Article

Serum Levels of Interleukin 35 as Risk Markers for Increased Mortality in Lung Cancer with Covid-19

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Abstract

Background: Worldwide, lung cancer is still the biggest killer when it comes to cancer, arising from uncontrolled cell division in lung tissues. A homeostatic chemokine with a high degree of conservation, SARS-CoV-2, the culprit responsible for the 2019 new coronavirus disease (COVID-19), has posed a serious threat to worldwide public health. Additionally, COVID-19 infection may predispose persons to hyperglycemia. Hyperglycemia, when combined with other risk factors, may modify immunological and inflammatory responses, predisposing patients to severe COVID-19 infection.

Methods: The materials and methods are a case-control study conducted on 180 participants (aged 45–77): There were 90 patients of lung cancer, and 90 were healthy controls. IL-35 levels were measured using ELISA, along with CBC, cholesterol, triglycerides, and liver enzymes (ALT, AST, ALP).

Results: The average age of all lung cancer patients with COVID-19 was 45-77 years. The patients with lung cancer and Coronavirus had a significantly lower lymphocyte count and platelet count compared with the healthy, but the neutrophil was significantly higher when compared with the same groups. In the severe disease group, the leucocyte count and neutrophil count were significantly higher when compared with moderate disease. D-dimer, ferritin, and alkaline phosphatase were significantly higher, but platelet and albumin were significantly lower when compared with the same groups.

Conclusions: Our results support the idea that COVID-19 should be considered a risk factor for COVID-19 disease progression and prognosis. covid should receive increased care in the event of rapid deterioration. To identify information gaps that necessitate additional research on COVID-19 in lung cancer

Key Words: coronavirus, lung cancer, Interleukin 35.

1-Introduction

The primary issue of global cancer mortality and prevalence is carcinoma of the lungs which has led to two million diagnoses and 1.8 million fatalities. The rising incidence of (LC) worldwide is mostly responsible for the increasing use of tobacco products and the industrialization of emerging nations' rise[1]. Radon, resulting from the natural decay of subterranean uranium, is lung cancer's secondary leading cause in affluent nations[2]. All environmental exposures, including air pollution, arsenic, and HIV and TB infection, as well as occupational hazards like asbestos, have been linked to lung carcinogenesis[3]. Simultaneously, it has been postulated that the risk of developing COVID-19, electronic cigarettes, heated tobacco products, and cannabis consumption is elevated[1]. Iraqi Cancer Register reported the annual report, which introduced the total number of new cancer cases during 2022 which was 39.068 lung cancer is the 3rd most common cancers in Iraq and In the initial report on cancer in males, there were 2,853 cases of lung cancer (872 in females and 1,981 in males), while in 2023, the total rose to 43,062, with lung cancer accounting for 3,020 cases (981 females and 2,129 males). The predominant histologic classifications of "small cell lung cancer (SCLC; 13%) and lung cancer are non-small cell lung cancer (NSCLC; 84%)", which inform therapeutic strategies[4]**.**

By screening at-risk populations, diseases may be caught early, when they are more easily treated or even cured[5]**.** According to a study published in Japan Radiographic Screening and Diagnosis, The mortality rate from lung cancer was reduced by 25% for individuals who underwent annual chest X-ray screenings at health clinics[6]. Bronchoscopy is the leading diagnostic technique for establishing a definitive histological diagnosis of lung cancer. Additionally, sputum cytological analysis, especially when multiple samples are examined, serves as another valuable method for detecting primary tumors within the larger bronchi[7].

