mg/dL)	0.044	0.1
WBC total 10^3/µl	-0.063	0.1
Lymph. 10^3/µl	0.169	0.07
Neutro. 10^3/µl	-0.761	0.0001
N/L Ratio	0.693	0.001
Hb g/dL	0.461	0.02
PLT 10^{3}g/L	-0.549	0.0002
ALT IU/L	0.519	0.01
AST IU/L	-0.691	0.001
AST/ALT	-0.281	0.04
ALP u/l	-0.76	0.0001

cell carcinoma patients (sensitivity: 0.635%, specificity: 0.926%), (AUC 0.689) (95% CI: 0.578-0.800; p<0.005), and the AUC determined best cut-off value (4.88700 pg/mL), as shown in Figure 3and Table 4.

Discussion

Local tissues become increasingly susceptible to the initiation and progression of cancer due to chronic inflammatory responses [21]. Inflammatory sites can release a variety of cytokines that stimulate the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which in turn contribute to DNA damage and genomic instability [22].Inadequate management and control of lung cancer can lead to a wide range of complications. Consequently, this highlights the need to explore and evaluate novel candidate biomarkers that offer greater accuracy and effectiveness in early detection and diagnosis [23].

In this study, we assessed the expression level of "interleukin-39" in the blood samples of lung cancer patient as potential early diagnostic biomarkers and examined their differential expression, furthermore, IL-39 appears to influence lipid metabolism, a factor often disrupted in cancer-associated metabolic syndromes.

