Association of serum level of stem cell factor receptor (c-Kit) with the severity of COVID-19 infection in a sample of Iraqi patients with Asthma

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Abstract
Background: SARS-CoV-2, an enveloped, positive-sense single-stranded RNA virus, was the cause of the pandemic COVID-19. It enters the host cells via the angiotensin-converting enzyme 2 (ACE2) receptor and causes diffuse alveolar damage, pulmonary capillary congestion, and a cytokine storm, which leads to respiratory failure and the deadly acute respiratory distress syndrome (ARDS). Asthma affects a sizable majority of COVID-19 patients. The effects of asthma on COVID-19 progression are still unknown, but a moderating effect is conceivable because respiratory viruses are known to be a significant cause of asthma attacks, and another factor, possibly SCF (stem cell factor and its receptor), is a pleiotropic cytokine that affects immune response activation and survival at various stages of bone marrow development. Therefore, the study's case control objective was to assess the blood levels of c-KIT and the gene expression of stem cell factors in various age groups (asthmatics, people infected with Covid-19, and asthmatics and infected patients compared to healthy subjects). Methods: A case-control investigation was carried out on This study included one handicapped patient who visited Al-Kadhimya Hospital, Medical City, and private clinics in Baghdad, Iraq. The study also included 50 control subjects (without asthma or covid 19). For all groups indicated, the serum level of C-Kit was calculated using ELISA methods. SCF's gene expression was evaluated using the Ct value and folding (2-ΔΔCt) and standardized to the level of a housekeeping gene (GAPDH). Results: The expression of c-KIT and SCF significantly increased in the aforementioned groups ($p < 0.001$ and $p < 0.05$, respectively). Conclusion: Serum concentrations of SCF and its soluble receptor c-kit appear to be prospective diagnostic targets for asthma and Covid-19 severity, indicating a function for these molecules in asthmatic inflammation as well as a potential treatment target for Covid-19 pathogenesis.
Keywords: c-KIT, SCF; Asthma" COVID-19, ELISA; RT-PCR.

1. Introduction

A new coronavirus known as severe acute respiratory syndrome coronavirus 2 is the cause of the COVID-19 pandemic (SARS-CoV-2). Most patients with Covid-19 involvement who were recorded had minimal symptoms. However, severe pneumonia may complicate up to 20% of Covid-19 cases, which could lead to acute respiratory distress syndrome (ARDS), which can result in abrupt hypoxemic respiratory failure. A new coronavirus known as severe acute respiratory syndrome coronavirus 2 is the cause of the COVID-19 pandemic (SARS-CoV-2). Most patients with Covid-19 involvement who were recorded had minimal symptoms. However, severe pneumonia may complicate up to 20% of Covid-19 cases, which could lead to acute respiratory distress syndrome (ARDS), which can result in abrupt hypoxemic respiratory failure (Bchetnia et al., 2020) . Infection or tissue damage that activates both innate and adaptive immune responses results in the release of the proinflammatory cytokine IL-6. 2. Beginning in or around December 2019, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the culprit behind the present coronavirus disease-2019 (COVID-19) outbreak in Wuhan (Guan et al., 2020). COVID-19 was deemed a pandemic health emergency by the World Health Organization (WHO) on January 30, 2020. (Sablerolles et al., 2022). Since that time, COVID-19 has swiftly spread and grown to be the most serious pandemic in more than a century. New data suggests that COVID-19 should be viewed as a systemic disease involving the cardiovascular, pulmonary, gastrointestinal, neurological, hematopoietic, and immune systems in addition to the respiratory tract infection that it is traditionally described as (Scherer et al., 2022). Asthmatic respiratory syndrome is actually a recurrent condition in the general population (Sablerolles et al., 2022). Interleukin-6 (IL-6) was once thought to be a stimulant that T cells secrete to trigger the production of antibodies by B cells. Later, it was shown that more immune cells, such as macrophages and granulocytes, as well as non-immune cells, like bronchial epithelial cells, contribute to its glow (Levin et al., 2022). When it escapes its confines, it is often brought on by cellular injury or stress. Numerous research, some of which

