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Impact of IL-10-1082A\G promoter gene polymorphism and production in lung cancer patients

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Abstract---Lung cancer a deadliest malignant disease, Cytokines play a critical role in regulating host immune response toward cancer and determining the overall fate of tumorigenesis. So this study aimed to investigate the impact gene variation of IL-10 promotor region on production of IL-10 cytokine and their effect on lung cancer outcome. The aim of this study is the detection of IL-10-1082A\G polymorphism and IL-10 serum level with it correlation to progression of disease. A Case-control study was performed to 150 Lung cancer patients patients 54 females and 96 males and matched with age and gender attending to Middle Euphrates Cancer Center in AL-Najaf province with group of 60 healthy individual as control. Blood sample was collected from all patients and control. IL-10 level were measured by enzyme-linked immunosorbent assay (ELISA). Single nucleotide polymorphism detected by ARMS-PCR technique. The result shown that IL-10-1082 G/A significantly ($P<0.05$) high frequencies of homozygous GG, and G allele carrier in lung cancer patients, in contrast homozygous AA and AG genotype and A allele appear at low frequency with patients. The data showed that genetic variants of the IL-10 affect the IL-10 production and associated with the progression of disease. In conclusion, IL-10-1082 A\G, genotype contribute to the predisposition of lung cancer progress and there was significant association among genotype of this gene and level of cytokine as well as development of the disease. Also observed an association between this gene and serum level of cytokine. GG genotype and G allele consider a risk factor of asthma and progress the disease.

Keywords---IL-10, polymorphism, PCR-SSP, lung, cancer

Introduction

Lung cancer is one of the most common cancer that causes high morbidity and mortality in all industrial countries comprise 12.7% of the total cancer diagnoses as well as the leading cause of cancer death 18.2% of the total cancer deaths among all cancer patients worldwide. Lung cancer critically can be divided into two groups include Non-Small Cell Lung Carcinoma (NSCLC) and Small cell lung carcinoma (SCLC), which the first one accounts for about 80% of all lung cancers. Although, the mean onset age for lung cancer has been estimated ranged 60 to 70 years, less than 10% of all cases occurred at an early age. Although tobacco smoke is probably the predominant etiological risk factor for lung cancer, the pathoetiology of lung cancer is not fully understood(Jafari-nedooshan *et al.*, 2019). Interestingly, lung cancer develops only in a small proportion of chain smokers (less than 11%), which indicating that genetic factors might play a critical role in its carcinogenic mechanisms (Cavic *et al.*, 2014). Interleukin-10 (IL-10), also known as human cytokine synthesis inhibitory factor (CSIF), is a highly pleiotropic cytokine with multifunctional proprieties anti-inflammatory and anti-immune activities that produced by T helper type 2 (Th2) cells, regulatory T cells (Tregs), CD8+ T cells, macrophages, and even non-immune cells such as keratinocytes, epithelial cells, and tumor cells(Gao *et al.*, 2020).

It is an important cytokine in immunity and cancer and plays a role in inhibiting the initiation and development of tumors by activating natural killer cells and cytotoxic T lymphocytes. Surviving tumor cells express IL-10, thus allowing them to escape immune recognition by reducing the expression of MHC class II (Siegel *et al.*, 2017). Human interleukin-10 gene (*IL-10*) is located on chromosome 1q32.1 contains 4 introns and 5exons that encode 178 amino acids , IL-10 promoter region that significantly affect the gene transcription and expression(Y. H. Zhang *et al.*, 2019). A large number of association studies have found that polymorphisms of *IL-10* are involved in the susceptibility to many diseases, such as systemic lupus erythematosus(Gateva *et al.*, 2009) and interleukins gene polymorphisms with the susceptibility of lung cancer(Y. M. Zhang *et al.*, 2015). (Li et al., 2020) shown that IL-10 plays an important role in the initiation and development of breast cancer and found that expression of IL-10 is higher in breast cancer patients than in healthy persons

Materials and Method

The study was done at Laboratories of Bacteriology and Molecular in Biology Department, Faculty of Sciences, University of Kufa , Iraq.

Patients and control characterization

A Case - control study was adopted, during the period October 2021-febreuary 2022. 150 patients attending to Middle Euphrates Cancer Center in AL-Najaf province from that included 18(12%) small cell carcinoma patients and 132 (88 %) non-small carcinoma patients from which squamous cell carcinoma patients represent 69 (46%), Adenocarcinoma 40 (26.6 %) and large–cell lung carcinoma 23 (15.4%). as well as 60 apparently healthy subjects as control group.