Elevated leukocyte levels are often thought to result from bacterial infections, especially when granulocytes are the most numerous. However, it is important to consider additional factors, including advanced cancer, bleeding, and the use of corticosteroids.[8]**.** Fever serves as a distinguishing characteristic that is more frequently observed in individuals with infections. In fact, a notable correlation exists between the likelihood of lung cancer and various circulating inflammatory and immunological markers.[9].The researchers found evidence for a positive relation between count of white blood cell and lung cancer risk, A number of studies have looked at how NSCLC patients' clinical responses are related. patients and the ratio neutrophil to lymphocyte (NLR)[10]**.**

Interleukin-35 has been shown to have a variety of beneficial effects, including anti-inflammatory, anti-oxidative, and anti-apoptotic properties. By inhibiting

inflammatory responses, IL-35 protected against acute liver and kidney damage caused by Lipopolysaccharide. [11] Numerous investigations have linked IL-35 as a novel anti-fibrotic effector in the treatment of liver fibrosis, cutaneous fibrosis, pulmonary fibrosis, and renal fibrosis, although its effects on cardiac fibrosis remain unknown. [12] Additionally, a rise in the serum level of IL-35 was seen in patients with both kinds of diabetes mellitus. Due to IL-35's immunosuppressive properties and its selective ability to proliferate regulatory T cells and inhibit Th17 cells, it is likely that IL-23 and IL-35 have antagonistic interactions. However, no such association was identified in our investigation, which could be explained by the fact that both biomarkers were evaluated in the serum. [13]

2- Materials and Methods:

2-1 The Patients groups and controls

This study received approval from a local medical ethics council, and prior to its commencement, all participants consented to the sharing of their personal information. The case-control research included 90 samples of lung cancer, which were collected from, Center of Karbala Health Al Hussain Oncology and Hospital of Imam Sadiq, Babylon Oncology Center (Babelon, Iraq).

The control group consisting of 90 individuals seemed to be in a good health. Participants were registered and given a file for recording their details, like names, weight, sex, height, age, and other relevant information, ensuring that their age and sex matched these of patient groups. Individuals with other chronic conditions, including diabetes, systemic immunological diseases, thyroid gland disorders and heart disease, were not included in the work.

2-2 Data Collecting

The period for sample collection spanned from February 2024 to September 2024, sanctioned by the ethical approvals from both the MOH under order 253/in 5/2/2024 and MOHSER 527/on 4/2/2024 in Iraq. Participants' blood was analyzed for various factors, including IL35 sourced from Melsin Company in China using ELISA, as well as the effects of neutrophils, lymphocytes, platelets, and the neutrophil-to-lymphocyte ratio (NLR). Additionally, assessments were made for hemoglobin, total cholesterol, and triglycerides using kits from Linear Company in Spain and France/BIOLABO, along with alkaline phosphatase (ALP) from France/Biolabo, aspartate aminotransferase (AST) alanine aminotransferase (ALT), from Cobas /Roche, and albumin via the method of BCG from Tunisia/Biomaghre.

2-3 Statistical analysis

To guarantee the accuracy of each data point, it was entered into a computer several times during an Excel verification process. Additionally, specific values were

calculated using formulas. The variable was represented as "mean & (SD)" to facilitate comparisons between the small and non-small cell carcinoma groups, utilizing the t-test for this analysis. All statistical data for the variables were examined through IBM SPSS Statistic ver. 25, with significance determined at P leas than 05.

3-Results

Generally, the total patients' number involved in the current work was 90, comprising 36 individuals with SCLC and 54 with NSCLC. Participants had an average age of 64.500 years, alongside 90 samples from healthy individuals. A significant difference was observed between the groups ($P < 0.05$). In comparisons, NSCLC stage four patients exhibited higher levels than those at stage three, as did SCLC stage four compared to stage three. When utilizing il35 to assess SCLC stage four against NSCLC at the same stage, results indicated that SCLC stage four levels were greater than those of NSCLC. Similarly, when il35 was used to compare stage three of both SCLC and NSCLC, SCLC stage three was found to be higher than NSCLC at that same stage.

The significant positive correlation observed in the lung cancer patient group between il35 and various factors, including triglyceride (TG), total cholesterol, Alanine Transaminase (ALT), neutrophil to lymphocyte ratio (NLR), Alkaline Phosphatase (ALP), and Aspartate Transaminase (AST), was confirmed by the linear regression analysis. Conversely, a notable negative correlation was found between il35 and high-density lipoprotein (HDL) and Hemoglobin levels (Hb) in relation to levels of serum of il35 within the same patient group, as illustrated in table 3.