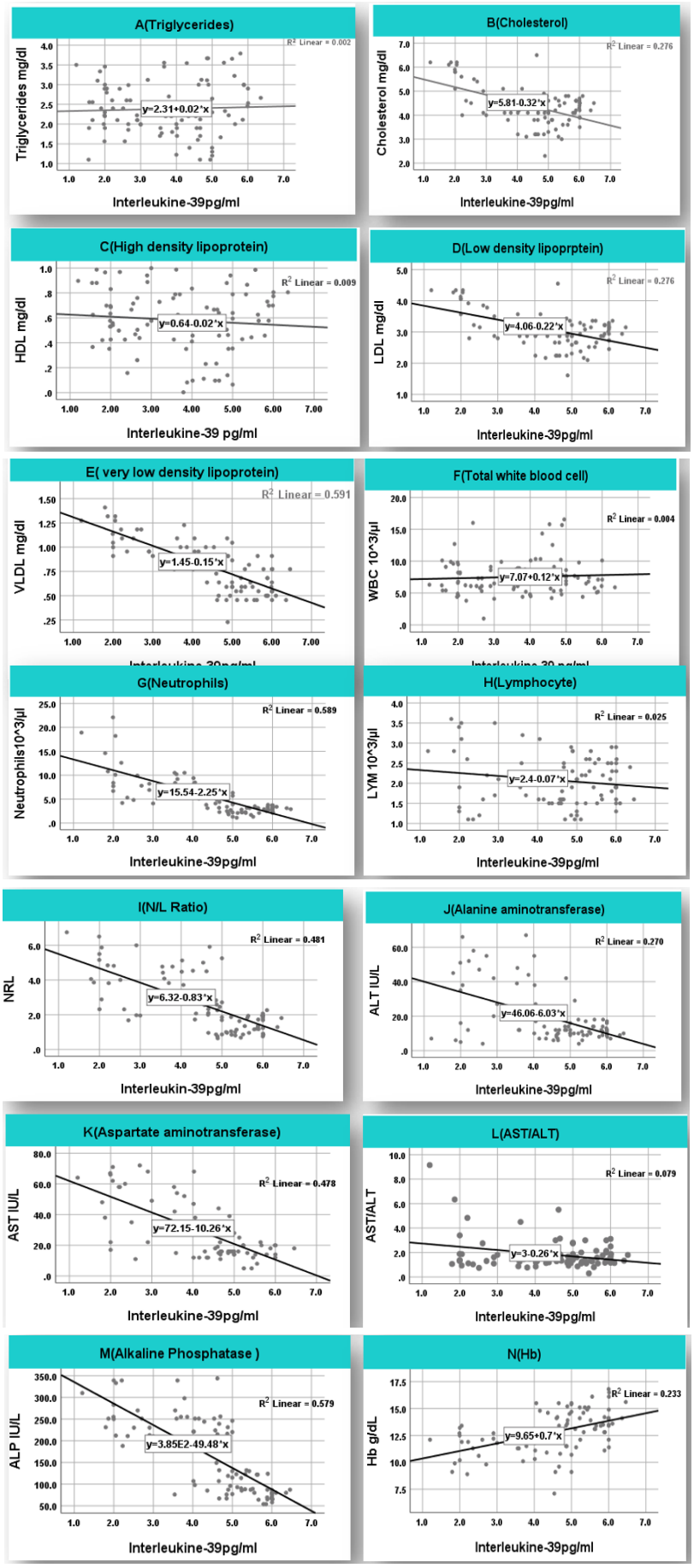

Figure 1. Linear Regression Analysis between Serum Level of Studied Interleukin-39 with Parameters where (A: TG, B: TC, C: HDL, D: LDL, E: VLDL, F: WBC, G: Neut., H: Lymph., I: NRL, J: ALT, K: AST, L: AST/ALT, M: ALP ,N:Hb

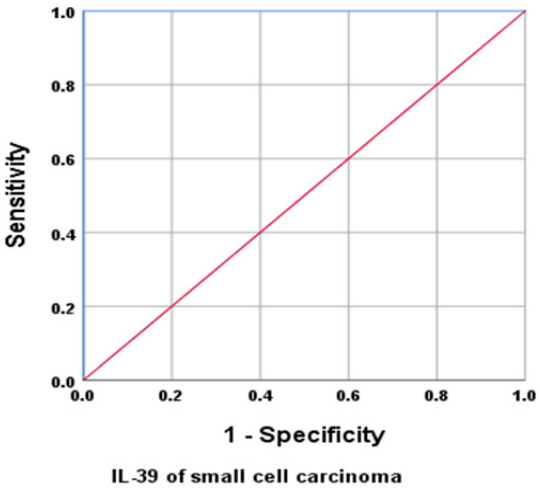

Figure 2. ROC Curve of Interleukin-39 Display Recognition of "small-cell carcinoma" Patients Group

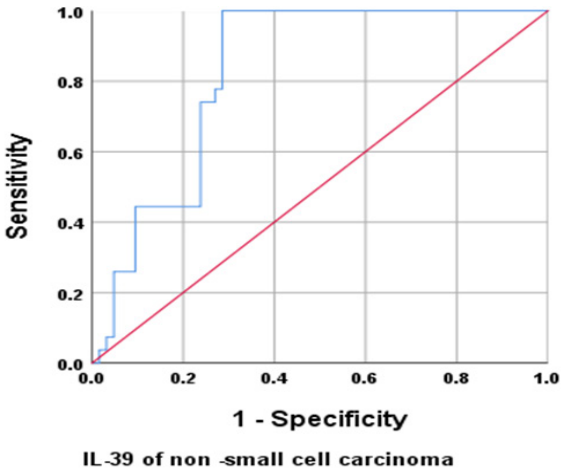

Figure 3. ROC Curve of Integrin Interleukin-39 Display Recognition of Non "small-cell carcinoma" Patients Group

Table 4. Receiver Operating Characteristic-Area under Curve Analysis of the Measured IL-39 in Small and Non-Small Cell Carcinoma Patients

Variable	Cut-off concentration	Sensitivity %	Specificity %	AUC	95% CI of AUC	p-value
Interleukin-39Pg/ml						
in small cell ca.	3.269	1.000	1.000	1.000	1.000-1.000	0.000
Interleukin-39Pg/ml in non-small cell ca	4.587	%69.5	%63.6	%68.9	0.578-0.800	0.005

Hypocholesterolemia and reduced levels of LDL-C and HDL-C have been observed in patients with advanced-stage lung cancer, while hypertriglyceridemia has been documented as a potential indicator of disease progression [24]. hypertriglyceridemia has been documented as a potential indicator of disease progression. The regulatory effect of IL-39 on cytokine networks may indirectly contribute to lipid imbalance through its interaction with key inflammatory mediators such as IL-6 and TNF-α, which are known to affect hepatic lipid synthesis and transport [25].Recent investigations have increasingly highlighted the multifaceted role of interleukin-39 (IL-39) in modulating systemic inflammatory responses and metabolic disturbances, particularly in the context of malignancies such as lung cancer [26].

