بسم الله الرحمن الرحيم

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تم رفع هذه الرسالة بواسطة / سامية زكى يوسف

بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

ملاحظات: لا يوجد

Evaluation of Serum Interleukin (IL)-17A and IL-22 in Pediatric Patients with SARS CoV-2 Infection

Thesis

For Partial Fulfillment of Master Degree in **Pediatrics**

By

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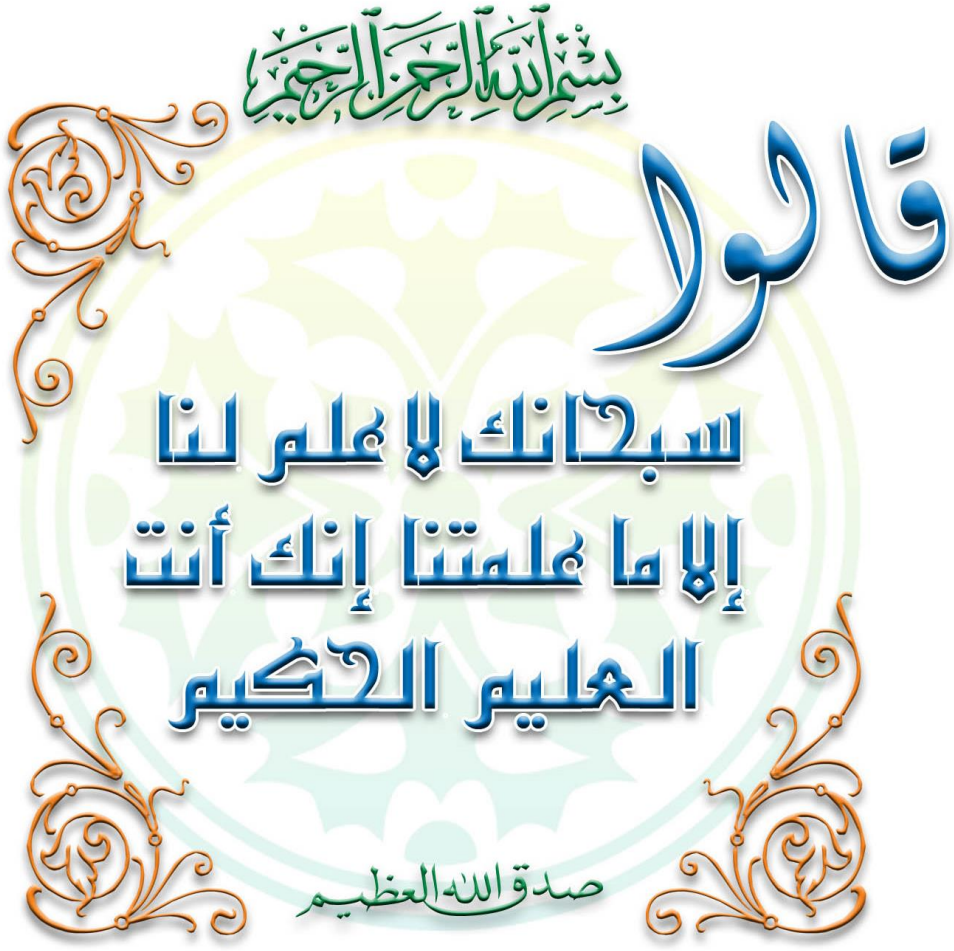

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Nada AboAbdoun Soliman

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List of Abbreviations

Abb.	Full term
ACE-2	*Angiotensin-converting enzyme 2*
Ad26.COV2.S	*Janssen COVID-19 vaccine*
AKI	*Acute Kidney Injury*
ARDS	*Acute Respiratory Distress Syndrome*
BNP	*Brain Natriuretic Peptide*
BNT.16252	*Pfizer-Biotech COVID-19 vaccine*
CA	*Coronary Artery*
CBC	*Complete Blood Count*
CD+4	*Cluster of differentiation 4*
CD+8	*Cluster of differentiation 8*
CDC	*Centers for Disease Control and Prevention*
CK	*Creatine Kinase*
CORADS	*A categorical CT Assessment Scheme for patients Suspected of having COVID-19 Definition and Evaluation.*
COVID-19	*Coronavirus Disease*
CRP	*C - reactive protein*
CS	*Cytokine Storm*
CT	*Computed Tomography*
ECHO	*Echocardiography*
ESR	*Erythrocyte Sedimentation Rate*
FDA	*Food and Drug Administration*
ICU	*Intensive Care Unit*
IL-17	*Interleukin 17*
IL-17A	*Interleukin 17A*
IL-17F	*Interleukin 17F*
IL-22	*Interleukin -22*
IL-6	*Interleukin-6*

List of Abbreviations (cont...)