The biomarkers of chemokine IL-35 demonstrated remarkable diagnostic accuracy in patients with small-cell carcinoma, with a cut-off value of 2.198 pg/mL predicting lung cancer, yielding a specificity of 71.4% and sensitivity of 100%, resulting in an AUC of 0.846 (CI: 0.767-0.925; 95%, $p = 0.000$), as illustrated in Table 3 .

Table 1 the comparison of parameters for groups of Patients and controls

Parameter		Groups of Patients **Mean ± SD**			p-value
		healthy group (3)	**Non-small cell ca and covid-19**	**Small cell ca. and covid-19**	
Male/Female female % male%		**68/22 24.5 75.5**	**40 /14 26.0 74.0**	**24/12 33.4 66.6**	
Age (years)		**60.177 ± 5.762**	**62.652 ± 7.211**	**64.111± 7.640**	**A 2.011 B 0.486**
Hb (g/dL)		**13.958±2.93**	**11.723±2.705**	**11.201±1.660**	**A 2.51E-07 B 2.63E-08**
WBC	**NEUT. 10^3/µl**	**2.664±1.282**	**6.935±3.241**	**10.084±5.235**	**A 1.64E-05 B 0.003**
	Total 10^3/µl	**6.310±1.569**	**7.509±3.418**	**7.845±2.848**	**A 0.069 B 0.060**
	N/L	**3.615±1.577**	**3.630±1.126**	**4.125 ±5.91**	**A 1.9E-06 B 0.007**
	LYM. 10^3/µl	**2.205±0.812**	**1.974±4.288**	**2.527±0.984**	**A 0.352 B 0.515**
PLT 10^3/µl		**217.620±52.54**	**291.020 ±93.33**	**299.200±75.01**	**A 0.000 B 0.000**
T C(mmol/l)		**4.990 ± 0.861**	**4.070 ± 0.803**	**5.333 ± 0.802**	**A 0.002 B 0.000**
TG (mmol/l)		**1.382±0.861**	**1.931 ± 0.469**	**2.464 ± 0.264**	**A0.000 B0.005**
LDL. C(mmol/l)		**2.950±0.603**	**2.868± 0.585**	**3.702± 0.581**	**A 0.002 B 0.000**
HDL. C(mmol/l)		**0.610±0.320**	**0.346 ± 0.291**	**0.480 ± 0.288**	**A 0.003 B 0.005**
VLDL. C(mmol/l)		**0.692± 0.141**	**0.878± 0.203**	**1.121± 0.160**	**A0.000 B0.004**
AST (IU/L)		**18.110±6.222**	**31.250± 8.235**	**49.500±15.351**	**A4.07E-06 B 0.001**
ALT(IU/L)		**12.000±4.280**	**22.750±3.828**	**32.500 ±4.412**	**A0.000 B0.007**
ALP(IU/L)		**88.422±22.83**	**224.259±64.692**	**255.888±47.379**	**A4.54E-12 B 1.41E-11**

AST/ALT	1.592±0.651	1.790±1.067	2.424±2.232	A 0.137 B 0.387
IL35	50.301±2.890	130.386± 10.939	133.371± 11.583	A 7.02E-17 B 1.56E-25

Data reported as Means±SD: standard deviation, Hb: hemoglobin, WBC: Wight blood cells, NEUT: neutrophils, LYM: lymphocytes, PLT: Platelets, N/L: neutrophils/ Lymphocytes, AST:aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, B=p-value (non -small cell ca.+healt), A= p-value (small cell ca. +healthy)

Table (2) Correlation between (interleukin-35) level with other Parameters Infected of Lung cancer patient group

Parameters	r	p.value
Age (year)	0.326	0.1740
BMI kg/m^2	0.571	0.4334
LDL-C (mg/dL)	0.315**	0.0012
VLDL-C (mg/dL)	0.717*	0.0002
HDL-C (mg/dL)	-0.230	0.0141
TC (mg/dL)	0.353*	0.0001
TG (mg/dL)	0.101**	0.0071
WBC total 10^3/µl	0.418**	0.0001
Lymph. 10^3/µl	0.370**	0.0001
Neutro. 10^3/µl	-0.828*	0.0120
N/L Ratio	-0.209*	0.0420
Hb g/dL	-0.458**	0.0222
PLT 10^3g/L	0.519**	0.0001
ALT IU/L	0.394**	0.0002
AST IU/L	0.679**	0.0001
AST/ALT	0.289**	0.0060
ALP u/l	0.799**	0.0001