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have already been discussed, have focused on the role of IL-6 signaling in the patho-physiology of asthma (Moreau et al., 2022). Clinical studies have discovered elevated IL-6 levels in asthmatics, both systemically and in the airways (Wang et al., 2022). High levels of IL-6 have also been connected to worsening disease symptoms and a decline in lung function (Rubin et al., 2022). The stem cell factor receptor (c-kit) is necessary for the growth, survival, and diversity of hemopoietic stem and progenitor cells as well as a number of nonhematopoietic organs (Goldberg et al., 2022). Several studies have demonstrated that SCF mediates eosinophil-induced degranulation, cytokine production, and survival. SCF is also involved in the production of IL-4, AHR, and airway inflammation (Kampf et al., 2020). C-kit-deficient mice have reduced allergic asthma inflammation, indicating that c-kit is important in the emergence of allergic inflammation (Lin et al., 2014). A trans-membrane tyrosine kinase receptor with a high degree of homology to additional growth factor receptors with kinase activity, such as "macrophage colony stimulating factor (c-fms) or platelet-derived growth factor," is encoded by the proto-oncogene c-kit (PDGF). The SCF pledges its properties by binding to the c-kit receptor, which results in receptor dimerization and activation of several signaling pathways, including the Erk1/2 and p38 mitogen activated protein kinase (MAPK) pathways. Both the c-kit receptor (KR) and its newly cloned ligand, c-kit ligand (KL), The hematopoietic progenitor cells and lymphoid lines, melanocytes, germinal cells, eosinophils in the peripheral circulation, basophils, and mast cells are among the cells that respond to SCF and articulate the Kit receptor (Mego et al., 2016). Mast cell stimulation by SCF can cause them to adhere to extracellular matrix and degranulate, which causes histamine and pro-inflammatory cytokines and chemokines to be produced and released. SCF promotes eosinophil adhesion and activation as well (Dougherty and Fahy, 2009). In COVID-19, the targeted organs are the lungs. When used for immune-modulation therapy, stem cells like mesenchymal stem cells (MSCs) can assist regulate immune cell proliferation, activation, and effector functions (ARR Weiss, 2019). Neutrophils and macrophages' activity and cytokine production can be immune-suppressed by stem cells (Kim et al., 2016). By engaging anti-inflammatory pathways in the wounded organ, MSCs can also control target cells of innate and adaptive immune systems. In order to minimize cell damage, it will also decrease pro-inflammatory mediators (IL-1, TNF-, IFN-, and IL-6) and boost anti-inflammatory cytokines (IL-10, basic fibroblast growth factor (bFGF), TGF-, and TGF-) (Abdelgawad et al., 2021). Surfactant-protein A, surfactant-protein D, and mannose-binding lectin are additional innate-immunity molecules that are produced by alveolar type-2 cells and have antiviral properties. Patients with conditions involving chronic inflammation, such as asthma and respiratory allergies, have more sensitivity to these chemicals. These compounds were developed to interfere with the SARS-CoV-2 spike protein, blocking its interaction with ACE2, and so preventing the virus from activating the alveolar macrophage (Ho et al., 2020). Additionally, the increased eosinophils associated with asthma may help the lungs of people with COVID-19 infection. Eosinophil counts in peripheral blood are lower in patients with COVID-19 infections. Patients with asthma may be protected from the excessive inflammatory response caused by the severe COVID-19 phenotype by the growing amount of eosinophils in their airways (Cruz-Teran et al., 2021). Both SARS-CoV and SARS-CoV-2 use ACE2 as their cellular receptor. In vitro susceptibility to SARS-CoV is improved by increased ACE2 expression, and researchers looking into factors influencing the ACE2 gene expression found that increases in ACE2 expression were connected to COVID-19 severity, smoking, hypertension, and diabetes (Wisnu Wardana and Rosyid, 2021a). Patients' severe asthma attacks are frequently triggered by respiratory virus infections. Asthma was not included as a risk factor for a severe COVID-19 disease in a significant epidemiological assessment of the disease in China. Investigations into asthma in COVID-19 continue to produce inconsistent findings (Rasmussen and Thompson, 2020). While many have noted that having asthma may increase the chance of COVID-19 severity, enough has also suggested that having asthma may actually protect against COVID-19 infection. The lowered expression of the ACE2 gene in alveolar cells can downregulate the rate of SARS-CoV-2 infection, according to other articles, and asthma and other allergy illnesses do not have the likelihood of causing severe COVID-19 infection (Jackson et al., 2020a). Angiotensin-I (Ang I) is changed to angiotensin-II (Ang II) by the ACE, a potent decapeptide and vasoconstrictor. In kidney and other tissues, the ACE2 catabolizes Ang-II to Ang-(1-7). As a result, ACE2 is thought to act as a natural inhibitor of ACE and Ang-negative II's properties in the pathophysiology of hypertension, renal disease, diabetes, and lung injury (Richardson et al., 2020). The severity of COVID-19 in asthma patients with other comorbidities, such as type-2 diabetes mellitus, had a higher frequency of COVID-19 than asthma alone, according to the statement. While there are no discernible variations in the incidence of COVID-19 for other conditions such bronchiectasis, obesity, gastroesophageal reflux disease, and cardiovascular illness (Gautret et al., 2020).