Collection of sample

4 ml of Blood were collected from all subjects 2ml put in gel tube to separate serum and kept at -20 ◦ C used to evaluated IL-10 by ELISA system (Solarbio) and 2ml –in EDTA tube for DNA extraction and determine IL-10 gene variation .

PCR amplification and genotyping

Genomic DNA was extracted from fresh peripheral blood (3 ml in EDTA) using a commercially available kit according to the protocol of FAVERGEN™ Micro gDNA Extraction Kit, FAVORGEN, China and then stored at -20 C till use. Single nucleotide polymorphisms (SNPs) related to the IL-10 (-1082) were determined using PCR with sequence-specific primers (PCR–SSP) in two reactions employing one common forward and two reverse primers.The reaction mix was done in 25 µl volumes include 5µl of template DNA ,GoTaq®Promega Green Master Mix 2X 12.5 µl ,Primers(foreword 2 µl and reverse 2 µl)and Nuclease Free water 3.5 µl (Applied PCR system, USA).The sequences of designed primers Table1 and PCR conditions for IL-10 gene are shown in Table (2).The resultant PCR products were resolved by electrophoresis(UV - Trans illuminator) on 1g agarose gel stained with 2 µl (0.5 % concentration) from ethidium bromide, the run lasted for 1 hour for 100 V. The gel was then photographed (digital camera) on UV light and scored for the presence or absence of an allele specific band.

Table 1
The sequences of designed specific primers

Primer	Sequences (5́-3́)	Amplicon product	Reference
IL-10-1082 G\A	F:AGCAACACTCCTCGTCGCAAC R1: CCTATCCCTACTTCCCCC R2:CCTATCCCTACTTCCCCT	179 bp	Ali and Settin.,2013 [32]

Table 2
PCR conditions for IL-0-1082A\G gene

Step	Temperature	Time
Initial Denaturation	94 ◦C	5 Minutes
Denaturation	94 ◦C	30 Seconds
Annealing	60 ◦C	60 Seconds
Extension	72 ◦C	60 Seconds
Final Extension	72 ◦C	7 Minutes

Inclusion and Exclusion Criteria

Patients suffering from lung cancer were included while patients with chronic disease, other type of cancer, pneumonia, RTI were excluded

Ethical considerations

The study concept was accepted by Institutional Ethics Committee for Human

Studies from Middle Euphrates Cancer Center and the College of Science at Kufa University. In addition, all of the subjects provided written informed consent prior to participating in the research.

Statistical analysis

The one-way ANOVA Scheffe's method was employed represented as mean ±standard deviation (S.df). A $p < 0.05$ was considered statistically significant to compare between patients and healthy.

Results and Discussion

Demographic study

Demographic characteristics for 150 patients attending to Middle Euphrates Cancer Center in AL-Najaf province by patients-control study revealed that male were 96(64)% and female were 54(36)% and the statically analysis revealed a significant difference between male and female, as shown in Table (3).

Table 3
Distribution of patients according to sex, age and type of lung cancer

Variable	Group	N	%	Healthy group	%
Sex	Male	96	64	18	60
	Female	54	36	12	40
Age (years)	< 40			5	16.6
	40 - 50	24	16	3	10
	51 - 60	42	28	7	23.3
	61 - 70	48	32	9	30
	71 - 80	30	20	4	13.4
	81 - 90	8	4	2	6.7
Pathological type	Squamous cell carcinoma	69	46		
	Adenocarcinoma	40	26.6		
	large-cell lung carcinoma	23	15.4		
	Small cell carcinoma	18	12		

(Peddireddy *et al.*, 2014)confirmed that the majority of lung cancer patients are diagnosed to be non-small cell lung cancer (NSCLC) and revealed that among the NSCLC patients, 48.65 % and 43.24 % had adenocarcinoma and squamous cell carcinoma, respectively. Most of the patients presented with advanced stages of cancer were stage IV (58.11 %) followed by stage III (34.23 %).

IL-10 concentration in lung cancer patients and healthy

The result illustrated that serum level of IL-10 significantly increased in lung cancer patients (115.2 ±35.77) pg/ml compare to healthy group (8.69 ± 1.87) pg/ml.