Table (3) ROC-Area under Curve Analysis of the Measured Biomarkers in lung Cancer

Variable	Specficity %	Cut-off concentration	Senstivity %	95% CI of AUC	AUC	p-value
Interleukin-35Pg/ml	**2.831**	**%100**	**%70.8**	**%85.1**	**0.774-0.928**	**0.000**

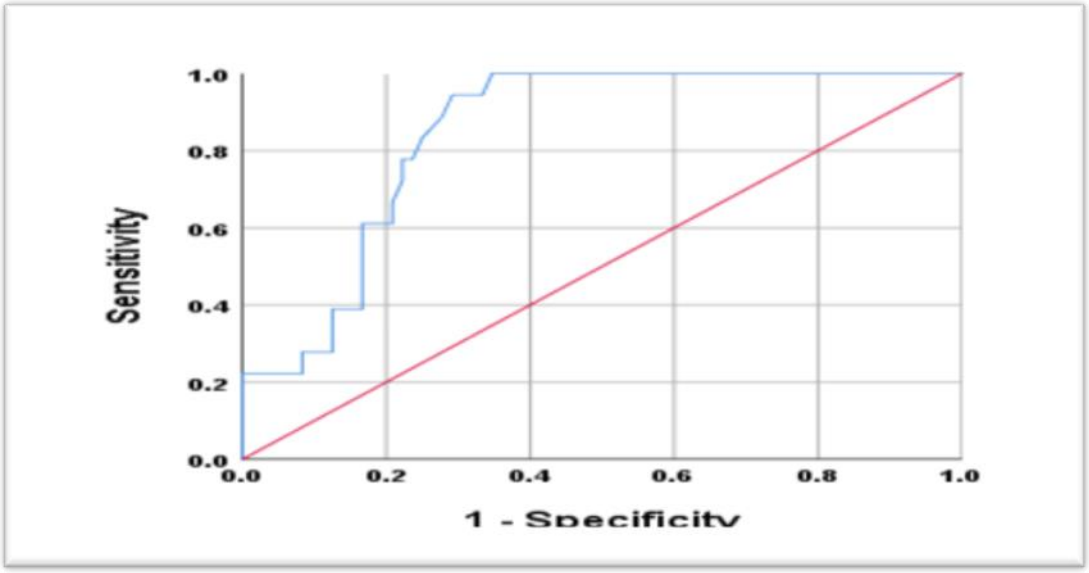

Figure 2 ROC Curve of Interleukin-35 Display Recognition of lung cancer Patients

4-Discussion

IL35 is expressed in multiple organs, indicating its role in maintaining systemic homeostasis. This chemokine is highly present along the intestinal lining and exhibits significant gene silencing in clinical samples of colon cancer. Such silencing suggests a potential link between IL35 suppression and the ability of cancer cells to evade immune responses[14]**.**

Marked disparities in a regulation of (il35) expression were seen in human colorectal carcinoma neoplasms and murine colon cancer models. Clinical tumor tissues frequently exhibit silencing of IL35, but new tumors in mice demonstrate upregulation of the gene[15]. A clinical tumor sampls we examined are the product of clonal differentiation, extensive mutations, and prolonged in vivo selection. Human tumor tissue frequently grows over several years or even decades before detection[16]**.** Conversely, mouse tumor samples are primary tumors that evolve over months, allowing less opportunity for mutation and selection. Consequently, the stages of

malignancy vary between mice and humans. Secondly, it is crucial to acknowledge that the expression of IL35 diminishes as cancer cells increase in malignancy. Nonetheless, IL35 expression is elevated in specific cancers[17].

