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Original Article

Assessment of Interleukin-13(rs20541) Genomic Polymorphism in Patients with Acute Respiratory Distress Syndrome in Relation to COVID19 Infection

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Abstract

Elevated Interleukin-13 (IL-13) may play an important role in the pathophysiology of COVID-19, yet, the attenuated response did not notice across all severe cases. Susceptibility to asthma in specific populations is associated with several SNPs of multifunctional cytokines, such as IL-13, IL-31 and IL-33. This prospective case-control study is designed to investigate the extent of genetic susceptibility in subsets of Iraqi patients with COVID-19 by targeting the variants of interleukin IL-13rs20541 polymorphism in relation to disease susceptibility and severity of clinical presentation. One hundred samples were obtained from the throat, nasopharyngeal and nasal swabs enrolled in this study. Eighty samples of the throat, nasopharyngeal and nasal localization swabs were obtained from patients with acute respiratory distress syndrome (ARDS) (both COVID-19 and non-COVID19 patients), while other 20 nasopharyngeal swabs were included as a healthy control group (AHC). Detection of IL-13rs20541 polymorphism was done by ARMS technique. The frequencies of GG-genotype in ARDS- patients with COVID-19, non-COVID19-, and AHC groups were respectively 14%, 12% and 3%, where, and as compared to the control group, showed a significant increase in COVID-19 patients. The AA- genotype in patients with COVID-19 group, non- COVID-19 group and healthy control group documented the frequency of 9%, 7%, and 14%, respectively, where the frequency decreased in the patient's groups as compared to the AHC group. Finally, and among the studied groups, an increase of AG- genotype (as rate OR=1.89) was documented compared to genotype GG and A-. Genetic polymorphisms in the IL-13rs20541 gene might influence its functions in patients with SARS-associated respiratory tract infection and thus might involve the pathogenicity of patients with COVID-19.

Keywords: Interleukin-13, Genomic Polymorphism, Distress Syndrome

1. Introduction

During the ongoing global COVID-19 pandemic, the infected patients with SARS-CoV-2 are recognized to have a course that clinically varies from asymptomatic infection to life-threatening respiratory failure followed by death (1). The SARS-CoV-2 infection is at its severe stage, characterized by immunological dysregulation. In addition, an inflammatory cytokines storm revealed early in that pandemic led to the development (and progression) of severe clinical forms of acute respiratory distress syndrome (ARDS) in SARS-CoV-2 infected patients and their requirement for hospitalization and/or assisted ventilation with end-organ damage and/or death (2). The hypothesis is that

individual cytokines and the associated inflammation are both thought to be the primary drivers involved in severe outcomes in patients during the later stages of COVID-19 and are evidenced by 29% decreased mortality in those COVID-19 patients on mechanical ventilation by using anti-inflammatory steroids (3).

IL-13, located on human chromosome 5q31, has shown 25% DNA homology with IL-4 (4). Among the diverse biological pathways, *IL-13* mediates the regulation of hyper-responsiveness of the airways, allergic inflammation, eosinophilia of tissues, as well as the production of IgE antibodies and fibrosis (5). Many studies showed that *IL-13* has varied biological functions and is produced by diverse cells, including eosinophils, natural killer cells, and fibroblasts (4, 5).

In COVID-19 patients, hyaluronan polysaccharide (HA) increased in the lungs and plasma. To support the HA's importance as a pathogenic mediator in this respect, following experimental use of anti-*IL-13* treatment, the hyaluronan synthase 1 (Has1) gene was most downregulated, and the accumulation of HA was decreased in the lungs (6). In severe COVID-19 patients, *IL-13* levels were elevated in those needing mechanical ventilation, whereas treating them with Dupilumab blocked *IL-13* and IL-4 signalling and caused less severe disease (7). In the repair mechanism, the fibrotic phase of induced by the activation of M2-macrophages. In addition, the M2 macrophages are triggered by $CD4^+$ T-lymphocytes, IL-4 mediates the Th2 response, and the latter activates *IL-13*. The *IL-13* is an immune-regulatory cytokine primarily secreted by activated T helper-Type 2 cells to inhibit inflammatory cytokine production (8). Both IL-4 &*IL-13* differentiate M2 macrophages and consequently lead to fibrosis.