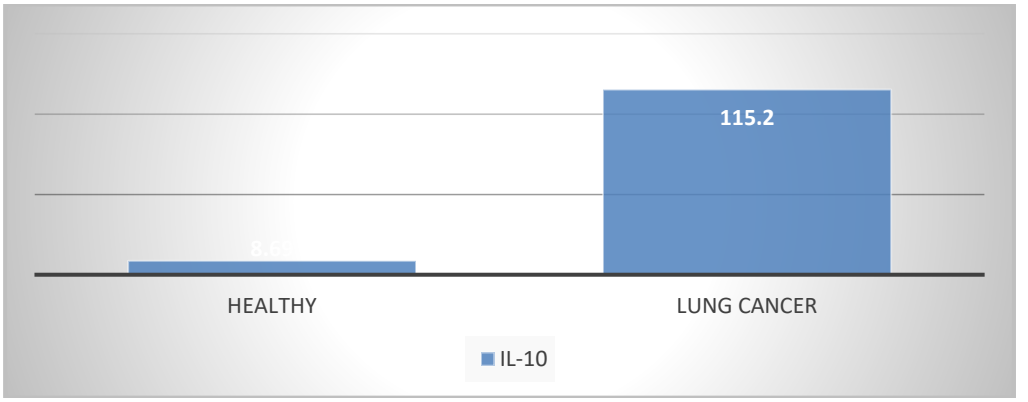

Figure 1. serum level of IL-10 in healthy and lung cancer patients

The results explain that IL-10 level increased more than ten fold in compar to healthy person this closed to (Karlicic *et al.*, 2016) whom found that Lung cancer patients had significantly increased serum IL10 compared with healthy controls (18±4 vs 9±2 pg/mL). (Hsu *et al.*, 2016) indicated that the IL10 levels in the sera of the lung cancer patients (38.16 pg/mL) were significantly higher than that in the normal individuals (32.55 pg/mL) and patients with higher IL10 expression presented lower survival rates, also concluded that IL10 from cancer cells and tumor-associated macrophages is involved in lung cancer progression. Jarnicki *et al.*, (2006) reported that significant increased production of IL10 and TGFb1 by cancer cells induced infiltration of growing tumor by CD4+ and T reg that induce lung cancer growth(Vahl *et al.*, 2017) found that elevated serum level of IL-10 by tumour-associated macrophages (TAMs)lead to inhibit tumor cell apoptosis. (R. Wang *et al.*, 2011) observed that increased of IL-10 expression could promote progression and poor clinical outcomes of lung cancer . Also, (Kim *et al.*, 2006) found that the expression of IL-10 was associated with progression of tumors including lung cancer. (Y. Wang *et al.*, 2016) found that the IL-10 level in exosomes of LC cells was increased, and IL-10 was involved in the migration of tumor cells.

IL-10 serum level in small and non –small lung cancer ptients

This study demonstrated that non-small cell carcinoma higher IL-10 serum level (138 ±21.66 pg/ml) then small cell carcinoma (112± 10.45pg/ml) with sighnificant diffrence as show in figure 2.