Some studies in lung cancer patients have observed elevated levels of IL35, CXCL13, and CCL20 and compared them with controls to identify inflammatory factors. Therefore, IL35 was initially proposed as a potential diagnostic marker for lung cancer[18]

Hyperlipidemia was demonstrated to elevate a risk of cancer. Cancer cells typically amass substantial quantities of cholesterol by upregulating cholesterol production or augmenting cholesterol absorption, resulting in accelerated cancer progression. Variations in blood cholesterol levels (either declines or elevations) are significant occurrences in numerous cancers[19]. Research indicates that the cholesterol levels in tissue cells associated with breast, ovarian, and kidney cancers are elevated. The overproduction of LDLR is a critical mechanism enabling cancer cells for obtaining more necessary fatty acids via LDLR endocytosis. Research indicates that in the majority of malignancies, the overexpression of LDLR facilitates the accelerated uptake of LDL. In normal human prostate cells, LDLR expression is modulated by feedback regulation of LDL-C levels, whereas this regulatory feedback is typically lacking in prostate cancer cells[20]**;**[21]**.**

The growth of breast cancer is positively correlated with low-density lipoprotein cholesterol (LDL-C), which is a kind of unhealthy cholesterol. Based on the findings of a prospective research conducted in Portugal, it was shown that breast cancer patients who had higher levels of LDL-C at the time of diagnosis had tumors that were bigger, more differentiated, and developed more quickly. LDL-C levels in the plasma were shown to have a positive correlation with tumor volume[22].

Our purpose was to study the link between distinct lipid profiles and various cancer locations. We noted a propensity for an inverse correlation between HDL levels and cancers of the digestive organs, breast, skin, urinary tract, and lymphoid and hematopoietic tissues; however, the relatively small sample sizes precluded the determination of significant associations in site-specific cancer analyses. Furthermore, we noted a trend indicating a favorable correlation between total cholesterol and cancers of the respiratory organs and urinary system.[23]**.** In the Atherosclerosis Risk in Communities (ARIC) study cohort, we found that low levels of HDL-cholesterol correlated with an increased incidence of lung cancer among former smokers and in the whole population. Certain investigations identified a slight inverse correlation between HDL-cholesterol levels and the incidence of lung cancer[24]

This study revealed a notable positive correlation between cholesterol levels and lung cancer patients, with the exception of HDL cholesterol, which showed a negative association. Additionally, cholesterol levels varied with the type and stage of lung cancer, being elevated in patients with small-cell lung cancer compared to those with non-small-cell lung cancer.

Many recent studies have demonstrated a correlation between mortality and the "AST/ALT" ratio. Furthermore, an elevated "AST/ALT" ratio was an independent one-year predictor of polymyositis/dermatomyositis-associated interstitial lung disease[25]**.** Likewise, a higher "AST to ALT" ratio has been associated with mortality from all causes, especially cardiovascular disease. Studies related to cancer survival have shown that an elevated "AST/ALT" ratio is associated with a poor prognosis in renal cell carcinoma, head and neck cancer, oral cavity and oropharyngeal cancer, and other types of cancer[26]**.**

Understanding the mechanisms underlying its development and progression is essential, as lung cancer remains the most common malignancy and the leading cause of cancer-related deaths worldwide. Studies suggest that inflammation plays a significant role in the occurrence of various cancers. Neutrophils are not only key players in the inflammatory response but also integral components of the tumor microenvironment. Tumor-associated neutrophils (TANs) infiltrate tumors and actively contribute to their growth and progression. Moreover, they impact the therapeutic response and prognosis of lung cancer by modulating the immune microenvironment[27].

5-Conclusion

This study examines the relationship between chemokine IL35 and lung cancer among patients with as well as healthy individuals. An increase in chemokine IL35 was observed in patients "small and non-small cell carcinoma.with covid-19" This research elucidates how IL35 facilitates the metastasis of lung cancer, potentially linking to signaling pathways that lead to cellular migration. Furthermore, serum levels of chemokine IL35 may serve as promising early diagnostic performance indicators for lung cancer, meriting further investigation.

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Conflict of Interest: None

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