Additionally, several studies showed significantly higher plasma levels of IL-13 in COVID-19 patients (9, 10). The COVID-19 severity is directly proportional to higher levels of *IL-13* expression (11). Recently, a study revealed elevated *IL-13* serum levels in COVID-19-infected patients who required ventilation support. In addition, COVID-19 patients prescribed with *IL-13* inhibiting drug (Dupilumab) have shown fewer dreadful symptoms (12). Moreover, a previous study revealed that anti-*IL-13* drugs have a significant role in controlling the 'Th2 high'phenotype of asthma (13). The contribution of the immune system, especially the role of both *IL-13* in aggravation of COVID-19 severity, has crucial implications in immunotherapy for the treatment of COVID-19 and other pulmonary diseases (11).

The present study was designed as a case-control study aimed to unravel the detection rates of Interleukin-13 genomic polymorphisms and to predict their possible implications in a group of Iraqi patients with acute respiratory distress syndrome, especially in relation to COVID19 infection.

2. Materials and Methods

2.1. Study Design

This prospective case-control study was conducted on 100 individuals; eighty patients included with COVID-19 infection as well as patients without COVID-19 infection who have admitted for ARTI in Central Teaching Hospital of AL-Sadiq; Merjan Medical City, and twenty healthy persons (included as a control group).

The specimens from these individuals were collected during the period from

February 2021 to September 2021. These nasopharyngeal, nasal and throat swabs were collected and processed to detect *IL-13* (rs20541) polymorphism.

Nasopharyngeal and/or throat samples were collected and processed to screen for human IL13 rs20541 gene polymorphism. To detect *IL-13*(rs20541) SNP in nasopharyngeal, nasal and throat swabs samples from patients and AHC, DNA products were obtained and processed by ARMS technique to detect these *IL-13*(rs20541) SNP. The primers have been designed explicitly for this study (Table 1). The PCR thermocycler device was used to amplify the intended SNPs and then used the gel electrophoresis technique to document the movement and sizes of the SNPs in the gel.

2.2. Age Distribution of Patients with COVID-19 Infection Versus Non-COVID-19 Infection (ARTI)

The mean age of patients with COVID-19 infection (40.6±9.56 years) was higher than the mean age of either the patients in the non-COVID-19 infection group (38.62±10.27 years) or those healthy control individual group (37.9±11.13 years). There were no significant statistical differences (P>0.05) among these groups according to mean age (Table 2).

2.3. Statistical Analysis

SPSS program (Version– 24) & P value was considered significant (P<0.05) and was used to explain the statistical variable between study populations.

Table 1. Primer sets that are used for the detection of *IL-13*(rs20541) polymorphism

Gene	Sequences	Product Size	Source\Origin
IL13 IF1	GAAACTTTTTCGCGAGGGCCA	A allele: 108	IDT\USA
IL13 IR1	GATGCTTTCGAAGTTTCAGTTGACCC	G allele: 168	IDT\USA
IL13 OF1	CTAACAGTACCCACCTCATGGGGACTT	Product size of two	IDT\USA
IL13 OR1	GAAGGCTGAGGTCGGCTAGGCT	outer primers: 280	IDT\USA

Table 2. Distribution of study groups according to their age

Study groups	N	Mean age (years)	SD	SE	Minimum	Maximum
Patients with COVID-19 Infection	40	40.6	9.56	1.62	17.0	68.0
Patients with Non-COVID-19 Infection (ARTI)*	40	38.62	10.27	2. 96	22.0	65.0
Apparently, Healthy Control (AHC)	20	37.9	11.13	3.35	19.0	54.0
Statistical Analysis	Non Significant differences (P>0.05)					