2. Materials and Methods

2.1. Subjects

Participants in this study included single patients who visited Al-Kadhimya Hospital, Medical City, and private clinics in Baghdad, Iraq. Based on some clinical and biochemical tests conducted by a respiratory consultant, fifty patients were identified

as having asthma, and another fifty patients were identified as having COVID 19 with asthma. The patients' average age was 50 30 years (range: 25 - 70 years). The wholesome control participants came from the general community of Baghdad, Iraq, and had a mean age of 51 ± 30. (range: 25 – 50) The Iraqi ministry of health and environment in Baghdad has given its approval to the study plan and protocol. All patients and healthy control participants gave their consent, which was also approved.

2.2. Samples collection and preparation

Ten milliliters of venous blood were drawn, an aliquot was distributed into a gel tube to separate the serum, and the serum was then centrifuged to remove it (3000 rpm for 10 min). Five milliliters of blood were exposed to the total RNA extraction procedure using Trizol (TRI Reagent®; ZYMO RESEARCH, USA), and the serum was refrigerated at -20°C until evaluation for testing.

2.2. Measuring of soluble c-KIT

A quantitative sandwich ELISA kit for c-KIT; CUSA Biotechnology; China. Was used to measure serum level of c-KIT I patient. and control.

2.4. Primers used in this study

The free website https://www.ncbi.nlm.nih.gov/tools/primer-blast/primertool was used to create and show the primer sequences used in the laboratory work. The primers for the Homo sapiens SCF were 5' GAGCTCCAGAACAGCTAAACG 3' for the forward primer and 5' CACTCCACAAGGTCATCCAC 3' for the reverse primer. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) from Homo sapiens was utilized as a housekeeping gene in this investigation. The forward and reverse primers were 5' TGATGACATCAAGAAGGTGGTGAAG 3' and 5' TCCTTGGAGGCCA TGTGGGCCAT 3', respectively. According to the producer Takara Bio Inc., Shiga, Japan, the primers were created and used.

2.5. Preforming the Expression of SCF

The RNA was isolated from blood samples using Direct-zol™ RNA MiniPrep, Zymo-Research/ USA. LunaScript Reverse Transcriptase/ Biolabs/England RT reagent Kit is designed to perform the reverse transcription optimized for real-time RT-PCR.The reaction was performed using a SaCycler-48 thermal cycler, Sacace, Italy. For quantitative PCR (qPCR), the reaction mixture was prepared using LunaScript RT Mix/ Biolabs/ England. the GAPDH housekeeping gene was used as the endogenous control. Lastly, the melting curve analysis was achieved the separation features of dsDNA during cycles with increasing denaturing temperature.