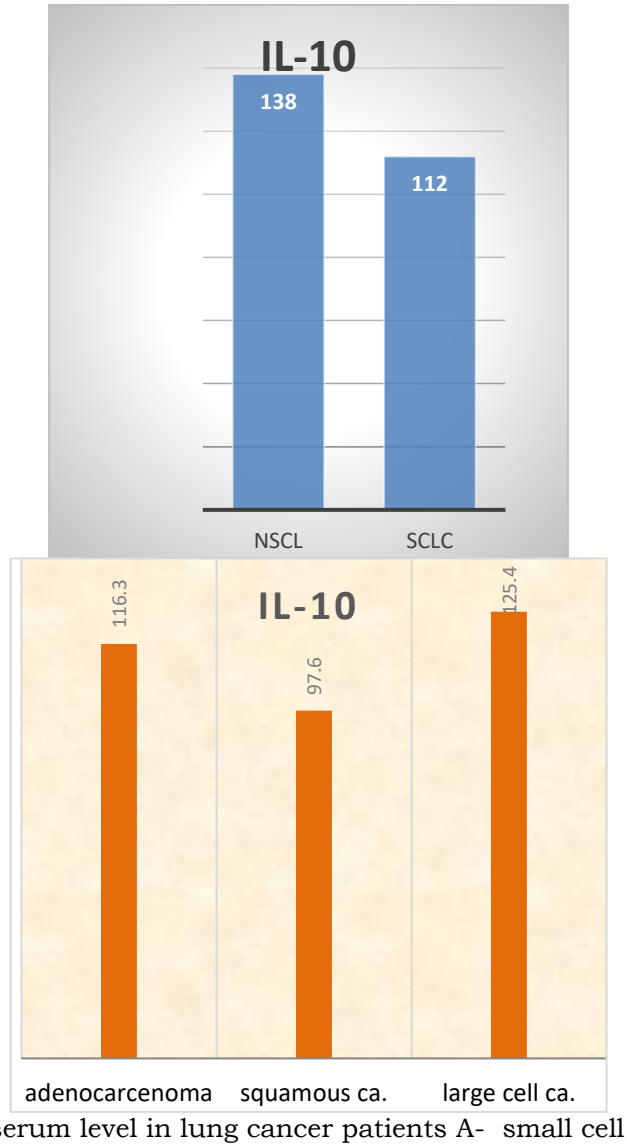

Figure 2. IL-10 serum level in lung cancer patients A- small cell and non- small cell LC. B –type of NSCL

This result consist with Aggarwal & Gehlot, 2009 who revealed that concentration of IL-10 in serum of lung cancer highly elevated in non small cell lung cancer followed by small cell lung cancer (138 ± 38.16 , 112 ± 26.27) pg/ml with significant different at P ≤ 0.05. Also, (Karlicic *et al.*, 2016) observed that the highest mean IL10 concentration in the microcirculation of the tumor was detected in NSCLC (30.33 ± 20.32)pg/ml which was significantly higher compared with SCLC patients (16 ± 13) pg/ml. (Gandara *et al.*, 2015) showed a significant elevated IL-10 mRNA as well as serum levels in SCLC as compared to healthy controls which shown to be associated with poorer prognosis. (Hatanaka *et al.*, 2000) explain that elevated IL-10 serum level in NSCLC patients lead significantly to poorer prognosis ,also IL10 expression associated with significantly worse of survival. Pang *et al.*, (2017) founded elevated IL-10 in the

serum of NSCLC patients with clinic pathological features of the patients. Karlicic *et al.*, (2016) founed Large cell and adenocarcinoma patients had the highest mean serum IL10 concentrations (37 ± 28 , 32 ± 33)pg/ml , in compare to squamous cell patients (14 ± 10)pg/ml. Vahl *et al.*, (2017) Increased IL-10 expression in the lung control region (CTR), surrounding the tumour, directly correlated with the tumour diameter in patients who suffered from ADC and they analysed IL-10 mRNA from a larger cohort of these patients with NSCLC and confirmed that the control region of patients with ADC had more IL-10 mRNA also We then analysed IL-10 mRNA from a larger cohort of these patients with NSCLC and confirmed that the control region of patients with ADC had more IL-10 mRNA (Figure 1C) as compared with those bearing a SCC.(Soria *et al.*, 2003) found that squamous type had the elevation frequent IL10 expression and reported that lack of IL10 expression in tumor tissue was associated with a significantly worse outcome. (R. Wang *et al.*, 2011)found that increased expression of IL10 mRNA in tumor associated macrophage s was significantly associated with histological types of NSCLC, with lowest value in squamous and highest in adenocarcinoma.

IL-10 serum level in patients according to stage of disease

The results appear that IL-10 serum level was increased significantly in stage IV compare to stage I-II and no significant difference in stage III (125.2 ± 36.22).

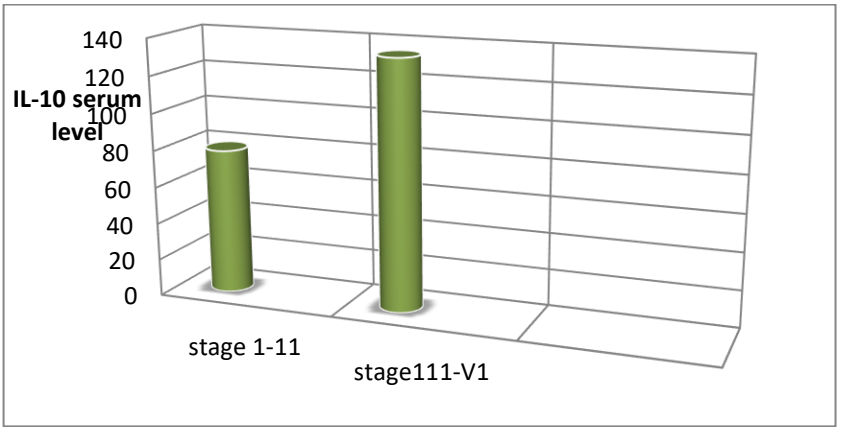

Figure 3. Illustrate the IL-10 serum level in lung cancer patients according to stages