*(ARTI): Patients with Acute Respiratory Tract Infection

3. Results

3.1. Distribution of Patients and AHC according to their Gender

The percentage of the males with COVID-19 was higher (55%: 22) than the percentage of their female counterparts (45%: 18). Regarding the patients who were suffering from ARTI, the percentage of males was also higher (52.5%: 21 and 47.5%: 19, respectively), than the percentage of female counterparts. However, within the healthy individual's control group, the percentage of female counterparts was higher (60%:12) than the percentage of females (40%:8). The statistical analysis showed a non-significant difference (P>0.05) among the studied groups (Table 3).

3.2. Results of *IL-13* Gene Polymorphisms in Patients Presenting with Acute Respiratory Distress Syndrome

The amplification results have revealed the presence of two bands (G Allele= 162 bp and A Allele= 108bp) due to the presence of the G>A mutation, while a single 270 bp fragment identified the wild type. The results of amplified *IL-13* target sequences by ARMS technique in the studied groups are summarized in table 4 and figure 1.

The frequency of GG genotypes in patients with COVID-19, Non-COVID19-ARDS, and AHC groups reached 14%, 12% and 3%, respectively, significantly increased in COVID-19 patients in Control. The

frequency of AG genotypes in patients with COVID-19, Non-COVID19-ARDS, and AHC groups reached 34%; 32% and 6%, respectively, significantly increased in COVID19 & Non- COVID-19 patients than AHC control group. On the other hand, the frequency of AA genotype in patients with COVID-19, non- COVID-19 and AHC groups was 9%, 7%, and 14%, respectively, where the frequency decreased in the patient's groups as compared to the AHC control group. Finally, the AG genotype increased at a rate OR=1.9 compared with GG and AA genotypes among the studied groups.

According to these results, GG and AG were statistically higher in patients than in the control group according to the gene expression levels (P<0.05); however, AA was statistically lower in patients than in the control group table 4.

3.3. Spearman's Rho Statistical Testing

The recorded data showed that the SNPs *IL-13* were highly associated in COVID-19 (r= 0.873, P= 0.006). In addition, HAdV21 and SNPs *IL-13* were highly associated with age of patients who have COVID19 as well as non-COVID19 infection (r= 0.644, P= 0.002); (r=0.785, P= 0.004) (Table 5).

Table 3. The study groups according to the gender

Gender		Patients Groups			Pearson Chi-Square (P-value)
		Apparently healthy control	COVID-19 Infection	Non-COVID-9 Infection	
Male	N	12	22	21	P= 0.234 Non Sign. (P>0.05)
	%	60	55	52.5	
Female	N	8	18	19	
	%	40	45	47.5	
Total	N	20	40	40	
	%	100.0%	100.0%	100.0%	

Table 4. Comparison between patients with and without COVID19 infection based on a percentage of *IL-13* expressed gene polymorphism

IL-13	Study Groups			*P*-value	OR [Control]	95% C. I for OR [Control]		OR [Patients]	95% C. I for OR [Patients]	
Genotype	Control N=20	COVID-19 N=40	NON COVID-19 N=40			Lower	Upper		Lower	Upper
AG	6%	34%	32%	0.001	1.6	1.54	2.3	1.89	1.93	1.78
GG	3%	14%	12%	0.001	1.8	1.7	2	1.73	1.8	1.92
AA	14%	9%	7%	0.01	1.7	1.9	1.74	1.8	1.9	1.8