2.6. Statistical analysis

The software GraphPad Prism8 was used to obtain mean and SE, P<0.05 considered as non-significant. The fold change was calculated by the equations, ΔCT = CT of target gene – CT of U gene, ΔΔCT = ΔCT of each sample - average control ΔC and the Fold change = 2-ΔΔCt, respectively.

3. Results

In this study, 140 Iraqi patients (82 men and 58 women) were included. They were divided into three groups: controls, patients with asthma, and those with asthma and Covid-19 infection. 35 (or 25%) of the population were divided equally among them based on the aforementioned groups. Ages of the guys (58%) ranged from 35 to 72. 58 (42%) of the patients were women, ranging in age from 28 to 67. Using the data of healthy volunteers, case-control research was carried out in Baghdad between February and July 2022. Cases were defined as patients with COVID-19, COVID-19 with asthma problems (such as assisted ventilation, ICU hospitalizations, or death), and controls were patients who were discharged with no significant issues.

3.1. Serum level of C-Kit

The findings demonstrated that there was a significant difference between the patient groups as compared to the control (p< 0.05) in terms of serum levels of SCF-R. In which the level of c-Kit was somewhat higher in the asthmatic group compared to the controls (79.88±25 vs. 11.17±1.489) pg/ml. Asthma and COVID-19 infection groups had somewhat higher SCF-R levels (p=0.048) compared to control participants (43.31±14.36 vs 11.17±1.489 pg/ml vs 14.98±4.169 vs 11.17±1.489 pg/ml). (Table 3-8), (Figure 3-1).

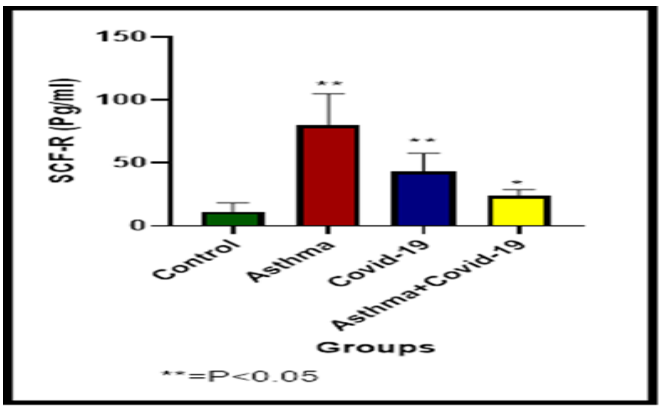

Figure (3-1): serum levels of SCF-R (c-Kit) in the Asthma, Covid-19, Asthma-Covid-19 groups, and healthy individuals.
*NS: P value>0.05, *= P value<0.05, **=P value<0.0001*

3.2. Gene Expression of SCF

The fold change (2-ΔΔCt) analysis of SCF after normalization with housekeeping gene (GAPDH) revealed that SCF was quantitatively overexpressed in the sick groups compared to controls, respectively (P<0.05; P<0.001). In comparison to the control group (1.5140.136), a higher expression was observed in COVID-19 (23.829±4.73) infected groups, followed by asthmatic (9.353±1.69) groups, and COVID-19+ Asthma + groups (2.759829±1.43). (* P < 0.05; ** P< 0.001; (Figure3-2**).**

Table (3-9): Gene expression of Stem cell factor (SCF) in blood samples in patients and controls			
Groups	SCF-ΔCT Mean ±SE	ΔΔCT	Folding
Control	-0.7±0.04	0.8±0.024	1.514±0.136
Asthma	-0.6± 0.074	0.9±0.083	9.353±1.69**
COVID-19	-0.1±0.00	-4.62±1.63	23.829±4.73***
Asthma-Covid-19	-2.7±0.658	-1.2±0.071	2.759829±1.43*
*, **, ***= p value<0.05, significant differences			