(Yang *et al.*, 2019) showed that both IL-10 and IL-10RA mRNA expression in stage III tumor tissues was significantly higher than that in stage I and II tumor tissues ($p < 0.05$, and conclude that the IL-10 and IL-10RA expression signatures closely correlate with NSCLC stage. Karlicic *et al.,* (2016) confirmed that the mean IL10 concentration in patients with advanced lung tumor stages III and IV(26 ± 21) was significantly increased compared with the stage 1 and 11 (8.5 ± 3). (Vita *et al.*, 2000) investigated elevated IL10 level in serum samples of NSCLC patients in stages III and IV compare to patients in stageI. Another study revealed that NSCLC patients with late-stage disease (stage III, and IV) show increased levels of TAM-derived IL-10 which is accompanied by lymph node metastases, pleural invasion, and lympho vascular invasion(R. Wang *et al.*, 2011).

Molecular and immunological study
Distribution of IL-10 Gene "-1082 A/G" polymorphism in lung cancer patients
Detection IL-10 gene variation in lung cancer patients and IL-10 level

The distribution of IL-10 -1082 A\G polymorphism was detected by ARMS-PCR technique, at this locus there're three genotype; AA, AG and GG with band sizes of 179bp as shown in Figure 4.

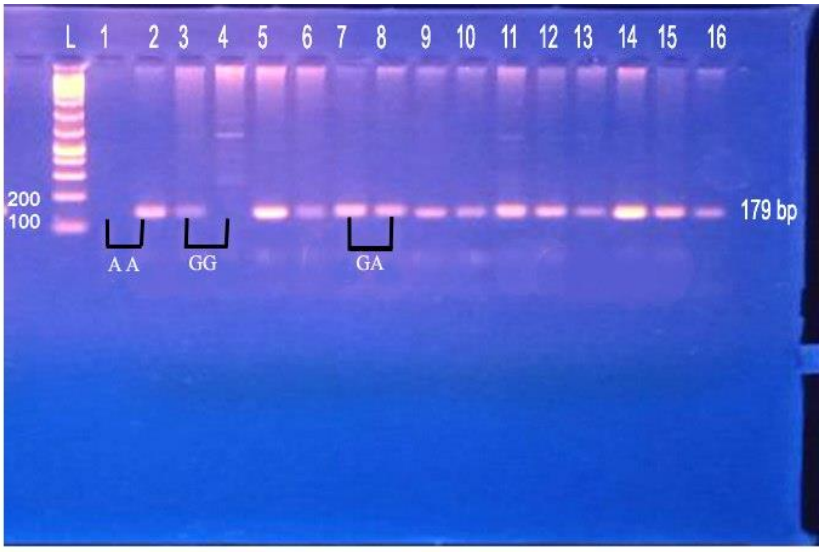

Figure 4. Ethidium bromide-stained agarose gel of PCR amplified 179bp of IL-10 gene in lung cancer patients

The results revealed that IL-10 gene distribution in lung cancer were homozygous genotype GG frequency was higher in lung cancer patients (56.7%) when compared to the healthy controls (16.7)%, GA genotype (31.3%) in the patients, whereas (30%) in control was statistically not significant (p=0.8403). Homozygous genotype AA prevalent was significantly different between the control and patients, and approximately 18 (12) % in lung cancer patients and 32 (53.3)% in the healthy controls as shown in Table 4.

Table 4
IL.10 polymorphism in patients with control

IL-10	Patients n=150	Control n=60	OR(95 % CI)	P-value
A/A	(18) 12%	(32) 53.3%	0.119 (0.0588 to 0.2420)	0.000***
G/A	(47) 31.3%	(18) 30%	1.064 (0.5552 to 2.0418)	0.8503 ns
G/G	(85) 56.7%	(10) 16.7%	6.538 (3.0828 to 13.8677)	0.000***
Allele frequency				
A allele	83	82	0.177 (0.1119 to 0.2809)	0.0001***
G allele	217	38	5.641 (3.5602 to 8.9401)	
*(P<0.05): significant , **or***(P<0.05) higher significant				

(Peddireddy *et al.*, 2016)found that GG genotypic frequency is significantly higher in NSCLC patients when compared to the controls, with a 1.6-fold risk for the disease , also, allelic frequency of G in NSCLC patients was significantly higher when compared to the healthy controls, with a 1.76- fold risk for the disease .(Y. C. Wang *et al.*, 2013) observed that higher "G" allelic distribution and G/G heterozygous genotype of the IL-10 gene in NSCLC patients when compared to controls also demonstrated that prognosis, survival, and relapse in resected NSCLC patients were strongly associated with the IL-10 haplotype. This result illustrate that homozygous GG gene give high production of IL-10, homozygous AA give low production of IL-10, finally heterozygous AG genotype give intermediate production of IL-10.