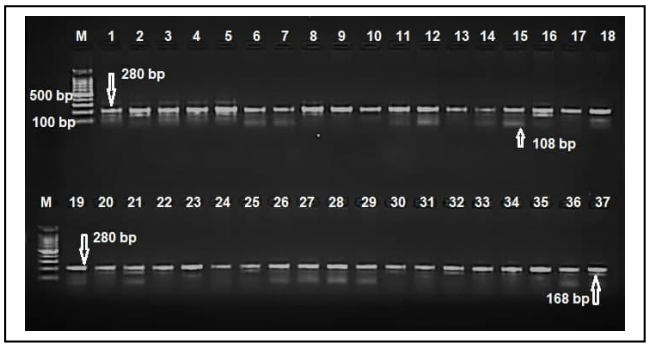

Figure 1. Allele typing patterns of *IL-13* gene using PCR-ARMS in patients with and without COVID19. The amplified products using PCR-ARMS migrated into 3% agarose, 75V, 20 mA for 120 min; 15 µl in each well; stained with ethidium bromide. The heterozygous allele (AG) had a two-band (molecular size 108 and 162pb), while the homozygous allele had a single band (molecular size 270 bp.)M= DNA ladder 100-1100 bp

Table 5. Spearman's Rho statistical testing of age, gender, and SNPs *IL-13* to evaluate the studied markers in patients with and without COVID19

Spearman's rho		Age group (Year)	*IL-13*	Gender
Age (years	R	0.644**	**0.873	
	P	0.002	0.006	
IL-13	R	0.785**		
	P	0.004		
Gender	R	0.188	-0.183	0.138
	P	0.272	0.393	0.047

4. Discussion

The role of *IL-13* has shown potential implications in the treatment of COVID-19, allergic or asthmatic inflammation, and other pulmonary diseases. The identification of *Has1* (the most down-regulated gene along with down-regulation of *Has2* and *Cd44*, two other genes involved in the HA pathway) following *IL-13* neutralization led to the route by which *IL-13* impacts the up-regulation synthesis of hyaluronan (11).

Previous studies have shown that the type 2 cytokine, *IL-13*, is associated with severe COVID-19, and the *IL-13* blocking drug, Dupilumab, in turn, is associated with better outcomes in COVID-19 patients and additionally, neutralization of *IL-13* in mice infected with SARS-CoV-2 protected them from death, in part by blocking hyaluronan synthesis and excessive deposition (7, 14). However, regarding the extreme heterogeneity of immune responses to COVID-19, it is unexpected for *IL-13* blockade will to work the same in all patients. The experimental downstream of hyaluronan production and the neutralization of hyaluronan receptors have improved survival (15). The *IL-13* neutralization not only decreased *Has1* gene expression but lowered hyaluronan deposition in the lung. Herein, this polysaccharide may contribute to lung inflammation by providing a matrix for the inflammatory cells to migrate and bind a large amount of water and very severe impairment of oxygen uptake in significant diseases in those hospitalized patients (7, 14) because of increased hyaluronan levels were observed in patients with COVID-19. Previous studies provided a potential mechanistic link between the association of *IL-13* and increased hyaluronan with severe COVID-19 disease (16).

There were no significant statistical differences (P>0.05) among these groups according to mean age**.** Regarding the previous population analyzed studies, the literature findings supported that the age of patients is a risk factor in the severe forms of COVID-19 and their fatal outcomes (17). In this study, we found that the percentage of males with COVID-19 was higher (55%: 22) than that of their female counterparts (45%: 18).

There were no significant statistical differences (P>0.05) among these groups according to gender. Although this study showed male prevalence in the COVID-19 group, no statistical difference in gender distribution was found. A consistent finding of male preponderance (66.6%) was found in a study by other researchers (18). The influence of age and the strength, as well as the duration of mechanical ventilation on the examined parameters in this research work, could not be excluded since COVID-19 lethality increased in these older than 65 years of patients with long periods of mechanical ventilation and as found in the results of other researchers (19).

In this study, the mean age of patients with COVID-19 infection (40.6±9.56 years) was higher than the mean age of either the patients in the non-COVID-19 infection group (38.62±10.27 years) or those healthy control individual group (37.9±11.13 years). A previous study found that COVID-19 patients have a predominantTh2 response. In addition, higher levels of M2 macrophages in COVID-19 patients may point to an activatedTh2 response. Moreover, the lymphopenia in these COVID-19 patients may support the M2 pathway for theTh2 response (8). It has shown that *IL-13* have roles in mucosal inflammation, including allergic asthma and fibrosis. Both IL-4 and *IL-13* have associated predominantly with fibrogenic inflammatory remodelling, whereas Th1 cells have an anti-fibrotic activity (secreting IFN-γ and IL-2) (20).