4. Discussion

Numerous airway cells, including bronchial epithelial cells, lung fibroblasts, bronchial smooth muscle cells, endothelial cells, peripheral blood eosinophils, and mast cells, express SCF in vitro. All cells that express the c-Kit receptor are affected when the SCF is produced. Studies on asthmatic patients also noted an increase in c-kit and SCF levels, suggesting that these markers may be useful for assessing acute allergies and determining the severity of bronchial asthma (Tayel et al., 2017). The measurement of C-kit and SCF in patients with COVID-19 infection has recently been limited, and other studies have suggested that elevated CD8+ cytotoxic T cells and decreased CD4+ lymphocytes are directly related to airway hyperreactivity and asthmatic diseases. In asthmatic rats, these modifications to CD4+ and CD8+ cells can reduce airway inflammation and hyperresponsiveness (Mirershadi et al., 2022). Previous studies have demonstrated that the transplantation of C-Kit+ cells enhanced Th-1/2 imbalance, clinical characteristics, and changes in pro-inflammatory mediators, leading mostly to the inhibition of pathological remodeling in asthmatic lungs. By decreasing the release of Th2 related pro-inflammatory cytokines IL-4, -5, and -13, together with an increase in type 2 macrophage IL-10, the pulmonary C-Kit+ cells are capable of restoring lung function (Li et al., 2019). Elevation of the NF-B and p-ERK/ERK signaling axis can result from asthma. According to reports, when compared to control and sensitized rats that received C-Kit+ cells and the control group, the S and patient groups had higher levels of pulmonary NF-B and p-ERK/ERK protein. It was suggested that MAPK/NF-B signal pathways might control cellular processes in the airways, such as cellular proliferation, differentiation, and apoptosis as well as the generation of immunomodulatory and pro-inflammatory mediators (Rahbarghazi et al., 2021). Through modifying signaling cascades like the MAPK/NF-B pathway, C-Kit positive cells can regulate immune system activity during asthmatic variations. Further research is necessary to determine whether C-Kit+ cells' juxtacrine or paracrine activity contributes to the inversion of the MAPK/NF-B axis (Damera et al., 2012). Injection of human lung C-Kit+ cells near the injured areas in female mice improved lung repair, as many prior research on asthma revealed and supports our findings (Mirershadi et al., 2020). According to other studies, there are other intracellular signaling pathways where c-Kit and SCF, a type III receptor tyrosine kinase (RTK), are complex. It is primarily thought of as a stem-cell receptor c-kit that contributes to essential bodily processes in mammals, including humans. In order for stem cells to differentiate, multiply, and survive, c-kit activation is essential. According to recent research, exercise training promotes the expression of the gene c-Kit in stem cells (Saheli et al., 2022). According to recent research, ischemia, inflammation, oxidative stress, and cell death are a few of the processes that contribute to the low cell survival rate in MSC therapy. Young athletes' bone marrow may be the best option for cell therapy in Omicron-infected patients because of the modulatory effects of exercise training on MSCs (such as potential anti-inflammatory effects, strengthening endogenic antioxidant defense, and protective effects against apoptosis), as well as additional benefits connected with using bone marrow from young people (Chakrabarty et al., 2022). A target marker for Covid-19 pathogenesis and asthma hypersensitivity, overexpression of c-kit snd stem cell factor in patients compared to controls suggests their significance.

5. Conclusions

1. There was an imbalance between Blood parameters (WBC, ESR, CRP, D-Dimer) and soluble (c-kit) in sera of patient groups and control.
2. Elevated level of WBCs in covid-19 and asthmatic patients infected patients, while normal in stable asthmatic patients and controls.
3. Elevated levels of ESR, CRP, D-Dimer in covid-19 and asthmatic patients infected patients, while normal in stable asthmatic patients and controls. suggested that could play an assessment role in the management of covid-19 severity in addition to the specific therapies.
4. Overexpression c-kit and stem cell factor in patients compared to control suggest their importance as a target markers for Covid-19 pathophysiology and asthma hypersensitivity.

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