Consequently, cytokines can determine the predictors of severe chronic diseases, it is meaningful to distinguish patients with high-severity of coronary artery diseases (CAD) from those who are suspected of having CAD. This would significantly enhance therapy, diagnosis, and prevention. In previous study investigation, discovered a strong correlation between serum cytokine levels and severe complications of CAD [27]. In serious diseases like cancer, lipid abnormalities manifest as hypertriglyceridemia, elevated free fatty acid (FFA) levels, and reduced cholesterol-containing lipoproteins, LDL, and HDL [28].Adipose tissue, which mostly includes fat cells, neurons, and immunological cells, has been recognized as a critical source of specific pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α [29].

IL-39 has been implicated in the regulation of hepatic function, with several studies reporting a significant correlation between altered IL-39 serum levels and elevations in liver enzymes, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP). These enzymes are critical indicators of hepatic stress or damage, and their elevation in lung cancer patients may reflect tumor-induced systemic inflammation or hepatic metastasis [30].

The progression of the disease is linked to the growth of atherosclerosis, which is aided by the upregulation of pro-inflammatory cytokines. In the latter phases of atherosclerosis, pro-inflammatory cytokines provoke apoptosis of plaque cells and matrix degradation, thereby contributing to the destabilization of atherosclerotic plaques. This results in the disintegration of atherosclerotic plaques and the formation of blood clots [31].On the other side, a Lowering of IL-39 levels in breast cancer patients. Serum IL-39 has the potential to serve as an early diagnostic performance indicator for breast cancer, necessitating further investigation [32]. Notably, differential expression patterns of IL-39 have been reported between small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC), with lower serum levels observed in late-stage SCLC patients [33]. This reduction may be indicative of immune exhaustion or tumor-induced cytokine suppression mechanisms. Collectively, these findings underscore the potential utility of IL-39 as a biomarker not only for early detection but also for evaluating liver dysfunction and metabolic imbalance in lung cancer patients [34].

The studies found evidence for a positive association between lung cancer risk and white blood cell count [35]. The neutrophil-to-lymphocyte ratio (NLR) is a blood-based parameter that is easily obtained and reflects the inflammation status of a patient [36]. Numerous studies have assessed the relationship between the clinical response of NSCLC patients and the NLR. Both single studies, meta-analyses, and comprehensive reviews have reported a negative association with the outcome [37].

Results showed that IL-39 increased inflammatory infiltration, hepatocyte necrosis, and serum levels of alanine and aspartate-aminotransferase [38]. By elevating levels of interferon-γ, tumor necrosis factor-α, and IL-17a in the blood, interleukin-39 also caused an inflammatory response. These and other research suggest that IL-39 may be able to affect the immune system, opening up new avenues for therapy [39].

In conclusion this study investigates Interleukin-39 (IL-39) levels in patients with small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC) compared to healthy individuals. Analyzing data from patients with advanced lung cancer revealed that IL-39 levels decrease more significantly in stage IV NSCLC compared to stage III, and a similar trend was observed in SCLC, where the reduction in IL-39 at stage IV was more pronounced than at stage III. Furthermore, when comparing stage IV SCLC to stage IV NSCLC, the decrease in IL-39 levels was greater in SCLC. Similarly, differences in IL-39 levels were noted when comparing stage III SCLC and NSCLC. These findings from ongoing clinical studies may contribute to future research and aid in developing comprehensive therapeutic strategies targeting immune responses, non-cellular components, and the tumor microenvironment, ultimately improving patient survival outcomes. Additional research is needed to establish if serum IL-39 can be used as an early indication of lung cancer diagnostic performance.

Author Contribution Statement

All authors contributed equally in this study.

Acknowledgements

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Ethical Clearance

The Research Ethical Committee at scientific research by ethical approval of both MOH By order 253/in 5/2/2024 and MOHSER 527/in 4/2/2024 in Iraq.

Conflict of Interest

None.

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