Although Vaz de Paula, de Azevedo (8) found IL-4 increased in the COVID-19 group, indicating a Th2

response; however, both *IL-13* and M2 macrophages decreased compared to H1N1 patients, suggesting no triggering of the Th2 proliferative phase. Since the same receptor (IL-4Ra) is shared by both interleukins, these participated actively in the Th2 pathway and induced an alternative activation of M2 macrophages, promoting the release of TGF-β and platelet-derived factors, leading to transient expansion of fibroblasts and formation of a temporary matrix and as well as the proliferation of airway progenitor cells and type 2 pneumocytes (21).

However, the increased levels of both IL-4 and *IL-13* (that promote the suppression of angiotensin-converting enzyme II) in asthmatic patients have revealed a lower risk of developing the severe form of COVID-19 (22). However, another study found no difference in the disease severity between asthmatic and those non-allergic children (23).

The SARS-CoV-2 destructs the type I and II pneumocytes, may lead to hyperactivation of macrophages and conducting the cytokines storm, and the higher release of interleukin-6 (IL-6) during this initial immune response may suppress T lymphocyte activation, leading to lymphopenia in COVID-19 patients (24).

Studies in the ICU- admitted SARS-CoV-2 infected patients (9,10,17,18.) showed low $TCD4^+$ and $TCD8^+$ lymphocytes and high serological levels of IL-6, TNF-α and PD-1 (programmed cell death protein 1), indicating that the immune system might be tilted abnormally towards Th2 response (25).

The frequency of AA genotype in patients with COVID-19, non- COVID-19, and AHC groups was 9%, 7%, and 14%, respectively, where the frequency decreased in the patient's groups compared to the AHC control group. Finally, the AG genotype increased at a rate OR=1.9 compared with GG and AA genotypes among the studied groups.

The present study, and up to our best knowledge, is the first at least on level of Iraqi studies that was designed as a case-control study to unravel the possible association and implications of Interleukin-13 genomic polymorphisms as related to COVID-19 infection in a group of Iraqi patients with acute respiratory distress syndrome.

The previous study correlated higher levels of *IL-13* with COVID-19 severity (have prolonged ventilation support) compared to others (26). It was also identified that the *IL-13* was inducing peptides in 5 different COVID-19 strains such as India (MZ340539.1), China (MT291829.1), USA (MZ319836.1), Brazil (MZ169911.1) and Japan (LC528233.2). Also, it was identified that *IL-13* inducing regions in Spike protein of Alpha (B.1.1.7), Beta (B.1.351) and Delta (B.1.617.2) variants of SARS-CoV-2 virus (26, 27). However, the induction of *IL-13* response in the patients was a very complex and multifactorial process.

Genetic polymorphisms in the *IL-13* gene might influence its function against

COVID-19 thus could be involved in the pathogenicity of

SARS-2 (28). Previous literature showed that it could effectively use the antibodies that block *IL-13* receptors in designing vaccines (28, 29).

Further explicatory studies on genetic polymorphisms in *the IL-13* gene concerning COVID-19 with asthma severity, especially in relation to different ethnic groups, are mandatory.

Authors' Contribution

Study concept and design: S. H. M.
Acquisition of data: A. M. N. A.
Analysis and interpretation of data: A. Y. A.
Drafting of the manuscript: Y. J. A.
Critical revision of the manuscript for important intellectual content: S. H. M. A.
Statistical analysis: S. H. M.
Administrative, technical, and material support: A. M. N. A.

Ethics

Ethical approval for this Study was obtained from the ethics committee at the Imam Sadiq Teaching Hospital, Hillah, Iraq.

Conflict of Interest

The authors declare that they have no conflict of interest.

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