Table 5
Serum level of IL-10 according to genotype variation in lung cancer patients and healthy

	Serum level	GENOTYPE		
	Mean + S.D	GG	GA	AA
Patient s	115.2 + 35.77	193.7± 15.6	110.9±20.4	42.5±9.7
Healthy	8.69 + 1.87	12.1+ 3.00	7.28+ 2.87	5.34+ 1.63
Significantly	P < 0.001			

Polymorphisms in the promoter regions of cytokine genes affect their production, thereby affecting the circulating levels in the plasma**.** (Miteva & Stanilova, 2008) revealed that the IL10−1082 (A > G) polymorphism caused alterations in the production of the IL-10 cytokine in peripheral blood mononuclear cells of healthy donors **.** (Rausch et al., 2012)observed that IL-10 gene polymorphism in the promoter region affect the expression of gene-encoded proteins associated with lung cancer susceptibility and prognosis**.** The amount of IL-10 secretion was affected by polyorphism at the −1082 position in its gene, and the high or low IL-10 production is related to G/A substitution (Turner *et al.*, 1997). Yang *et al.*, (2019)observed that IL-10 protein expression increased with increased progressive of disease and metastatic cancer has been associated with higher IL-10 levels than cancer without metastases.

(Shih *et al.*, 2005) whom confirmed that higher ORs for NSCLC have been observed that individuals with IL- 10-1082 GG/GA genotypes, these genotypes are generally thought to be associated with a higher IL-10 production. Also (J. Wang *et al.*, 2012) found that the individuals carrying GA or GA/GG were associated with a higher lung cancer risk than subjects with the AA genotype in Asians , which observed that the IL10-1082 GG genotype is associated with a 1.3-fold increase in IL-10 protein production compared to the low IL-10-producing AA genotype and elevated serum IL-10 levels were observed in patients with various solid tumors. Peng *et al.*, (2012) founded significant association of IL-10 at position 1082G/A with LC susceptibility. Therefore, IL-10 gene may play an important role in the pathogenesis of LC. Higher ORs for LC were observed for individuals with carried IL-10 -1082 G allele and these genotypes are generally thought to be associated with a higher IL-10 production. Rad *et al.*, 92004)

mention that carriers of the IL-10 -1082G allele had higher mucosal IL-10 mRNA than -1082A allele carriers .The IL-10-1082 G allele has been considered to be associated with higher production of IL-10 from peripheral mononuclear cells. (Schaaf *et al.*, 2003) confirmed that IL-10 allele G homozygous patients had the highest risk for septic shock and the G allele, associated with high IL-10 release that influence the outcome of pneumococcal infection via induced immunosuppression and impaired bacterial clearance.

Table 6
IL.10 polymorphism in Stage I,II with Stage III,IV patients

IL-10	Stage I,II n=64	Stage III,IV n=86	OR(95 % CI)	P-value
A/A	(7) 10.9%	(11) 12.8%	0.837 (0.3055 to 2.2950)	0.7300 ns
A/G	(19) 29.7%	(28) 32.6%	0.874 (0.4340 to 1.7625)	0.7078 ns
G/G	(38) 59.4%	(47) 54.6%	1.212 (0.6299 to 2.3349)	0.5638 ns
Allele frequency				
A allele	33	50	0.847 (0.5065 to 1.4185)	0.5291 ns
G allele	95	122	1.179 (0.7050 to 1.9745)	
*(P<0.05): significant , **or***(P<0.05) higher significant				

(Ding *et al.*, 2021)IL-10 rs1800896 could increase LC risk, also found higher serum expression of IL-10 in LC patients than healthy controls, as well as higher proportion of positive IL-6 staining of lung tumor tissue in advanced (IIIA-IV) LC than early (IA-IIB) LC. Sung *et al.*, (2013) IL-10 expression has been associated with poor outcome in stage I lung cancer, whereas in late-stage lung cancer, the presence of IL-10–positive macrophages at the tumor margins can be an indicator of poor prognosis. Association of locally produced IL10 and TGFb1 with tumor size, histological type and presence of metastases in patients with lung carcinoma.

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