Abb.	Full term
IQR	*Interquartile Range*
IVIG	*Intravenous Immune Globulin*
KD	*Kawasaki Disease*
LDH	*Lactate Dehydrogenase Enzyme*
LMWH	*Low Molecular Weight Heparin*
LV function	*Left Ventricular function*
MAS	*Macrophage Activation Syndrome*
MERS	*Middle East Respiratory Syndrome*
MIS-C	*Multisystem inflammatory syndrome in children*
MRNA-1273	*Modern COVID-19 vaccine*
NAAT	*Nucleic acid amplification test*
NLR	*Neutrophil-to-lymphocyte ratio*
PAMPs	*Pathogen associated molecular patterns*
PCR	*Polymerase Chain Reaction*
P-JIA	*Polyarticular juvenile idiopathic arthritis*
PMIS	*Pediatric multisystem inflammatory syndrome*
PMIS-TS	*Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2*
PPI	*Proton Pump inhibitor*
PRRs	*Pattern recognition receptors*
PT	*Prothrombin time*
PTT	*Partial thromboplastin time*
RSNA	*Radiological Society of North America*
RT PCR	*Real-time polymerase chain reaction*
SARS COV2	*Severe acute respiratory syndrome coronavirus 2*
SD	*Standard Deviation*

List of Abbreviations (cont...)

Abb.	Full term
S-JIA	*Systemic Juvenile Idiopathic Arthritis*
TH	*T-Helper*
TID	*Three times a day*
TNF	*Tumor Necrotic Factor*
WHO	*World Health Organization*

Abstract

Both IL-17A and IL-22 share cellular sources and signaling pathways. They have synergistic action on epithelial cells to stimulate their production of antimicrobial peptides which are protective against infections. However, both interleukins may contribute to ARDS pathology if their production is not controlled. This study aimed to investigate serum levels of IL-17A and IL-22 in relation to the disease outcome in patients with SARS-CoV-2**.** Serum IL-17A and IL-22 were measured by ELISA in 40 patients with SARS-CoV-2, aged between 2 months and 16 years, (18 had COVID-19 and 22 had multisystem inflammatory syndrome in children "MIS–C") in comparison to 48 age- and sex-matched healthy control children. Patients with COVID-19 and MIS–C had significantly higher serum IL-17A and IL-22 levels than healthy control children ($P < 0.001$). Increased serum IL-17A and IL-22 levels were found in all patients. Elevated CRP and serum ferritin levels were found in 90% of these patients. Lymphopenia, neutrophilia, neutropenia, thrombocytopenia and elevated ALT, LDH and D-dimer were found in 45%, 42.5 %, 2.5%, 30%, 32.5%, 82.5%, and 65%, respectively of these patients. There were non-significant differences between patients who recovered and those who died or had a residual illness in serum levels of IL-17A, IL-22 and the routine inflammatory markers of COVID-19. In conclusions, serum IL-17A and IL-22 levels were up-regulated in all patients with COVID-19 and MIS–C. Levels of serum IL-17A, IL-22 and the routine inflammatory markers of COVID-19 were not correlated with the disease outcome. Our conclusions are limited by the sample size.

Keywords

COVID-19, IL-17A, IL-22, MIS–C, SARS-CoV-2

Introduction

Cytokine storm has been observed in some COVID-19 patients that may progress to multiple organ dysfunction and death. Thus, the prevention and early treatment of cytokine storm in patients with COVID-19 are important. Measuring levels of serum pro-inflammatory cytokines have many potential applications in COVID-19 management, determination of prognosis and prediction of the response to treatment ***(Liu et al., 2021; Kim et al., 2021).***

T helper (Th) 17 cells, a distinct lineage of effector $CD4^+$ T cells, are characterized by production of interleukin (IL)-17. These cells also express IL-22, at substantially higher amounts than Th1 or Th2 cells. IL-6 enhances the generation of Th17 cells and both IL-6 and IL-17 synergistically promote viral persistence by the protection of the virus-infected cells from apoptosis ***(Hou et al., 2014).*** Similar to IL-17A, IL-22 expression was initiated by IL-6 and other pro-inflammatory cytokines ***(Liang et al 2006)***.

IL-17 family of cytokines consists of six ligands from IL-17A to IL-17F. IL-17A is considered to be the effector

and the classic cytokine of Th17 $CD4^+$ T cells. IL-17A plays a protective role in the host defense against pathogens through eliciting an acute immune response at the epithelial and mucosal barriers to induce the tissue healing after injury and to maintain the epithelial tight-junction barrier during the process of inflammation ***(Monin et al., 2019)***. However, uncontrolled and excessive production of IL-17A is one of the potential mechanisms underlying autoimmunity, chronic inflammatory conditions and neoplasms ***(McGeachy et al., 2020)***. Although the mediated responses of IL-17A play a role in the killing of the pathogens via neutrophil recruitment, this may occur at the expense of the tissue damage. This "double-edged sword" paradigm has been involved in the lung injury caused by acute respiratory distress syndrome and H1N1 influenza infection ***(Li et al., 2012; Mikacenic et al., 2016)***.

IL-22 is a member of the IL-10 family. It mediates its effects via the IL-22 receptor complex which is expressed by non-hematopoietic cell lineages of lung, skin, intestine, liver, pancreas and kidney ***(Dudakov et al., 2015)***. IL-22 has a dual role either protective or pathogenic functions during inflammatory, infectious and autoimmune diseases ***(Ivanov et al., 2013)***. It has a role in tissue regeneration and